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EFFECTS OF CONTINUOUS AMPHETAMINE INFUSION AND D1 DOPAMINE RECEPTOR ANTAGONISM ON BEHAVIOR AND BRAIN METABOLIC ACTIVITY IN THE RAT

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Heidi Paul

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Effects of Continuous Amphetamine Infusion and D1 Dopamine Receptor Antagonism on Behavior and Brain Metabolic Activity in the Rat," submitted by Heidi Paul in partial fulfillment of the requirements for the degree of Master of Science.

R.M. Cooper

Supervisor, Dr. R.M. Cooper
Department of Psychology

Dr. J.C. Abra
Department of Psychology

Brian H. Bland

Dr. B.H. Bland
Department of Psychology

Richard Williams

Dr. R. Williams
Department of Psychiatry

August 31, 1989

ABSTRACT

Continuous infusion of amphetamine in the rat via Alzet osmotic pumps was adopted as an animal model of amphetamine psychosis. Amphetamine and related psychostimulants can induce a psychotic state which may resemble paranoid schizophrenia, and it has been hoped that a greater understanding of the mechanisms of action of these DA agonists may provide insights into the processes underlying paranoid schizophrenia. The effects of 5-6 days of continuous amphetamine infusion at two doses (12 and 16 mg/kg/day) on regional cerebral glucose metabolism were assessed using the [^{14}C]-2-deoxy-D-glucose (2-DG) technique, and in a separate set of preliminary experiments, the stereotypy and locomotor responses to continuous administration of amphetamine over 7 days at these two doses were examined. In light of the evidence which has accumulated in recent years suggesting that the D1 dopamine receptor has an important role in the expression of behaviors mediated by dopamine systems, the ability of a selective D1 receptor antagonist, SCH 23390, to inhibit the usual consequences of amphetamine infusion was a particular focus of interest in this study.

Previous findings of a selective enhancement in glucose metabolism in nucleus accumbens after several days of continuous amphetamine treatment were not replicated, possibly reflecting limitations in the sensitivity of the semi-quantitative 2-DG technique employed here. Rather, more widespread metabolic stimulation within the nigrostriatal dopamine system was observed, suggesting that this pattern of activation is not associated exclusively with acutely administered amphetamine. While significant increases in locomotion were present only during the initial period of amphetamine

infusion, a biphasic stereotypy response was noted over the 7 days of treatment, which was especially prominent at the higher dose of amphetamine. A slower development of tolerance to the initial phase of amphetamine-induced stereotypies seen at the higher dose seems inconsistent with suggestions appearing in the literature that this tolerance may occur primarily as a result of dopamine depletions produced by continuous administration of amphetamine. Both the metabolic and behavioral components of this research suggested that the dose of continuous amphetamine employed is an important parameter, as is the case with acutely administered amphetamine.

The partial suppression of amphetamine-induced behavioral stimulation found with the concurrent infusion of SCH 23390 provides support for the view that the D1 receptor is involved in the mediation of dopamine-related behaviors. However, some behavioral activation in comparison with animals which received SCH 23390 alone appeared to remain, most notable in an increased frequency of stereotyped grooming on the first day of treatment, and in increased locomotion appearing late over the course of concurrent treatment. These results suggest that the actions of D1 antagonists may not be identical to those of D2 or mixed D1/D2 antagonists, and serve to reinforce the importance of considering chronic models in addition to acute models of dopaminergic drug administration.

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CHAPTER 1

INTRODUCTION

Overview

The introduction several years ago of the selective dopamine (DA) D1 receptor antagonist SCH 23390 led to the demonstration of a behavioral role for the D1 receptor, and implicated this receptor subtype in numerous behaviors which had previously been associated with the DA D2 receptor. A great deal of interest has since been shown in delineating the behavioral effects associated with the D1 receptor, and also more specifically, in its possible involvement in schizophrenia. Continuous amphetamine (AMPH) infusion in the rat was employed in this study as an animal model of AMPH psychosis, which in turn has been considered to be a model of paranoid schizophrenia. This research comprises a preliminary investigation seeking primarily to evaluate the participation of the D1 receptor in the behavioral effects of continuous AMPH, by examining the outcome of the concurrent administration of AMPH and SCH 23390. In addition, the impact of continuous AMPH administration on regional glucose metabolism in rat brain was estimated using the semi-quantitative [^{14}C]-2-deoxy-D-glucose (2-DG) technique, in order to assess the viability of this approach for quantifying the metabolic effects of continuous AMPH treatment.

The phenomenon of AMPH psychosis and approaches to modelling this condition will be discussed in the next section of this chapter, followed by a brief review of the substrates of AMPH action and the physiological effects of continuous AMPH infusion. Evidence for the classification of DA receptors into two subtypes, and the results of research directed at elucidating the behavioral role of the D1 receptor will subsequently

be presented. The selectivity of SCH 23390 for the D1 receptor will also be evaluated, since much of the work in this field rests on this presumed selectivity. Finally, the objectives of the current research will be outlined in greater detail.

Amphetamine Psychosis

AMPH psychosis has been widely used as a model for paranoid schizophrenia (Groves & Rebec, 1976; Kokkinidis & Anisman, 1980). A psychotic state can develop in humans after ingestion of AMPH or related psychostimulants, which are believed to interact with brain DA systems, either after a single dose, or much more commonly after several days of chronic intake (Angrist & Gershon, 1969; Bell, 1965; Connell, 1958; Ellinwood, 1967; Post, 1975). This condition has been experimentally induced in numerous nonschizophrenic subjects, within 1-5 days with hourly administration of AMPH (Angrist & Gershon, 1970; Angrist et al, 1974b; Griffith et al, 1972), or by a single large dose of methamphetamine (Bell, 1973). Small doses of AMPH have been shown to exacerbate existing symptoms in schizophrenic patients (Janowsky et al, 1974). The symptoms of AMPH psychosis are often indistinguishable from those of paranoid schizophrenia, typically involving an early phase of hyperarousal, which may lead to the development of repetitive behaviors, and ultimately to paranoid delusions, altered social behaviors, blunted affect and/or hallucinations. Neuroleptic drugs used in the treatment of schizophrenia are effective in reversing AMPH-induced psychosis (Snyder et al, 1974; Angrist et al, 1974a), which also dissipates spontaneously soon after AMPH ingestion is terminated.

It has been suggested that there may be notable differences between the two disorders, particularly that auditory hallucinations are more common in schizophrenia while visual hallucinations may be more prominent in AMPH psychosis, and that the

cognitive disturbances characteristic of schizophrenia may not occur in AMPH psychosis (Bell, 1965; Griffith et al, 1972). However, others have argued that auditory hallucinations and thought disorders are in fact often present in AMPH psychosis (Angrist & Gershon, 1970; Angrist et al, 1974b; Janowsky & Risch, 1979), particularly when the condition has evolved gradually over time (Snyder et al, 1974).

There has thus been considerable interest in developing valid animal models of AMPH psychosis as a means of elucidating the physiological processes underlying both schizophrenia and stimulant-induced psychoses. AMPH has been shown to produce marked behavioral effects in animals which may in some respects resemble the effects seen in humans (Ellinwood et al, 1973; Ellison & Eison, 1983; Lyon & Nielsen, 1979; Randrup & Munkvad, 1967). Relatively low acute doses of AMPH and other DA agonists produce hyperactivity, with increased locomotion and exploratory activity, in many species including rats, mice, cats and monkeys (Ellinwood & Balster, 1974; Randrup & Munkvad, 1967; Schiorring, 1979; Ljungberg & Ungerstedt, 1977). At higher doses an initial period of hyperactivity is replaced with the appearance of repetitive, purposeless behaviors referred to as stereotypies. AMPH-induced stereotypies in rats include behaviors such as sniffing and head and limb movements, and at higher doses, oral behaviors such as licking or gnawing, although the form of the stereotypies varies across species. As doses are increased, these stereotypies become more intense and repetitive, with the animal restricting itself to a small area of its cage.

Locomotion and some components of stereotypy intensify with repeated AMPH administration, a process known as behavioral sensitization (Rebec & Segal, 1980; Segal & Mandell, 1974), and an increased sensitivity to subsequent AMPH persists for long periods of time after termination of chronic treatment (Magos, 1969). Thus some

investigators have proposed chronic intermittent AMPH administration, typically involving daily injections, as a model of AMPH psychosis, arguing that sensitization parallels the augmentation of symptoms and long-lasting enhanced sensitivity to subsequent AMPH seen in AMPH psychosis and schizophrenia (Robinson & Becker, 1986). Further, a chronic model may be more appropriate since these conditions generally develop over time, and neuroleptic treatment of schizophrenia is usually effective only after prolonged administration (Baldessarini, 1980).

Continuous AMPH Administration. However, it has been suggested that continuous infusion of AMPH via subcutaneous implants, compared with repeated injections, more closely approximates the drug regimen leading most readily to human AMPH psychosis, since both lead to the continuous presence of AMPH in the bloodstream (Ellison & Eison, 1983). Among rats housed in social colonies and continuously administered AMPH for one week by silicone-tubing pellet, designed to release 40 mg of AMPH base over ten days, (equivalent to an average of approximately 15 mg/kg/day of d-AMPH sulfate), a reliable sequence of behavioral stages was noted (Ellison et al, 1978a). A few hours of initial hyperactivity was followed by the development of intense motor stereotypy, consisting predominantly of head-bobbing, sniffing, straw-sifting or grooming, which declined after two to three days. This was replaced with a short period of reduced activity, and finally the emergence of a late stage after approximately five days characterized by disrupted social behaviors, particularly increased fighting and fleeing, increased startle responses, and only occasional bouts of stereotypy.

During this late stage, rats housed individually typically showed somewhat increased activity, startle responses, attempts to escape when approached, and

persistent grooming and biting of the skin, in addition to infrequent limb flicks and wet-dog shakes which are usually associated with the administration of hallucinogens (Huberman et al, 1977; Nielsen et al, 1980). Monkeys similarly treated also often demonstrated a late stage with increased startle, wet-dog shakes, biting of the skin, and orienting, pouncing or flight apparently in response to non-existent stimuli (Ellison et al, 1981). It was proposed that this progression of behavioral stages resembles that often seen in humans with AMPH psychosis, and that these late stage 'hallucinatory-like' behaviors may parallel the hallucinations, delusions of parasitosis, and paranoid behaviors which frequently occur in human AMPH psychosis or schizophrenia (Ellison & Eison, 1983; Lyon & Nielsen, 1979). These observations of late-stage behaviors are interesting, but clearly any interpretations of these behaviors in animals are highly speculative.

Some apparent discrepancies from the effects noted above have been reported in subsequent studies employing continuous infusions of AMPH via silicone pellet or Alzet osmotic pumps, which provide a more nearly constant release rate over time than do pellets. However, comparisons among studies in this area are complicated by differences in mode and dose of AMPH administration, and by considerable variation found in methods and time frames of behavioral assessment. Further, several studies employing Alzet minipumps have used d-AMPH base, which reportedly interferes with the operation of these pumps (Nielsen, 1981; Nielsen et al, 1983), rendering determination of actual doses delivered difficult.

Taking these factors into account, it appears that continuous pump infusions of AMPH in doses which were likely lower than those used in the studies reported above have resulted in less intense stereotypies during the first several days, while increased

locomotion may be present (Eison et al, 1983). Doses which are probably higher have produced more intense stereotypies during the first two to three days (Gately et al, 1987), which may be replaced with significant increases in locomotor activity within four to five days in pump or pellet infused rats (Eison et al, 1983; Gately et al, 1987). This interpretation is consistent with Nielsen's (1981) report of dose-dependent stereotypies among rats receiving pump infusions of AMPH. Rapid declines in these initial stereotypies are reliably seen after two to three days. Small increases in some forms of stereotypy have been noted after 5 to 6 days among pellet-infused rats (Ellison et al, 1978a; Huberman et al, 1977). In contrast to most other studies, Eison et al (1983) found grooming to be generally suppressed during both pump and pellet infusions, particularly during the first two days of treatment. The limb flicks and wet-dog shakes noted occasionally in early work have not been reported in subsequent studies, which might reflect the shorter durations of behavioral observations generally used here, or differences resulting from mode of administration. It is not clear whether significant behavioral differences result from pump vs. pellet administration.

Continuous AMPH administration has been criticized as a model of AMPH psychosis because it leads to the development of tolerance to AMPH-induced motor stereotypies over the course of treatment and shortly thereafter to DA agonist challenge, rather than to the sensitization which some believe to be an important feature of AMPH psychosis and schizophrenia (Robinson & Becker, 1986). However, some sensitization may in fact be reflected in the increased locomotor activity which is sometimes observed after four to five days of continuous AMPH, while increased stereotypy to a challenge dose of AMPH has been reported a week after a five-day period of continuous AMPH administration (Ellison & Morris, 1981). Costall et al (1982) found biphasic

increases in hyperactivity during a two-week continuous infusion of DA into nucleus accumbens, and a pronounced, long-lasting sensitization in locomotor response to DA agonist challenge two weeks later, although the latter effect occurred only among rats which showed a low response in initial screening. It may be noted that repeated injections of AMPH have been shown to produce tolerance to oral stereotypies over the first several weeks of treatment (Eichler et al, 1980; Rebec & Segal, 1980). Thus sensitization is not necessarily dependent on an intermittent injection regimen, nor is tolerance associated exclusively with continuous infusion of AMPH.

A further criticism of this model is that the behaviors observed after several days of continuous amphetamine administration may simply be the result of the significant depletions of DA and other neurotransmitters, and damage to DA terminals in caudate, associated with this treatment (Robinson & Becker, 1986), an issue which is discussed further in the next section. However, Ellison and Eison (1983) have argued that it is possible that these central changes may occur in human AMPH psychosis or during acute episodes of schizophrenia, and therefore may be integral aspects of this model. This point is difficult to evaluate, since there is conflicting evidence on neurochemical and structural changes accompanying these conditions (Bracha & Kleinman, 1986; Robinson & Becker, 1986).

Perhaps more importantly, AMPH psychosis and the various forms of schizophrenia likely involve complex and heterogeneous processes which may vary at different stages (Ellinwood et al, 1973; Seidman, 1983; Snyder et al, 1974), and perhaps cannot be adequately modelled by any one approach. It has been suggested that the usefulness of animal models lies in their ability to generate hypotheses concerning the mechanisms involved in particular aspects of a disorder and in their treatment, and

a viable model need not reflect all features of the particular human condition (Bond, 1984). To date, it appears that there is no consensus on which model in this area is most appropriate, and it is conceivable that both intermittent and continuous AMPH will prove to be viable models of different aspects of AMPH psychosis.

Physiological Basis of Amphetamine Effects

Neurochemical Substrates. The most prominent effects of AMPH administration appear to be the release and reuptake inactivation of DA and norepinephrine (NE) (Besson et al, 1969; Fuxe & Ungerstedt, 1970; Liang & Rutledge, 1982; Niddam, 1985; Parker & Cubeddu, 1986a, b). AMPH may also have smaller effects on serotonin release, and indirect actions on cholinergic systems (Geyer et al, 1975; Hernandez et al, 1987; Parker & Cebeddu, 1986a, b). It is believed that the locomotor activation and stereotypy produced by AMPH result primarily from central DA rather than NE stimulation (Groves & Rebec, 1976; Kokkinidis & Anisman, 1980), through presynaptic effects on DA release and reuptake rather than postsynaptically via any direct effect on DA receptors (Creese & Iversen, 1975). AMPH is thus considered to be an indirect DA agonist.

The time frame of behavioral effects produced by a range of AMPH doses has been found to correspond closely to brain DA release in awake rats, suggesting that this behavioral activation may be directly related to DA release (Sharp et al, 1987). AMPH-induced motor responses are prevented when animals are pretreated with a DA synthesis inhibitor or DA receptor blockers (Hollister et al, 1974; Maj et al, 1972; Randrup & Munkvad, 1966; Rolinski & Scheel-Kruger, 1973), and similarly, AMPH-induced hyperactivity is markedly attenuated and stereotypy is blocked after selective 6-OHDA lesions of DA pathways (Creese & Iversen, 1975; Hollister et

al,1974; Roberts et al, 1975). In contrast, NE synthesis inhibitors, NE receptor antagonists, and chemical or electrolytic lesions of NE projections are typically reported either to have no effect on AMPH responses (Creese & Iversen, 1975; Hollister et al, 1974; Roberts et al, 1975), or to partially inhibit locomotion (Ogren et al, 1983; Rolinski & Scheel-Kruger, 1973) and/or slightly enhance stereotypies (Corrodi et al, 1970; Mogilnicka & Braestrup, 1976).

Recently Dickinson et al (1988), employing more highly selective alpha-1 and alpha-2 adrenoreceptor antagonists than in previous studies, found that these compounds differentially modified AMPH-induced locomotion and stereotypy in opposite directions, which may account in part for the discrepancies in earlier reports. The effects of alpha-1 and alpha-2 receptor agonists on AMPH-induced motor behaviors (Mueller & Nyhan, 1982; Pifl & Hornykiewicz, 1985), are generally consistent with the notion of opposing actions of these receptor types. Thus NE appears to have a modulatory role with respect to AMPH behavioral effects. Manipulations of serotonergic and cholinergic systems have also been shown to alter the motor effects of AMPH administration (Breese et al, 1974; Arnfred & Randrup, 1968), while some behavioral effects of very high doses of AMPH (>15 mg/kg) may be mediated by serotonin (Sloviter et al, 1978).

The psychotomimetic actions of AMPH in humans have also been attributed primarily to the stimulation of DA receptors, while the antipsychotic activity of neuroleptics is believed to result from their ability to block DA receptors and the resulting compensatory changes in DA turnover (Seeman, 1987; Snyder et al, 1974). The clinical potency of neuroleptic drugs has been found to correlate highly with their affinity for DA receptors in binding studies (Creese et al, 1976; Seeman et al, 1976),

while the clinical effectiveness of neuroleptics in schizophrenic patients has been correlated with decreases in plasma levels of the DA metabolite homovanillic acid (Pickar et al, 1984). In fact, the psychotomimetic effects of numerous DA agonists and the antipsychotic effects of DA antagonists have been major sources of evidence in support of the DA hypothesis of schizophrenia, which proposes that certain DA pathways are overactive in schizophrenia (Carlsson, 1988; Seeman, 1987; Snyder, 1976). NE, serotonin, acetylcholine and possibly other neurotransmitters may nonetheless be involved in the symptoms of AMPH psychosis and schizophrenia, and some have argued that these disorders may best be understood in terms of an interaction between several neurotransmitter systems (Carlsson, 1988; Kokkinidis & Anisman, 1981; Scatton & Zivkovic, 1984).

Neuroanatomical Substrates. Interest has also been directed at identifying the DA pathways which may be substrates of AMPH and neuroleptic action. Three major DA pathways have been identified in the rat brain, with cells of origin located in substantia nigra pars compacta and ventral tegmental area, often referred to as the A9 and A10 cell groups, respectively (Beckstead et al, 1979; Bjorklund & Lindvall, 1984). The majority of neurons in the nigrostriatal system originate in substantia nigra pars compacta and project mainly to the caudate-putamen, as well as to globus pallidus and subthalamic nucleus. The dendrites of the nigral DA neurons extend into substantia nigra pars reticulata, where DA release has been demonstrated. The caudate-putamen sends its major projections back to substantia nigra pars reticulata, forming a feedback loop, as well as to globus pallidus. The subthalamic nucleus is richly interconnected with the globus pallidus and substantia nigra pars reticulata. The mesolimbic system projects mainly from the ventral tegmental area to nucleus accumbens, olfactory

tubercle, septum, amygdala and other limbic regions, while the nucleus accumbens sends prominent efferents back to the ventral tegmental area, as well as to the ventral pallidum and substantia nigra. The mesocortical system also originates predominantly from the ventral tegmental area, projecting to frontal, entorhinal and other cortical regions.

The nigrostriatal system has been associated primarily with AMPH-induced stereotypy and with the extrapyramidal motor side-effects of neuroleptics, while the mesolimbic system in contrast has been thought to mediate AMPH-induced locomotion and psychotic symptoms, and the antipsychotic effects of neuroleptics (Arnt, 1987; Bunney, 1984; Matthysse, 1973; Stevens, 1979). Less is known in regards to the mesocortical DA system to date. Particular attention within the mesolimbic system has focussed on the nucleus accumbens (Swerdlow et al, 1986; Swerdlow & Koob, 1987), in part because this structure may represent an interface between the limbic and motor systems, receiving afferents from much of limbic cortex, a region classically associated with emotionality, and sending a major efferent projection to the motor system via the ventral pallidum (Mogenson et al, 1980). Thus nucleus accumbens has been hypothesized to have an important role in the filtering of motivational information and initiation of goal-directed behavior, with dopaminergic projections from the ventral tegmental area appearing to modulate this filtering mechanism.

While chronic administration of classical neuroleptics produces a decrease in spontaneous activity of DA neurons in both substantia nigra and ventral tegmental area, numerous atypical antipsychotics, with a lower incidence of extrapyramidal side-effects, reduce spontaneous cell activity of the ventral tegmental area only (Chiodo & Bunney, 1983; White and Wang, 1983). DA turnover is preferentially enhanced in

the limbic system by atypical neuroleptics, while classical antipsychotic drugs produce a similar increase in DA turnover in limbic structures and striatum (Bartholini, 1976). Atypical neuroleptics also preferentially block DA agonist-induced locomotion, in contrast to classical neuroleptics which potently antagonize both locomotion and stereotypy (Ljungberg & Ungerstedt, 1978; Ogren et al, 1978).

6-OHDA lesions of DA terminals in rat striatum have frequently been found to reduce or abolish AMPH-induced stereotypies, particularly intense forms, without affecting locomotion, while lesions of nucleus accumbens DA terminals selectively inhibit locomotion and weaker stereotypies, including sniffing and sometimes head movements (Costall et al, 1977; Kelly et al, 1975; Makanjuola & Ashcroft, 1982). Electrolytic lesions of the olfactory tubercle have also been shown to antagonize the weaker forms of stereotypy (Costall & Naylor, 1974). These findings suggest involvement of the nigrostriatal system in more intense stereotypy and of the mesolimbic system in locomotion and the weaker components of stereotypy.

Consistent with this hypothesis, injection of AMPH into nucleus accumbens has been reported to produce locomotion, rearing and sniffing but very little continuous stereotypy, while injection into caudate has produced intense, continuous stereotypy (Staton & Solomon, 1984; Towell et al, 1987). The locomotion and sniffing produced by a low dose of peripheral AMPH was selectively blocked by injection of the DA antagonist haloperidol into nucleus accumbens, while the continuous stereotypy produced by a high dose of AMPH was selectively inhibited by intrastriatal injection of a small volume of haloperidol, although use of a considerably larger injection volume in nucleus accumbens could also antagonize this stereotypy (Pijnenburg et al, 1975a, b; Towell et al, 1987). Employing intracerebral dialysis to measure DA release in

striatum and nucleus accumbens of awake rats, Sharp et al (1987) found that AMPH-induced head and forelimb movements correlated best over a wide dose range with DA release in striatum, while locomotion and sniffing correlated with DA release only in nucleus accumbens.

However, Fink and Smith (1979) found that 6-OHDA lesions of caudate reduced long traverses of the cage, suggesting that striatum may be involved in some aspects of locomotion. Further, a very selective lesion of nucleus accumbens by itself failed to significantly attenuate the locomotor response to AMPH (Fink & Smith, 1980), and it appeared that concurrent denervation of nucleus accumbens and adjacent terminal fields, including striatal areas, was required to abolish AMPH-induced locomotion. After peripheral administration of apomorphine, Arnt (1985a) found that sulpiride injected into certain regions of caudate antagonized oral stereotypy, while locomotion and weaker stereotypies, including sniffing and rearing, could be readily inhibited by injection into other areas of caudate and into nucleus accumbens. Striatum appears to be functionally heterogeneous, with injection of AMPH into various subregions producing either oral stereotypies or small increases in locomotion and rearing (Kelley et al, 1988; Carr & White, 1987). It may be noted that electrolytic lesions of substantia nigra, caudate or the nigrostriatal pathway, or 6-OHDA lesion of substantia nigra have failed to significantly block AMPH-induced stereotypy (Costall et al, 1972; Costall & Naylor, 1974; Costall et al, 1977), while electrolytic lesions of nucleus accumbens have typically failed to modify AMPH-induced hyperactivity (Costall & Naylor, 1974; Makanjuola & Ashcroft, 1982).

Some discrepancies in the studies discussed above may result from the heterogeneity of striatum, in addition to methodological limitations, particularly

variations in the extent of DA depletion induced by lesions, and difficulty in achieving selective lesions and discrete intracerebral drug injections. Furthermore, locomotion and stereotypy may be competitive rather than independent components of behavior, since enhanced stereotypy may occur at the expense of reduced locomotion (Kokkinidis & Anisman, 1980), while increased locomotion can itself be stereotyped in nature (Schiorring, 1979). Nonetheless, it appears that intense forms of stereotypy are associated most closely with striatum, while nucleus accumbens seems to participate in the mediation of locomotion and sniffing. However, investigations to date have failed to localize either locomotion or stereotypy completely to any particular structure or DA pathway, and many view the functional distinction between the nigrostriatal and mesolimbic systems as an oversimplification (Arnt, 1987; Rebec & Bashore, 1982).

Physiological Effects of Continuous AMPH Administration. Continuous pellet infusion of AMPH for two to five days has been reported to produce significant depletions of DA and NE in several brain regions (Ellison et al, 1978b; Ellison & Ratan, 1982). DA was significantly depleted in caudate by 40-60%, but not in other regions studied, including nucleus accumbens. Employing a similar regimen of pellet AMPH infusion, Eison et al (1983) found a substantial, although statistically insignificant, DA depletion in caudate after two days, but unchanged levels at five days relative to control animals. DA concentrations were found to be significantly decreased in frontal cortex after two days, and increased in nucleus accumbens after five days. The only significant changes in DA levels after infusion of what was likely a slightly lower dose of AMPH via pump were increases in caudate and nucleus accumbens after two days, with no changes after five days. With pump infusion of a dose of AMPH which was likely somewhat higher than in Ellison's studies, Gately et al (1987) reported marked DA depletions in striatum

after three or five days, and an increase in nucleus accumbens after three days.

NE levels were significantly reduced in pellet as well as in pump infused rats after two or five days in several structures, including cortex (Ellison et al, 1978b; Eison et al, 1983). A significant depletion of serotonin appeared in nucleus accumbens but not in caudate after three days of pellet infusion, but brain serotonin levels were unchanged in animals which had received acute AMPH injections soon after five days of pretreatment with AMPH pellets, a regimen which elicits frequent occurrences of the limb flicks and wet-dog shakes reported with continuous AMPH infusion (Ellison & Ratan, 1982).

Selective damage to DA terminals in caudate but not in other regions has been reported with continuous AMPH in rats after five days of pellet infusion (Ellison et al, 1978b), and after three days of pump infusion at a dose of 16 mg/kg/day (Ricaurte et al, 1984), as well as in mice (Nwanze & Jonsson, 1981; Steranka & Sanders-Bush, 1980). No neurotoxic effects have been shown on noradrenergic or serotonergic neurons as a result of continuous AMPH administration.

As mentioned previously, continuous administration of AMPH has been criticized as a model of AMPH psychosis because of its association with these depletions and terminal damage. However, these neurotoxic effects seem to be relatively selective for striatum, and do not appear to directly involve those structures which may be more relevant to psychosis. In addition, it may be noted that considerable sparing and recovery of function is typically found within dopaminergic systems. Significant behavioral disruptions have generally been demonstrated only with very large 6-OHDA-induced DA depletions, often greater than 95% (Castaneda et al, 1985), while DA depletions of 50-90% and over 95% have been reported to be necessary before

spontaneous firing rates of Type I and Type II striatal neurons, respectively, are altered (Orr et al, 1987). Antagonism of stereotypy in response to acute AMPH in 6-OHDA lesioned rats is generally associated with large depletions of striatal DA, of approximately 50-65% (Asher & Aghajanian, 1974; Makanjuola & Ashcroft, 1982). Nonetheless, response to challenge by continuously administered AMPH cannot be predicted from this data.

Eison et al (1981) determined the brain distribution of radioactivity by scintillation counting after administration of [^{3}H]2-DG to provide an indicator of regional neural activity, in rats pretreated with acute AMPH or continuous pellet infusions of AMPH for two or five days. Acute administration of 1.5 mg/kg of d-AMPH sulfate was associated with a trend towards an increased proportion of 2-DG counts in caudate relative to control animals, while continuous infusion of AMPH base for five days, at a dose equivalent to approximately 15 mg/kg/day of d-AMPH sulfate, produced a significant increase in nucleus accumbens relative to controls. Mesolimbic brain regions, including nucleus accumbens and olfactory bulbs, showed trends towards enhanced proportions of 2-DG counts, while nigrostriatal areas, including caudate and substantia nigra, showed trends towards small declines as infusions extended from two to five days. Similarly, in rats administered [^{3}H]-labelled AMPH, a pattern of progressively increasing proportions of AMPH accumulation in limbic areas, including nucleus accumbens, olfactory bulbs and olfactory tract, and a trend toward declining accumulations in caudate was found with five-day infusions relative to two-day infusions, and with infusions compared to acute injections.

Thus the late stage which emerges after five days of continuous AMPH appeared to be associated with significantly enhanced glucose utilization and AMPH accumulation in

mesolimbic but not nigrostriatal areas, as well as with selective damage to striatal DA terminals and possibly a selective DA depletion in striatum. It was suggested that the locus of control of AMPH effects may shift over time from the nigrostriatal to the mesolimbic system, consistent with the hypothesized predominant role of nucleus accumbens in mediating psychotic reactions (Eison et al, 1981; Ellison & Eison, 1983).

Employing the quantitative autoradiographic 2-[^{14}C]DG method in partially restrained rats, Orzi et al (1983) found results similar to those reported above. An acute intraperitoneal dose of 5 mg/kg of AMPH, which produced stereotypic behaviors, was associated with increases in glucose utilization throughout the dopaminergic extrapyramidal motor system, with the most pronounced effects in subthalamic nucleus, substantia nigra pars reticulata and caudate nucleus, but no alterations within the mesolimbic system. The only significant effects of continuous pump administration of 12-15 mg/kg/day of d-AMPH sulfate for seven days were increases in glucose utilization in nucleus accumbens and substantia nigra pars reticulata, and a reduction in the lateral habenula. On the basis of apparently brief periods of observation, rats which received the latter treatment were reported to be mildly hyperactive but demonstrated no stereotypy.

However, Porrino et al (1984) reported significant increases in glucose utilization in nucleus accumbens with relatively low acute doses (0.2 - 1.0 mg/kg) of intravenously administered AMPH, which were associated with locomotor stimulation. Significantly increased metabolic activation was seen in the extrapyramidal motor system with higher, stereotypy-inducing doses (1 - 5 mg/kg), and in addition, increases in glucose utilization were found in ventral tegmental area and several other

mesolimbic structures, although not in nucleus accumbens at the highest dose. Thus it appears that metabolic activation of nucleus accumbens is not dependent on continuous AMPH treatment, but rather may be dose dependent, and could potentially be associated with the behavioral states which are thought to be mediated by this structure, notably locomotion and possibly psychotic states. These 2-DG studies also reinforce the likelihood that the mesolimbic and nigrostriatal systems overlap to some degree in the control of hyperactivity and stereotypy, and possibly of psychosis.

Dopamine Receptor Subtypes

D1/D2 DA Receptor Classification. The classification of DA receptors into two distinct categories based on the association between the receptor and adenylate cyclase (AC) activity is currently well accepted (Stoof & Kebabian, 1984; Clark & White, 1987). This scheme was derived primarily from discrepancies which emerged in the effects of various classes of dopaminergic agents. DA was found to activate AC in neural tissue leading to an increase in cyclic AMP synthesis (Kebabian et al, 1972; Brown & Makman, 1972), and inhibition of this DA-stimulated AC correlated well with the potencies in vivo of phenothiazine and thioxanthene neuroleptics as antipsychotic drugs in humans or antidopaminergic agents in animals. However, this correlation did not hold for the butyrophenones and other neuroleptics (Miller et al, 1974; Iversen, 1975; Seeman, 1977). Further, it was reported that several ergot derivatives stimulate DA receptors in the pituitary gland, but in contrast to the effects which were expected of a DA agonist, these compounds block DA-induced activation of AC in striatum (Pieri et al, 1978; Schmidt & Hill, 1977).

Thus two distinct DA receptors were postulated, a D1 receptor associated with AC activation, and a D2 receptor with no effect on AC activity (Kebabian & Calne, 1979;

Spano et al, 1978). It has since been shown that D2 receptor stimulation leads to an inhibition of AC activity in the pituitary (Decamilli et al, 1979; Cote et al, 1982) and striatum (Onali et al, 1985; Cooper et al, 1986). The DA receptor in the anterior pituitary has been considered a prototype D2 receptor, with stimulation of this receptor leading to inhibition of prolactin release (Caron et al, 1978; Weiner & Ganong, 1978), thereby providing a useful functional indicator of D2 receptor activity (Clark & White, 1987).

The D1/D2 classification scheme has been supported by the identification of numerous compounds showing selectivity for either receptor type. Butyrophenones such as haloperidol and spiperone (Hess & Creese, 1987; Hyttel, 1982), and particularly certain substituted benzamides such as sulpiride and raclopride (O'Connor & Brown, 1982; Ogren et al, 1986), are considered selective D2 antagonists, elevating plasma prolactin but showing no inhibition of DA-stimulated AC, while quinpirole (LY 171555), RU 24213 and RU 24926 are frequently used selective D2 agonists with opposite biochemical effects (Titus et al, 1983; Tsuruta et al, 1981; Euvrard et al, 1980). Several substituted benzazepines have more recently been identified as compounds selective for D1 receptors, facilitating the comprehensive investigation of D1 receptor function. SCH 23390, discussed in a later section, is considered a selective D1 antagonist (Hyttel, 1983; Iorio et al, 1983), while SKF 38393 is considered a selective partial D1 agonist (Setler et al, 1978; Sibley et al, 1982), demonstrating stimulation of AC but no inhibition of prolactin release. The phenothiazines and thioxanthenes are antagonists with high affinity at both D1 and D2 receptors, while apomorphine and AMPH are considered mixed D1/D2 agonists (Hess & Creese, 1987; Hyttel, 1982; Seeman & Ulpian, 1988; Creese & Iversen, 1975).

Radioligand binding studies appear to identify two separate populations of DA receptors (Hyttel, 1983). When D1 receptors are labelled by [^{3}H]-thioxanthenes such as [^{3}H]-flupentixol (with D2 receptors occluded by inclusion of an unlabelled D2 selective antagonist) or by [^{3}H]-SCH 23390, the resulting antagonist competition curves suggest the presence of a homogeneous population of D1 sites, while agonist competitions support a two-site model consisting of high and low agonist affinity binding components (Leff et al, 1985; Hess et al, 1986b; Schultz et al, 1985). Similarly, antagonist competition curves for D2 selective [^{3}H]-antagonists suggest the presence of a single D2 binding site, while agonist competition curves suggest the existence of high and low agonist affinity binding sites for D2 receptors (Hamblin et al, 1984; Leysen et al, 1978). However it has proven possible to convert both D1 and D2 high affinity agonist binding sites into low affinity sites in the presence of guanine nucleotides (Seeman et al, 1985; Grigoriadis & Seeman, 1985). It is therefore generally believed that D1 and D2 receptors each exist in two interconvertible agonist affinity states, and the D3 and D4 DA receptors proposed at one time by Seeman (1980) are now considered to be the high agonist affinity states of D1 and D2 receptors, respectively (Clark & White, 1987; Seeman et al, 1985).

Studies employing selective ligands have indicated differences in the distribution of the two receptor types, discussed further below. In addition, Dumbrille-Ross et al (1985) have shown that D1 and D2 receptors labelled by selective antagonists can be physically separated by steric exclusion-HPLC and appear to be distinct proteins.

Selective changes in receptor number and function can be produced with selective antagonism of D1 or D2 sites, supporting the concept of two separate populations of DA receptors. Studies employing N-ethoxycarbonyl-2-ethoxy-1, 2-dihydroquinoline

(EEDQ), which produces an irreversible inactivation of a variety of receptors including D1 and D2 DA receptors (Hamblin & Creese, 1983), have found that pretreatment with SCH 23390 or SKF 38393 protects D1 but not D2 receptors from blockade by EEDQ, while pretreatment with sulpiride or a variety of other D2 agents selectively protects D2 receptors (Meller et al, 1985; Nowak et al, 1988). Chronic treatment with SCH 23390 results in an increased D1 receptor density with no change in D2 receptor numbers (Hess et al, 1988; Parashos et al, 1987; Porceddu et al, 1985), while chronic administration of the D2 antagonists spiperone or haloperidol produces a selective increase in D2 receptor numbers in striatum (Hess et al, 1988; Burt et al, 1977). Similarly, chronic SCH 23390 has been shown to potentiate D1 agonist-induced AC stimulation without affecting D2 functional activity in striatum, nucleus accumbens and substantia nigra, while chronic D2 antagonism with sulpiride increased the ability of a D2 agonist to inhibit AC activity without changing D1 functional activity (Memo et al, 1987).

The two receptor types can be discriminated on the basis of electrophysiological evidence. Extracellular single-unit recordings have shown that the inhibitory effects of iontophoresed D1 and D2 agonists in nucleus accumbens and in striatum are selectively blocked by D1 and D2 antagonists, respectively, suggesting that the effects of the two agonists are mediated by separate DA receptor subtypes (White & Wang, 1986; Hu & Wang, 1988). Further, some neurons in nucleus accumbens were found to be selectively responsive to either D1 or D2 compounds (White & Wang, 1986). It has been suggested that increased basal activity in the substantia nigra pars reticulata is mediated primarily by D1 receptor stimulation, while D2 receptor activation mediates the attenuation of GABAergic inhibition within this structure (Graf & Waszczak, 1986).

Differential biochemical and other functional effects, in addition to those described previously in regard to AC and prolactin, distinguish D1 and D2 receptors. Preliminary evidence suggests that D1 and D2 receptors may have opposing effects on the release of acetylcholine (Fage & Scatton, 1986; Saller & Salama, 1986), GABA (Girault et al, 1986) and CCK (Conzelmann et al, 1984; Meyer & Krauss, 1983) in the striatum, and of substance P (Sonsalla et al, 1984) in the substantia nigra. Parathyroid hormone release is stimulated by D1 receptors in the parathyroid gland (Attie et al, 1980), while alpha-melanocyte stimulating hormone release is inhibited by D2 receptors in the intermediate pituitary (Cote et al, 1980). D2 receptor stimulation in the area postrema is associated with emesis in dogs (Christensen et al, 1984; Setler et al, 1978). Considerable evidence suggests that DA autoreceptors are of the D2 type (Lehmann, 1983; Tissari et al, 1983; Carlson et al, 1986; White & Wang, 1984). DA synthesis, release and impulse flow are selectively inhibited by D2 agonists activating DA autoreceptors, while these effects are blocked by D2 antagonists but not by SCH 23390.

Several behavioral models support the existence of distinct D1 and D2 receptors. While D1 and D2 agonists both induce circling in rats with unilateral 6-OHDA lesions of the nigrostriatal pathway, and similar hyperactivity and stereotypy in bilaterally lesioned or chronically reserpinized rats, D1 agonist-induced effects are selectively blocked by SCH 23390, and D2 agonist-induced effects are selectively inhibited by D2 antagonists, suggesting that these effects in rats with supersensitive DA receptors are produced by stimulation at separate D1 and D2 sites (Arnt & Hyttel, 1985; 1986; Arnt, 1985b, c; Breese & Mueller, 1985). Drug discrimination studies have shown that D1 and D2 agonists produce distinct centrally-mediated discriminative stimulus properties

which are selectively blocked by D1 and D2 antagonists, respectively, suggesting mediation by separate receptor sites (Arnt, 1988; Kamien et al, 1987). While tolerance to the cataleptogenic effects of D2-selective neuroleptics, including haloperidol and spiperone, is observed after chronic treatment (Ezrin-Waters & Seeman, 1977; Hess et al, 1988), tolerance does not develop to the cataleptogenic action of SCH 23390 after chronic administration (Hess et al, 1988), suggesting separate mechanisms of cataleptogenic action by D1 and D2 receptors.

There is thus considerable evidence favoring the classification of DA receptors into two distinct subtypes. It may be noted that the possibility remains nonetheless that there are subtypes of both D1 and D2 receptors (Carlsson, 1988; Mailman et al, 1986). Of particular interest here, an absence of DA-sensitive AC has been reported in rat amygdala and human frontal cortex, regions which are labelled with high affinity by [^{3}H]-SCH 23390 (Mailman et al, 1986; De Keyser et al, 1988b), suggesting that there may be some D1 receptors which are not linked to AC. Similarly, the pharmacological characteristics of [^{3}H]-SCH 23390 binding and of DA-sensitive AC have been found to be consistent with the presence of both AC-coupled and uncoupled D1 receptors (Andersen & Braestrup, 1986).

D1/D2 Receptor Localization. Although biochemical, electrophysiological and radioligand homogenate binding studies have provided considerable information on the distribution of D1 and D2 receptors in the rat brain, in vitro receptor autoradiography using selective ligands has more recently been widely employed to provide a more precise visualization of DA receptor subtypes and quantification of receptor densities (Dawson et al, 1986c; Palacios & Pazos, 1987). The highest densities of D1 receptors have consistently been reported in the caudate-putamen, olfactory tubercle, nucleus

accumbens and substantia nigra pars reticulata, using tritiated or iodinated forms of the D1 antagonists SCH 23390 and related analogues, or the D1 agonist SKF 38393 as ligands (Aiso et al, 1987; Boyson et al, 1986; Dawson et al, 1986a, b; Dubois et al, 1986; Savasta et al, 1986). Very high densities of D1 receptors are usually reported in substantia nigra pars compacta as well, although there are also reports of a low concentration in this structure (Dawson et al, 1986a, b). A moderate concentration of D1 receptors is located in subthalamic nucleus, a lower density found in globus pallidus, and a low density reported in frontal cortex, the deeper layers of other cortical regions, and usually in ventral tegmental area.

In studies employing a variety of D2 antagonists and agonists as ligands, D2 receptors are found in greatest numbers in caudate-putamen, nucleus accumbens, olfactory tubercle and the islands of Calleja (Bouthenet et al, 1987; Boyson et al, 1986; Charuchinda et al, 1987; Dubois et al, 1986; van der Weide et al, 1987). Very high concentrations are also reported in olfactory bulb, a region devoid of D1 receptors. Substantia nigra pars compacta generally shows moderate concentrations of D2 receptors, while ventral tegmental area, substantia nigra reticulata, subthalamic nucleus and entorhinal cortex typically show lower concentrations. Low concentrations of D2 sites are found in globus pallidus and usually in neocortex. The distribution of D1 and D2 receptors determined in these studies has generally been found to correlate well with dopaminergic innervation in rat brain.

It is apparent that structures which have been associated with the effects of dopaminergic agents contain both receptor subtypes. While D1 and D2 receptors coexist in many structures, there are also clear differences in their distributions. Data from autoradiographic and positron emission tomography studies suggest a similar

distribution in human brain, with high concentrations of D1 and D2 receptors in caudate-putamen and nucleus accumbens (De Keyser et al, 1988a; Palacios et al, 1988; Farde et al, 1987).

Behavioral Role of the D1 Dopamine Receptor

Prior to the development of selective D1 receptor agents, particularly a D1 antagonist, D2 receptors were believed to be of primary importance in mediating DA agonist-induced behaviors as well as the antipsychotic and other antidopaminergic effects of neuroleptics, while D1 receptors had no known behavioral role (Creese et al, 1983; Seeman, 1981). This position was formulated on the basis of indirect evidence, namely that the affinities of DA antagonists for D2 receptors correlated highly with antagonism of AMPH- and apomorphine-induced stereotypy and hyperactivity in rats, and with antipsychotic activity in humans (Ogren et al, 1978; Creese et al, 1976; Seeman et al, 1976).

Acute Studies. While some investigators in fact report an absence of significant behavioral activation in response to the administration of the D1 agonist SKF 38393 in intact rats (Setler et al, 1978; Koller & Herbster, 1988), most report a prominent grooming response and a slight increase in non-stereotyped sniffing (Arnt, 1985a), and some have found in addition weak non-stereotyped rearing and locomotion (Molloy & Waddington, 1984; 1985; Braun & Chase, 1986), particularly in well-habituated rats. These increases in grooming, sniffing, rearing and locomotion were stereospecifically produced by R-SKF 38393, while grooming and sniffing were stereospecifically blocked by the R-enantiomer of the D1 antagonist SKF 83566, and by SCH 23390 but not by the D2 antagonist metoclopramide (Molloy & Waddington, 1985; 1987). Affinity for the D1 receptor resides with the R-enantiomer of SKF 38393 and

of SKF 83566, while the weak D2, 5-HT1 and 5-HT2 antagonist properties of these compounds show little or no enantioselectivity (O'Boyle & Waddington, 1984; 1985). Repetitive mouth movements have also been reported after SKF 38393 administration (Rosengarten et al, 1983; Johansson et al, 1987). As noted previously, SKF 38393 has effects similar to D2 and mixed agonists in rats with supersensitive DA receptors induced by 6-OHDA lesions or chronic reserpine pretreatment. In addition, SKF 38393 produces discriminative stimulus properties which can be blocked by SCH 23390 but not by D2 antagonists, and which generalize to other D1 agonists but not to D2 agonists (Arnt, 1988; Cunningham et al, 1985; Kamien et al, 1987). These studies thus suggest a behavioral role for D1 receptors.

The D1 selective antagonist SCH 23390 was surprisingly found to have very potent effects similar to those of classical neuroleptics (D2 and mixed D1/D2 antagonists) in several models believed to predict antipsychotic potential, including antagonism of AMPH-, apomorphine- and methylphenidate-induced stereotypies and hyperlocomotion in rats, mice and dogs (Iorio et al, 1983; Mailman et al, 1984; Christensen et al, 1984; Molloy & Waddington, 1985; Boyce et al, 1985; Vasse et al, 1988), antagonism of AMPH- and apomorphine-induced circling in 6-OHDA lesioned rats (Christensen et al, 1984; Arnt & Hyttel, 1985), selective suppression of conditioned avoidance responding in rats and squirrel monkeys (Iorio et al, 1983), and attenuation of intracranial self-stimulation (Kurumiya & Nakajima, 1988; Nakajima & McKenzie, 1986). SCH 23390 has been shown to antagonize the discriminative stimulus effects of AMPH and cocaine in rats and rhesus monkeys, suggesting that D1 receptors have an important role in the behavioral effects of these DA stimulants (Arnt, 1988; Nielsen & Jepsen, 1985; Woolverton et al, 1987; Kleven et al, 1988). In

common with the actions of classical neuroleptics, inhibition of spontaneous locomotion and induction of catalepsy have been demonstrated after administration of SCH 23390 (Christensen et al, 1984; Morelli & Di Chiara, 1985)

Even more unexpected, in light of the opposing or independent biochemical effects of D1 and D2 receptor stimulation, were findings that the stereotypy and locomotor activation induced in intact rats by various D2 agonists, including RU 24213, pergolide and quinpirole, could be blocked not only by D2 antagonists, but also by SCH 23390 in a dose-dependent manner (Breese & Mueller, 1985; Longoni et al, 1987; Pugh et al, 1985). The stereotypy induced by RU 24213 was also potently blocked by R- but not S-SKF 83566, supporting the apparent D1 antagonist basis of this effect (Molloy et al, 1986). It was therefore proposed that SCH 23390 may produce this antagonism in normosensitive rats through blockade of tonic D1 activity, which in turn influences behaviors initiated by D2 receptor activation.

Consistent with suggestions of a functional interaction between D1 and D2 receptors, D1 agonists have been found to enhance many D2 agonist-induced effects. As noted above, SKF 38393 fails to induce any stereotypic behaviors. When administered alone in intact rats, many D2 agonists, including quinpirole and RU 24213 induce only low level stereotypies, involving rearing, sniffing, head movements and locomotion. Pergolide and -(-NPA), considered D2 agonists, also induce more intense oral stereotypies after high doses, but were the only D2 agonists among a series tested which stimulate AC at these high doses (Arnt et al, 1988; Pugh et al, 1985). However, low doses of SKF 38393 and any of these D2 agonists administered in combination reliably produce intense stereotypies similar to those observed with apomorphine or AMPH, in a synergistic rather than simply additive manner, and these effects of combined

administration can be completely blocked by either a D1 or D2 antagonist (Arnt & Hyttel, 1988; Arnt et al, 1988; Mashurano & Waddington, 1986; White et al, 1988; Braun & Chase, 1986). The D1 agonists SKF 38393 and three of its analogues have been shown to produce essentially the same results when coadministered with quinpirole (Arnt et al, 1988; Arnt & Hyttel, 1988). While SKF 38393 is ineffective and D2 agonists produce only weak rotation in normosensitive rats with hemitransection or quinolinic acid-induced striatal lesions, coadministration of SKF 38393 with a D2 agonist induces intense rotation which could be antagonized by either a D1 or D2 antagonist (Arnt & Hyttel, 1988; Barone et al, 1986). These studies have generally been interpreted as indicating that concurrent stimulation of D1 and D2 receptors is required in normosensitive rats to produce the full range of behaviors elicited by non-selective DA agonists such as apomorphine or AMPH, and more specifically, that D1 receptors may enable the expression of post-synaptic D2 agonist-induced behaviors.

These conclusions are supported in studies employing rats with acute DA depletion induced by pretreatment with the DA synthesis inhibitor alpha-methyl-p-tyrosine (AMPT). The D2 agonist quinpirole fails to induce stereotypy in these animals, while coadministration of a low dose of SKF 38393 reinstates typical D2 agonist induced stereotypies, and at slightly higher doses produces the intense stereotypies normally seen with this combination (Braun & Chase, 1986; Longoni et al, 1987; White et al, 1988). Apomorphine-induced stereotypies were unaffected by AMPT pretreatment. AMPT pretreatment has also been shown to block quinpirole induced rotation in rats with quinolinic acid-induced striatal lesions, while SKF 38393 reinstated intense circling (Barone et al, 1986). These authors conclude that endogenous DA may provide a certain level of tonic D1 stimulation in non-depleted

rats which is required for D2 agonists to induce D2 receptor mediated behaviors. Braun & Chase (1986) report that SKF 38393 alone was inactive in these DA-depleted animals, while White et al (1988) in contrast found that SKF 38393 administered alone continued to induce grooming in rats with DA levels depleted 99.5% by combined reserpine/AMPT pretreatment, suggesting that this D1 mediated behavior may not require D2 receptor stimulation.

Braun et al (1986) examined the behavioral effects of combined administration of a range of doses of both SKF 38393 and quinpirole in intact and AMPT-pretreated rats. Once an adequate level of D1 stimulation was reached, D2 stimulation was found to induce behaviors such as locomotion and exploration which are part of the animal's normal repertoire, accompanied by an increased responsiveness to environmental stimuli. As doses of SKF 38393 were increased, at any given dose of quinpirole, these behaviors became fragmented and repetitive, with the type of stereotyped behavior expressed determined in part by the level of D2 receptor stimulation, while the animal showed a reduced responsiveness to environmental stimuli. Thus increasing levels of D1 stimulation appeared to be associated with a qualitative shift from a state of hyperaroused but organized behavior to disorganized behavior. The authors point out that behavioral disorganization is associated with some kinds of schizophrenia, thus D1 receptors may have an important role in this disorder. Arnt et al (1988) employed a range of mixed and selective agonists with varying levels of receptor affinity and intrinsic activity, administered alone and in combination to intact and DA-depleted rats. It was similarly concluded that D1 receptor tone is necessary to enable DA agonist induction of hyperactivity and stereotypies, with the type of behavioral activation expressed dependent on the ratio of D1 to D2 receptor affinities and on the intrinsic

activity at the D2 receptor.

Interactive D1/D2 receptor effects which parallel the behavioral effects described above have been reported in electrophysiological studies. SCH 23390 significantly attenuated the excitatory effects of AMPH, apomorphine and quinpirole on cell activity in globus pallidus, a major basal ganglia output nucleus (Carlson et al, 1986). While the D2 agonists quinpirole and RU 24926 alone produce relatively small increases in tonic pallidal activity, and SKF 38393 produces an even smaller and more variable increase, combined administration resulted in a significantly potentiated increase in pallidal firing rates comparable to that produced by apomorphine (Carlson et al, 1987). AMPT pretreatment was shown to significantly attenuate the excitation normally produced by quinpirole while subsequent injection of SKF 38393 led to the marked increase in pallidal activity normally seen with combined administration of D1 and D2 agonists (Carlson et al, 1988). Apomorphine-induced excitation was unaffected by AMPT pretreatment. A similar synergistic effect on the inhibition of nucleus accumbens neurons has been demonstrated with iontophoretic application of SKF 38393 and quinpirole (White, 1987). The inhibitory effect of quinpirole was attenuated by AMPT pretreatment but reinstated by concurrent administration of SKF 38393.

It may be noted that the interactive effects of D1 and D2 receptor stimulation described above do not occur in all situations. The two receptor types have been found to have antagonistic actions on certain behaviors, particularly on abnormal mouth and jaw movements induced by D1 receptor stimulation (Rosengarten et al, 1983; Johansson et al, 1987). While selective agonists administered to supersensitive rats appear to induce behaviors normally associated with mixed D1/D2 agents, some interactive effects between D1 and D2 receptors remain nonetheless. In 6-OHDA lesioned rats a

synergistic effect of low doses of SKF 38393 and various D2 agonists has been demonstrated on rotation (Koller & Herbster, 1988; Robertson & Robertson, 1986; Sonsalla et al, 1988), which is paralleled by a synergistic inhibition of substantia nigra pars reticulata neuronal activity (Weick & Walters, 1987). AMPT pretreatment significantly attenuated the rotation induced in these animals by D2 agonists but not by SKF 38393 (Gershanik et al, 1983). In chronically reserpine treated mice, SCH 23390 blocked the locomotor activity induced by either D1 or D2 agonists, but AMPT or a D2 antagonist blocked only the effect of D2 agonists (Rubinstein et al, 1988). Thus D1 stimulation may be important in the production of motor behaviors even in supersensitive animals.

Studies employing acute administration of dopaminergic agents thus provide considerable evidence in support of the hypothesis that a synergistic interaction occurs between D1 and D2 receptors in the mediation of many dopaminergic behaviors, and in particular, that D1 receptors have an enabling role in the production of many D2 receptor mediated behaviors. The mechanism underlying these functional interactions is not currently understood, and the extent to which D2 receptors enable any D1 behavioral effects is unclear (Clark & White, 1987). Numerous investigators have advised caution in the interpretation of these results, given that the D1 agents employed to date all belong to a single class of compounds (Clark and White, 1987; Waddington, 1986). It is also not known to what extent the lack of strong behavioral activation observed with SKF 38393 may be due to the fact that this compound is only a partial agonist, with maximal stimulation of AC at 60-70% of that produced by DA (Arnt et al, 1988; Setler et al, 1978). While a full D1 agonist is not currently available, efficacy in stimulation of AC has been found to be uncorrelated with behavioral potency among

SKF 38393 and three analogues (Arnt et al, 1988).

In view of the multiple indications that D1 receptors have an important role in the mediation of DA-related behaviors and that D1 antagonists have numerous behavioral actions in common with classical neuroleptics, the antipsychotic potential of D1 antagonists has become a focus of interest (Clark & White, 1987; Seeman, 1987; Waddington, 1988). Studies involving chronic administration of selective DA agonists or antagonists, reviewed below, may be especially relevant in regards to this question.

Chronic Studies. As noted previously, daily injections of SCH 23390 (0.5 mg/kg) for 21 days produced a selective increase in D1 receptor numbers (Hess et al, 1988). However this pretreatment enhanced the subsequent behavioral response not only to SKF 38393 but also to the D2 agonist quinpirole. Further, while chronic spiperone treatment is associated with the development of tolerance to catalepsy, rats treated chronically with SCH 23390 fail to show decreases in catalepsy but do show a reduced cataleptic response to a subsequent injection of spiperone (Hess et al, 1988). Hess and colleagues have suggested that the results of these two studies may reflect an increased tonic dopaminergic activation resulting from up-regulated D1 receptors, consistent with the notion that D1 receptors may enable D2 receptor mediated behaviors.

Twice daily injections for 21 days of a lower dose of SCH 23390 (.05 mg/kg) than in the above studies produced no change in the behavioral response to subsequent SKF 38393 or quinpirole when administered alone, but did potentiate the stereotypy resulting from administration of a combination of low doses of these agents, or of apomorphine (Dall'Olio et al, 1988; Gandolfi et al, 1988). In rats with quinolinic acid-induced striatal lesions, pretreatment with three daily injections of .05 mg/kg of

SCH 23390 for 15 days potentiated the grooming response to subsequent SKF 38393, but quinpirole-induced rotation was decreased. Thus it appears that a cooperative interaction between D1 and D2 receptors in the production of some DA-mediated effects, including stereotypy and catalepsy, can be demonstrated with chronic D1 antagonist treatment. The magnitude of these effects may be partially dependent on the treatment regimen employed, while this cooperative form of interaction may not apply to all DA-mediated behaviors.

Chronic D1 agonist treatment with SKF 38393 twice daily for 18 days produced enhanced behavioral responses to subsequent challenge with SKF 38393 or apomorphine, while the only alteration produced by chronic quinpirole treatment was a subsensitive response to subsequent apomorphine (Braun & Chase, 1988). However, combined pretreatment with the D1 and D2 agonists led to an increased response to quinpirole as well as to apomorphine, with the enhanced apomorphine-induced stereotypy differing in nature from the potentiated stereotypy seen with chronic SKF 38393 treatment alone. These authors thus concluded that a functional interaction may occur between D1 and D2 receptor subtypes with chronic agonist treatment, and speculated that D1 stimulation may underlie the development of behavioral sensitization observed with chronic administration of nonselective DA agonists such as AMPH or apomorphine. Employing only once daily injection of SKF 38393, the D2 agonist PHNO, or both combined for 21 days, Koller & Herbster (1988) found no changes in the response to subsequent apomorphine, with a lower challenge dose of apomorphine being used than was the case in the previously-mentioned report.

Repeated administration of l-dopa for two weeks resulted in enhanced rotation in unilaterally 6-OHDA lesioned rats, and was associated with a smaller increase in D2

receptors than is normally produced by 6-OHDA-induced denervation, but with a larger than usual increase in DA-sensitive AC activity (Parenti et al, 1986). This similarly suggested that changes in D1 receptors may be responsible for the behavioral sensitization seen after chronic DA agonist treatment. In contrast, Levy et al (1988) found that daily injections of AMPH for up to two weeks resulted in an enhanced response to quinpirole but not to SKF 38393, while the only change after daily injections of relatively low doses of either SKF 38393 or quinpirole was an increased responsiveness to quinpirole in rats pretreated with this agent, suggesting that D2 receptors may be important in behavioral sensitization. Continuously administered AMPH via silicone pellets had no effect on subsequent challenge with SKF 38393 or quinpirole.

Martin-Iverson et al (1988a) administered the D2 agonist PHNO either by daily injection or continuously via osmotic pumps for approximately two weeks. Sensitization to the locomotor activation produced by this agent was reported with repeated injections, as well as during the dark portions of 12-hour light-dark cycles after the third night with continuous infusion, while tolerance developed within two to three days during light periods with continuous administration. SCH 23390 continuously infused with PHNO antagonized the behavioral stimulation produced by this agonist only for the first six days and first four to five nights, after which motor activity increased to the same level or above that seen with PHNO administered alone (Martin-Iverson et al, 1988b). It was hypothesized that autoreceptor stimulation by this D2 agonist may lead to a progressive inhibition of DA release, with the resulting decrease in D1 receptor activation by endogenous DA producing supersensitivity of D1 receptors. Daytime tolerance may therefore result from low levels of D1 receptor

stimulation, while nighttime sensitization may reflect stimulation of supersensitive D1 receptors by the markedly increased basal levels of DA found in rats at night relative to daytime. This hypothesis was supported by findings that the daytime tolerance associated with continuous PHNO administration could be reversed by an acute injection of SKF 38393 or by exposure to environmental stress, the latter possibly acting through stress-induced DA release, while acute administration of SCH 23390 attenuated this reversal of tolerance produced by stress. Thus the reversal of tolerance appeared to be mediated by D1 receptors. It was concluded that the motor response to a chronic D2 agonist may require the concurrent stimulation of normosensitive D1 receptors, and that the observed sensitization and tolerance may both reflect indirect effects at D1 receptors, which could potentially apply in the case of nonselective DA agonists, including AMPH.

The relatively few behavioral studies reported to date which employ chronic administration of selective DA agonists and antagonists suggest that the effects of these treatments may be rather complex. This complexity, in addition to differences in dose and schedule of administration of a variety of compounds employed, and in methods of behavioral assessment, may contribute to the inconsistencies which appear in this literature. These reports suggest nonetheless that D1/D2 receptor interactions are important in chronic as well as acute models, and that D1 receptors likely participate in the behavioral activation produced by chronic DA receptor stimulation.

It appears that SCH 23390 is able to antagonize the locomotor activity induced by continuous administration of a selective D2 agonist, although perhaps only for a certain period of time. Interestingly, chronic SCH 23390 has been reported to produce a selective decrease in the spontaneous activity of DA neurons in the ventral tegmental

area (Goldstein & Litwin, 1988) or a decrease in both the ventral tegmental area and substantia nigra pars compacta (Skarsfeldt, 1988), in common with atypical and typical neuroleptics, respectively. Enhanced DA-sensitive AC has been found in the brain tissue of schizophrenic subjects (Memo et al, 1983), and there is one report of decreased D1 receptor numbers in schizophrenic patients (Hess et al, 1987). Further, there has been speculation that the antipsychotic actions of atypical neuroleptics may be mediated by D1 receptors, particularly those coupled to AC (Andersen & Braestrup, 1986; Andersen et al, 1986; Altar et al, 1988). It therefore is possible that D1 receptors are in fact implicated in schizophrenia, while the therapeutic potential of D1 antagonists remains an open question. It is hoped that greater knowledge of the mechanisms of action of dopaminergic drugs will eventually lead to more effective treatment of schizophrenia and other disorders which are believed to be DA-related.

Selectivity of SCH 23390.

Given the ability of SCH 23390 to potently block numerous behaviors which had previously been associated with D2 receptors, the selectivity of this agent has frequently been questioned. While Iorio et al (1983) found that SCH 23390 had numerous behavioral effects similar to those of classical neuroleptics, this compound showed a considerably different profile of antidopaminergic activity compared with classical neuroleptics. SCH 23390 inhibited striatal dopamine-stimulated AC at a very low concentration while displacing spiperone binding only at a much higher concentration. Further, unlike classical neuroleptics, SCH 23390 failed to elevate plasma prolactin levels or antagonize apomorphine-induced emesis, considered D2 receptor effects. It was therefore suggested that SCH 23390 is a selective D1 antagonist. Subsequent studies have similarly found SCH 23390 to be a very potent

inhibitor of AC activity (Hyttel, 1984; Plantje et al, 1984) and of [^{3}H]-piflutixol binding (Cross et al, 1983; Hyttel, 1983).

The results of saturation analyses suggest stereospecific, high affinity binding of [^{3}H]-SCH 23390 to a homogeneous population of receptors in rat and mouse striatal membranes, with a density close to previously reported values for D1 receptors labelled by thioxanthene ligands (Andersen et al, 1985; Billard et al, 1984; Hess et al, 1986b; Hyttel & Arnt, 1987). Antagonist competition curves for [^{3}H]-SCH 23390 binding similarly suggest that this ligand labels a single population of sites, and the affinities of various antagonists for [^{3}H]-SCH 23390 binding sites correlate highly with their potencies in inhibiting both [^{3}H]-flupentixol binding and blocking DA-stimulated AC activity, supporting the D1 selective action of SCH 23390.

Displacement studies have found SCH 23390 to have very weak or no action at D2, alpha-1 and beta adrenergic, muscarinic, H1 histamine or benzodiazepine receptors (Hyttel, 1983; Cross et al, 1983; Billard et al, 1984; Christensen et al, 1984), but some activity at alpha-2 adrenergic (Cross et al, 1983), 5-HT_{1C} (Hoyer, 1988; Nicklaus et al, 1988) and 5-HT_2 (Hyttel, 1983; Cross et al, 1983; McQuade et al, 1988) receptors. These studies suggest that the affinity of SCH 23390 for D1 sites is at least 500-700 times greater than for D2 sites. The activity of SCH 23390 at alpha-2 adrenergic, 5-HT_{1C} and 5-HT_2 receptors is at least 23 times weaker than the effect on D1 receptors. In binding studies using relatively low concentrations of [^{3}H]-SCH 23390, typical particularly of quantitative autoradiographic studies, significant labeling of serotonin sites has sometimes been observed, but only in brain regions containing a high density of these receptors, particularly 5-HT_{1C} receptors in

choroid plexus (Nicklaus et al, 1988) and 5-HT_2 receptors in frontal cortex (Dawson et al, 1986a, b; Hess et al, 1986b).

The possibility that the unexpected behavioral effects of SCH 23390 are caused by actions at D2 receptors or metabolism in vivo to a compound with activity at D2 receptors has been raised (Clark & White, 1987; Waddington, 1986). SCH 23390's S-isomer SCH 23388, which has a much weaker affinity for D1 receptors but is nearly equipotent at D2 receptors, is approximately 3000 times weaker than SCH 23390 in inhibiting conditioned avoidance responding, suggesting that inhibition of this response by SCH 23390 is not mediated by D2 receptor antagonism (Iorio et al, 1986). Intracerebral administration of SCH 23390 has been found to potently inhibit AMPH-induced locomotion (Mailman et al, 1984) and apomorphine-induced stereotypy (Arnt, 1985a), suggesting that these antagonist effects seen after peripheral administration are not produced by an active metabolite. Further, in vivo binding studies in the mouse employing [^{3}H]-SCH 23390 produce results very similar to those of in vitro binding studies (Andersen & Gronvald, 1986; Andersen, 1988). The selective D1 receptor changes and selective protection from EEDQ inactivation resulting from in vivo administration of SCH 23390, in addition to the inability of SCH 23390 to induce hyperprolactinemia or to block emesis, discussed above, provide further support for the D1 selectivity of this agent in vivo.

Pretreatment with a relatively large dose of SCH 23390 (3 mg/kg) failed to protect alpha-2 sites from irreversible blockade by EEDQ but partially protected 5-HT_1 and 5-HT_2 sites (Meller et al, 1985), while .5 mg/kg of SCH 23390 did not protect 5-HT_2 receptors from EEDQ modification (Hess et al, 1986a). Thus SCH

23390 does not appear to interact with alpha-2 or 5-HT_2 receptors in vivo at doses above those which are behaviorally active. The 5-HT_2 antagonist ketanserin did not reverse DA-agonist induced effects on single-unit activity in substantia nigra pars reticulata or in globus pallidus (Carlson et al, 1986), while peripheral or intrastriatal administration of ketanserin has failed to attenuate DA-agonist induced behavioral stimulation (Arnt, 1985a, b), suggesting that the actions of SCH 23390 in these models is not associated with its serotonergic activity. Pretreatment with SCH 23390 at doses which block DA-agonist behavioral effects did not antagonize the classical serotonergic syndrome induced by the serotonin agonist 5MeODMT, suggesting an absence of significant blockade of serotonin receptors at these doses (Pugh et al, 1985).

The available evidence thus suggests that SCH 23390 has considerable selectivity for D1 relative to D2 or other non-dopaminergic receptors, and its behavioral effects appear to be associated with blockade of D1 receptors rather than activity at other receptor sites tested. It is of course possible that SCH 23390 interacts with receptor systems which have not yet been tested, and may exert some of its actions through mechanisms other than D1 receptor antagonism.

Research Objectives

In summary, diverse lines of evidence suggest that D1 receptors are importantly involved in many DA-mediated behaviors and potentially in the development of psychotic states. Relatively little work has been performed employing chronic administration of dopaminergic drugs, which may provide a more valid analog of AMPH psychosis, and ultimately of schizophrenia and its treatment, than do acute models. The purpose of this research was therefore primarily to assess the degree to which SCH 23390 is able to

antagonize the behavioral, and possibly the metabolic, effects of continuous AMPH administered via Alzet osmotic pumps, while also seeking to elucidate the nature of these effects.

2-DG Experiments. Palacios & Wiederhold (1985) reported that both SCH 23390 and the selective D1 agonist SKF 38393, unlike selective D2 receptor agents, failed to significantly alter regional 2-DG uptake. However, it appears that the effects of chronic SCH 23390 on 2-DG uptake and the ability of SCH 23390 to reverse the modifications in glucose metabolism produced by AMPH or other DA agonists have not yet been examined. As an initial step towards this end, the first component of this research involved a comparison of the 2-DG uptake in DA-innervated brain structures of interest among rats which had received 5- to 6-day infusions of either saline or d-AMPH sulfate. Two doses of AMPH, 12 and 16 mg/kg/day, were included, in part to facilitate comparison with previous research.

The 2-DG technique used here is a modification of the quantitative autoradiographic 2-DG technique developed by Sokoloff et al (1977), involving measurement of relative tissue radioactivity rather than direct measurement of rates of regional glucose utilization. 2-DG uptake provides an estimate of glucose uptake and metabolism, which in turn has been shown to be highly correlated with functional neuronal activity. This approach has been employed in our laboratory for some time primarily to generate interhemispheric comparisons within animals, rather than to measure differences in regional 2-DG uptake across animals. Thus the primary objective of this experiment was to evaluate the sensitivity of this technique in measuring alterations in regional metabolic activity, particularly an increase in nucleus accumbens, which previous research suggests are produced by continuous AMPH

infusion (Eison et al, 1981; Orzi et al, 1983). A secondary objective was to examine possible dose effects occurring with continuously administered AMPH.

This technique was found to lack sensitivity for the relatively small effects on glucose metabolism which may be produced by continuous AMPH in nucleus accumbens, which was a focus of interest in this study. Therefore, a 2-DG study of concurrent AMPH and SCH 23390 administration was not pursued.

Behavioral Experiments. As noted previously, Martin-Iverson et al (1988b) found that SCH 23390 reversed the locomotor activation produced by continuous infusion of a direct selective D2 agonist, PHNO, although only over the first several days of treatment. The current study represents a preliminary evaluation of the impact of D1 receptor blockade by SCH 23390 on the behavioral stimulation produced by infusion of AMPH, an indirect mixed D1/D2 agonist. This was accomplished through behavioral ratings over a 1-week period of rats which received infusions of either saline, AMPH (16 mg/kg/day), SCH 23390 (0.5 mg/kg/day), or a combination of AMPH and SCH 23390. Pilot observations suggested that SCH 23390 administered alone has a tendency to produce some generalized depression of normal activity, while SCH 23390 seems to suppress AMPH-induced behavioral activation to a considerable but probably incomplete degree. Animals administered this combination also seemed hyperresponsive to handling from an early stage of treatment, appearing to become increasingly hyperactive over time.

Additionally, a group of animals receiving a dose of 12 mg/kg/day of AMPH was included in this study, in an attempt to clarify the behavioral consequences of continuous AMPH treatment, and in order to provide behavioral indices for comparison with the metabolic effects at each of the two doses tested in the 2-DG experiments. Pilot

experimentation and a review of the literature suggested that higher doses of continuous AMPH appear to be associated with more intense stereotypy, and further that a more pronounced biphasic stereotypy response to continuous AMPH may occur at higher doses, with an early phase continuing for a longer duration and a second phase beginning at a somewhat later point in time.

CHAPTER 2

METHOD

2-DG Experiments

Subjects. The subjects were 12 male, Long-Evans, black-hooded rats, bred from parent stock obtained from Canadian Breeding Farms and Laboratories. The rats weighed 205-245 g at the time of pump implantation. They were individually housed with food and water freely available, and kept on a 12 h light-dark cycle.

Drug Treatment. The animals were randomly assigned to receive continuous subcutaneous infusions via Alzet osmotic pumps, model 2ML1 (Alza Corp., Palo Alto, CA) for 5 or 6 days of either (1) vehicle (sterile saline) (n=5), (2) d-AMPH sulfate, 12 mg/kg/day (n=3), or (3) d-AMPH sulfate, 16 mg/kg/day (n=4). Concentrations of AMPH solution were calculated according to the in vitro pumping rate determined by the manufacturer (8.94 microliters/h), after reducing this rate by 7.5% to allow for the 5-10% lower pumping rate which is expected under in vivo conditions. Sterile laboratory ware was used in the preparation of solutions, and all pumps were filled from syringes fitted with Millipore Millex-GV sterilizing filters (0.22 micrometer pore size). The loaded pumps were primed by leaving them overnight in a beaker of saline at room temperature prior to implantation. Daily weighing of all rats over the course of the infusions indicated substantial weight losses among animals in the AMPH groups but not those in the vehicle-only group, confirming delivery of the AMPH solution.

Surgical Procedures. A chronic jugular catheter was implanted under sodium pentobarbital anesthesia (65 mg/kg, i.p.) at the beginning of the experiment for later

2-DG delivery. One end of a length of heparin-filled tubing was inserted into the right external jugular vein, and the free portion of the catheter then plugged and guided under the skin to the back of the neck. The catheter was coiled within a small pocket formed beneath the skin and the end allowed to protrude through an overlying incision, where it was anchored with fine wire to two wound clips used to close the incision.

The following day, a second incision was made a short distance behind the catheter exit under ether anesthesia, and a pump was inserted into a pocket created under the skin of the back. A local anesthetic (Zylocaine) was applied to the wound, and the incision closed with wound clips.

The jugular catheters were flushed with heparin once or twice over the period of drug treatment to prevent plugging. This procedure was carried out under light ether anesthesia.

2-DG Injections and Preparation of Autoradiographs. The rats were left overnight in their home cages in the experimental room in order to habituate to this environment. The 2-deoxy-D-[1-^{14}C]glucose (specific activity 50-60 mCi/mmol, American Radiolabeled Chemicals, Inc.) was evaporated under a stream of nitrogen and reconstituted in saline. Rats were injected through the freed jugular catheter with a dose of 1.1 mCi/kg of 2-DG in a 0.5 ml volume, followed by a saline flush, and the catheter was subsequently trimmed and replugged.

After a 45-minute incubation period, a sodium pentobarbital injection was delivered via the catheter, and the rats were perfused with 40 ml of saline and 80 ml of modified Hand's fixative (Hand, 1981). The brains were removed, coated with Lipshaw embedding medium, frozen in methylbutane at approximately -60^{o}C, and mounted on pedestals with O.C.T. embedding compound. Coronal brain sections 30 micrometers in

thickness were cut in a cryostat at approximately -16°C, picked up on warm microscope slides and immediately dried on a hot plate. The sections, along with a set of Amersham [^{14}C]methacrylate standards, were exposed to DuPont Lo-Dose X-ray film for 3-6 weeks, which was then developed.

Autoradiographic Analysis. Film density in brain structures of interest was measured with a Spectra brightness spot meter (UB1/4), with readings digitized and analyzed by a Cromemco microcomputer. A circular reticule with a diameter of 260 micrometers, centered within a viewing field, delineated the region from which the readings were taken.

Two to six loci in each hemisphere were sampled in the nucleus accumbens, caudate, substantia nigra pars compacta, substantia nigra pars reticulata, subthalamic nucleus and globus pallidus, as indicated in Fig. 1. The ventral tegmental area was not included in this analysis, since it was not distinctly visible in the autoradiographs. Readings in nucleus accumbens and caudate were repeated over a series of 17-18 sections, while in all other structures readings were taken in 5-6 sections, spanning most of the rostro-caudal extent of these structures. The densitometric readings for each structure were averaged and converted to measures of tissue ^{14}C concentrations by comparison with readings through the standards of known radioactivity. In an attempt to correct for variations in brain glucose uptake across animals, the ^{14}C value for each structure was divided by the ^{14}C value obtained from mean densitometric readings from 5-6 sections through the corpus callosum, resulting in a ^{14}C ratio score for each area of interest. The corpus callosum was selected as a reference area since previous research has indicated that this structure is unaffected by continuous AMPH treatment. This entire procedure was repeated twice for each structure, with the resulting values

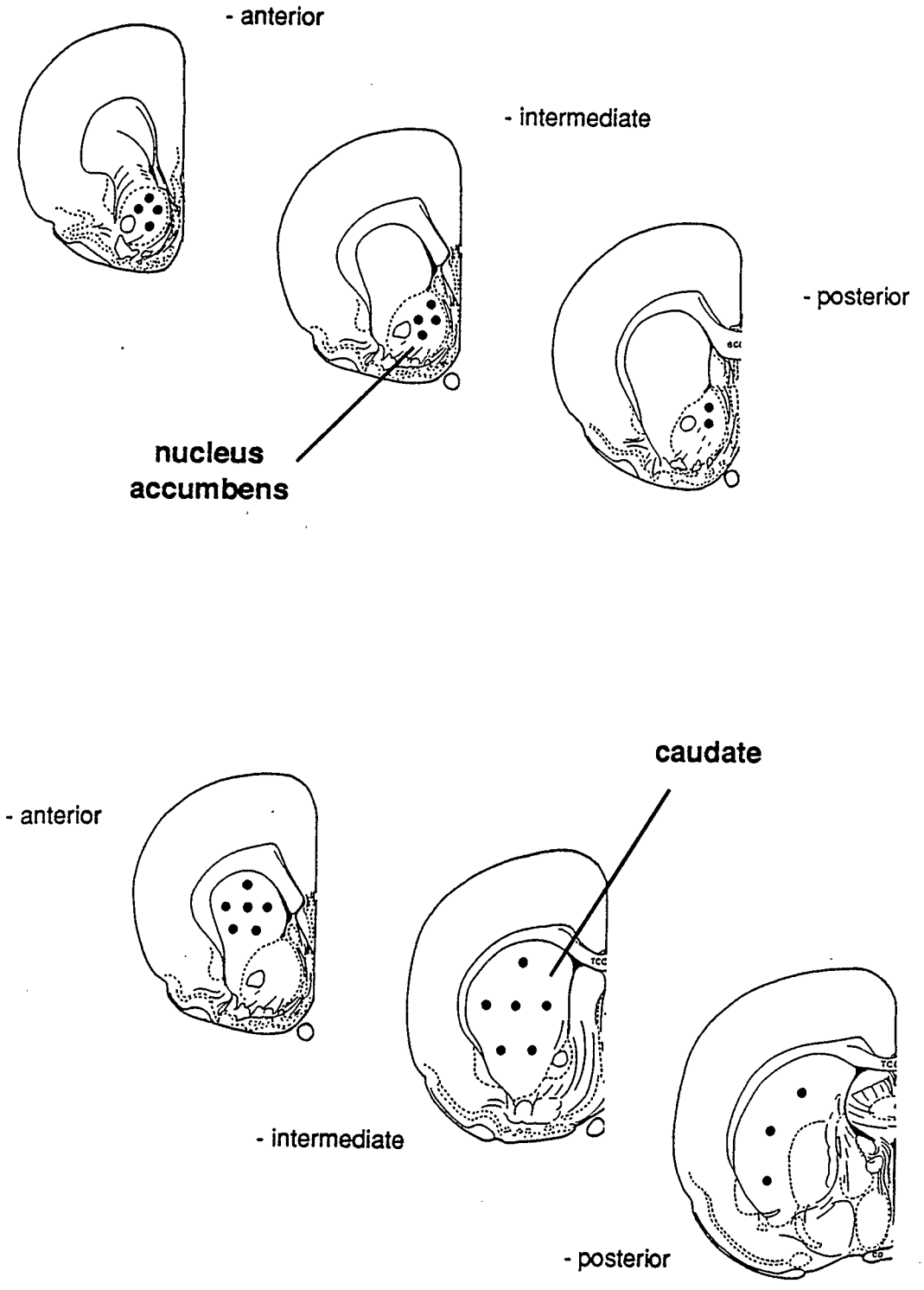


FIG. 1. Sample loci for densitometric readings in brain structures of interest. Sections are from the atlas of Konig and Klippel (1963).

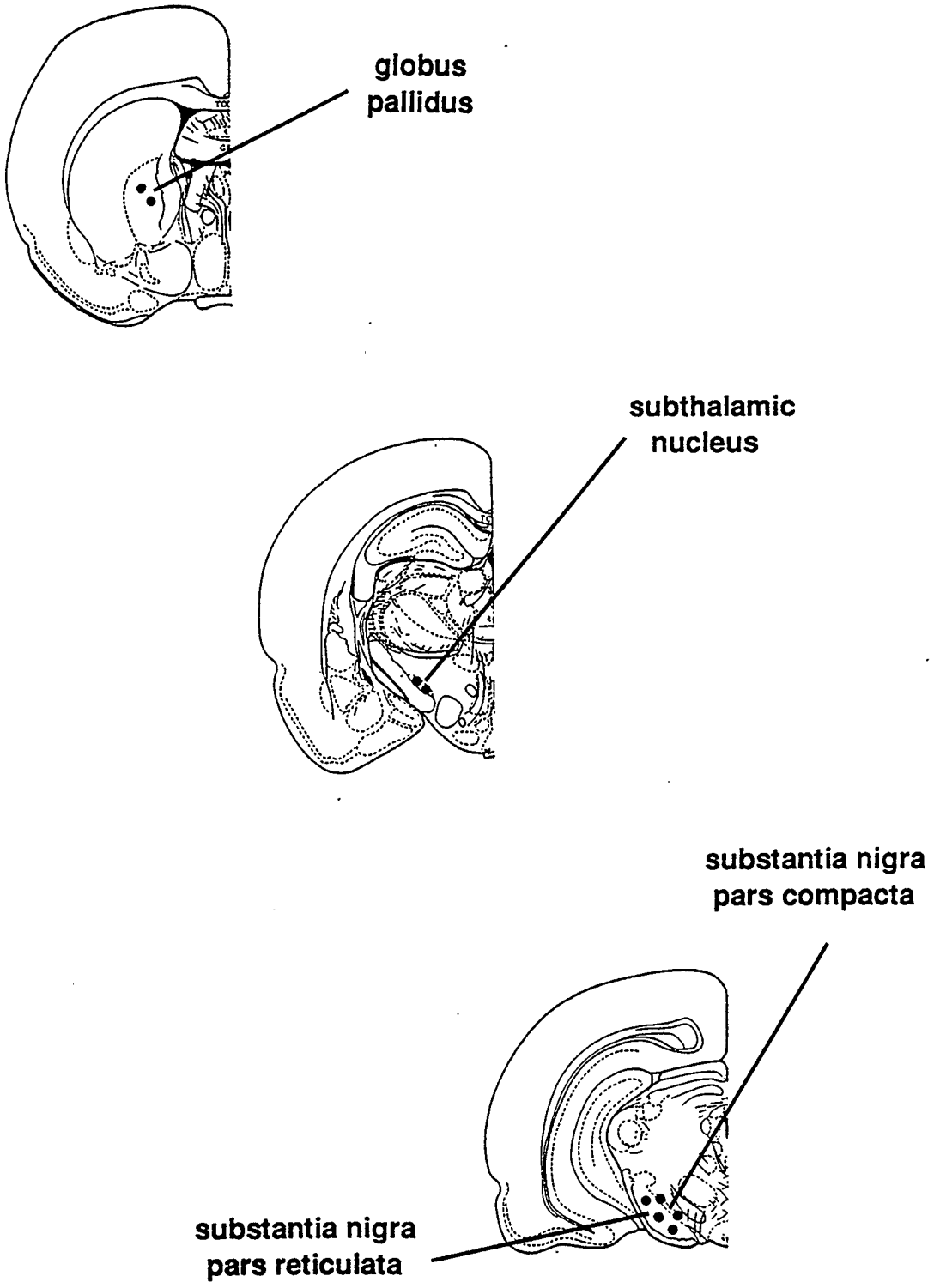


FIG. 1. . . . continued.

averaged to obtain final ^{14}C ratio scores. In addition, ^{14}C ratio scores were similarly determined for a control structures, the medial habenula, which is not known to be prominently associated with dopaminergic systems and has shown no significant alterations in response to continuous AMPH or to the acute administration of various DA agonists in previous work.

Statistical Analysis. Two comparisons were planned among treatment groups for each structure. Ratio scores for animals which had received either dose of AMPH were combined into one group and compared with control values using one-tailed independent t-tests, since differences if present were expected to be in the direction of increased scores for groups which were treated with AMPH relative to saline controls. A second comparison was carried out between the two AMPH-treated groups using two-tailed t-tests to test for differences in ^{14}C ratio scores between doses. Significance in all cases was determined using randomization test procedures (Edgington, 1980).

Behavioral Experiments

Subjects. The subjects were 25 male, Long-Evans, black-hooded rats, bred from parent stock obtained from Canadian Breeding Farms and Laboratories. The rats weighed 165-305 g at the time of pump implantation. They were individually housed in a quiet room in standard clear plastic cages (45x24x16 cm) with wire tops, and food and water was freely available. They were kept on a partially reversed 12 h light-dark cycle, with the light period from 15:00 to 03:00. A dim red light was left on to enable behavioral observation.

Drug Treatment. The animals were randomly assigned to five groups (n=5) to receive continuous infusions via Alzet osmotic pumps, model 2ML1, for 7 days of either: (1) vehicle (sterile saline), (2) d-AMPH sulfate, 12 mg/kg/day, (3) d-AMPH sulfate,

16 mg/kg/day, (4) SCH 23390, 0.5 mg/kg/day, or (5) d-AMPH sulfate, 16 mg/kg/day, + SCH 23390, 0.5 mg/kg/day. The pumps, with in vitro pumping rates of 10.12 or 11.60 microliters/h, were filled and implanted as in the previous experiments, with the exception that they were primed by placing them in a beaker of saline at 37°C for 4 hours. The pumps were removed and cut at the end of the experiment, revealing collapsed internal reservoirs in all cases, and thus verifying delivery of the contents.

Experimental Procedure and Behavioral Observations. The rats were allowed 10 days in the observation room to adjust to the reversed light-dark cycle, and were habituated to the brief presence of an observer three times per day for 3-4 days, prior to pump implantation. Pumps were implanted and fresh cages provided between 22:00 and 02:00 h, and behavioral observations were begun the following morning. The animals were subsequently not disturbed, except for the entrance of an observer to perform behavioral ratings three times daily, and for provision of fresh food and water once during the week of drug treatment.

Behavioral observations were performed with the rater unaware of the treatment condition of the animals, and 5-10 rats were observed during any given observation period. Two daily observation sessions occurred during the dark period at 07:00 and 13:00, and one during the light period at 20:00, times associated with a high probability that the rats would be awake based on activity monitoring during pilot experimentation. After a 10 min habituation period, each rat was observed and scored for the presence or absence of specific categories of behavior over a 10 s interval, while the occurrence of locomotion was scored over a 30 s interval, and observations were repeated for each animal every 10 min in a fixed sequence over one hour.

Behavioral categories, based on the response categories of Fray et al (1980), included: inactive (asleep or sitting/lying motionless, excluding brief pauses during other activities), locomotion (all four paws moving), rearing (front paws off the cage floor, except while grooming or feeding), repetitive head movements (repeated bobbing or weaving of the head), grooming (any kind of grooming for more than 3 s), head down (head near cage floor for more than 3 s, usually accompanied by sniffing, nibbling and/or sifting the cage litter, or vacuous mouth movements), and gnawing (gnawing of the cage top, wall or floor for more than 3 s). More than one category could be scored as present during a given observation interval. Overall activity levels were estimated by a total activity score representing intervals during which the category 'inactive' was not noted. The other behaviors, except for locomotion, were considered to be stereotyped when present without interruption over a 10 s interval, and only one type of stereotypy was scored during any given interval. A total stereotypy score was calculated representing intervals during which any type of stereotyped behavior was noted. Scores in each category for each animal were expressed as the total number of intervals daily during which that behavior was observed.

Statistical Analysis. The daily frequency scores were assessed for statistical significance by several planned comparisons among treatment groups for each day using one- or two-tailed independent t-tests (df = 8), with significance levels determined by randomization tests in all cases (Edgington, 1980).

CHAPTER 3

RESULTS

2-DG Experiments

The effects of continuous AMPH infusions for 5-6 days on ^{14}C ratio values in the seven brain structures examined are summarized in Table 1. No significant alterations in 2-DG uptake in the nucleus accumbens resulted from the administration of 12 or 16 mg/kg/day of AMPH, treated as a single group here for statistical purposes, compared with vehicle-infused controls, although a trend towards increased ^{14}C ratios among AMPH-treated animals appears in intermediate ($t(10) = 1.11$, $p = .15$, one-tailed) and posterior ($t(10) = 1.10$, $p = .13$, one-tailed) nucleus accumbens. Rather, the most pronounced effect of AMPH infusion on 2-DG uptake was a significant increase in the subthalamic nucleus ($t(10) = 3.10$, $p = .006$, one-tailed), which was also clearly evident on visual inspection of the autoradiographs. Significant enhancements in metabolic activity were also found in the substantia nigra pars compacta ($t(10) = 2.13$, $p = .033$, one-tailed) and substantia nigra pars reticulata ($t(10) = 2.13$, $p = .027$, one-tailed), while an increase approaching statistical significance was noted in globus pallidus ($t(10) = 1.68$, $p = .063$, one-tailed). AMPH treatment failed to produce significant effects on 2-DG uptake in caudate, although there was a trend towards an increase in this structure ($t(10) = 0.89$, $p = .16$, one-tailed) as well. While the medial habenula demonstrated no significant differences in 2-DG uptake between AMPH- and vehicle-infused groups ($t(10) = -1.47$, $p = .18$, two-tailed), the ^{14}C ratio scores tended to be lower among animals which received 16 mg/kg/day of AMPH compared with control values.

TABLE 1. Effects of continuous amphetamine administration (5-6 days) on 2-DG uptake in selected brain structures

Structure	Vehicle (n=5)	Amphetamine (mg/kg/day) 12 (n=3)	16 (n=4)
nucleus accumbens - anterior	2.87 (.44)	2.90 (.17)	2.92 (.08)
- intermed.	2.64 (.34)	2.80 (.17)	2.80 (.15)
- posterior	2.39 (.38)	2.63 (.21)	2.56 (.10)
caudate	2.73 (.57)	3.01 (.26)	2.93 (.16)
substantia nigra pars compacta	2.08 (.37)	2.43 (.26)*	2.50 (.29)*
- anterior	2.17 (.45)	2.49 (.20)*	2.71 (.19)*
substantia nigra pars reticulata	1.81 (.26)	2.13 (.33)*	2.09 (.17)*
subthalamic nucleus	2.41 (.40)	2.87 (.20)**	3.35 (.43)**
globus pallidus	1.79 (.21)	1.96 (.29)	2.00 (.08)
medial habenula	2.07 (.19)	2.02 (.32)	1.79 (.11)

Values are mean ^{14}C ratios, with S.D. indicated in parentheses.

* $p < .05$, one-tailed, statistically significant difference between amphetamine groups combined and vehicle (control).

** $p < .01$, one-tailed, statistically significant difference between amphetamine groups combined and vehicle (control).

Comparisons between the two AMPH-treated groups revealed no significant differences in 2-DG uptake in any of the structures assessed. However, the ratio scores and examination of the autoradiographs suggest a trend towards increased metabolic activity in anterior substantia nigra pars compacta ($t(5) = 1.44$, $p = .20$, two-tailed) and particularly in the subthalamic nucleus ($t(5) = 1.79$, $p = .11$, two-tailed) in the group which received the higher dose of AMPH.

Behavioral Experiments

Effects of AMPH. Behavioral responses among rats continuously administered vehicle only or AMPH (12 or 16 mg/kg/day) are shown in Fig. 2. Although there is insufficient data to permit a thorough analysis of this point, there was no evidence of a differential pattern of behavior during the light vs. dark periods, and thus scores shown represent daily frequencies for each category over the three observation sessions summed over the animals in each group. AMPH-induced stereotypy consisted primarily of continuous head-down behavior, rearing or grooming. Continuous episodes of repetitive head movements were rarely noted (on day 1 only), thus occurrences of repetitive head movements are presented rather than stereotyped instances. Gnawing, of the cage top or wall, was observed infrequently and always in conjunction with rearing. Therefore frequency of gnawing rather than of stereotyped gnawing is shown, and episodes of continuous gnawing were subsumed under stereotyped rearing.

Total activity levels among animals which received 16 mg/kg/day of AMPH demonstrate a marked initial elevation followed by a steady subsequent decline to reach a low on day 3, and thereafter show an increasing trend again. Increases in activity level are significant compared with vehicle-treated controls on days 1 ($t = 5.69$, $p = .004$, one-tailed) and 7 ($t = 2.40$, $p = .028$, one-tailed). While control animals show a trend

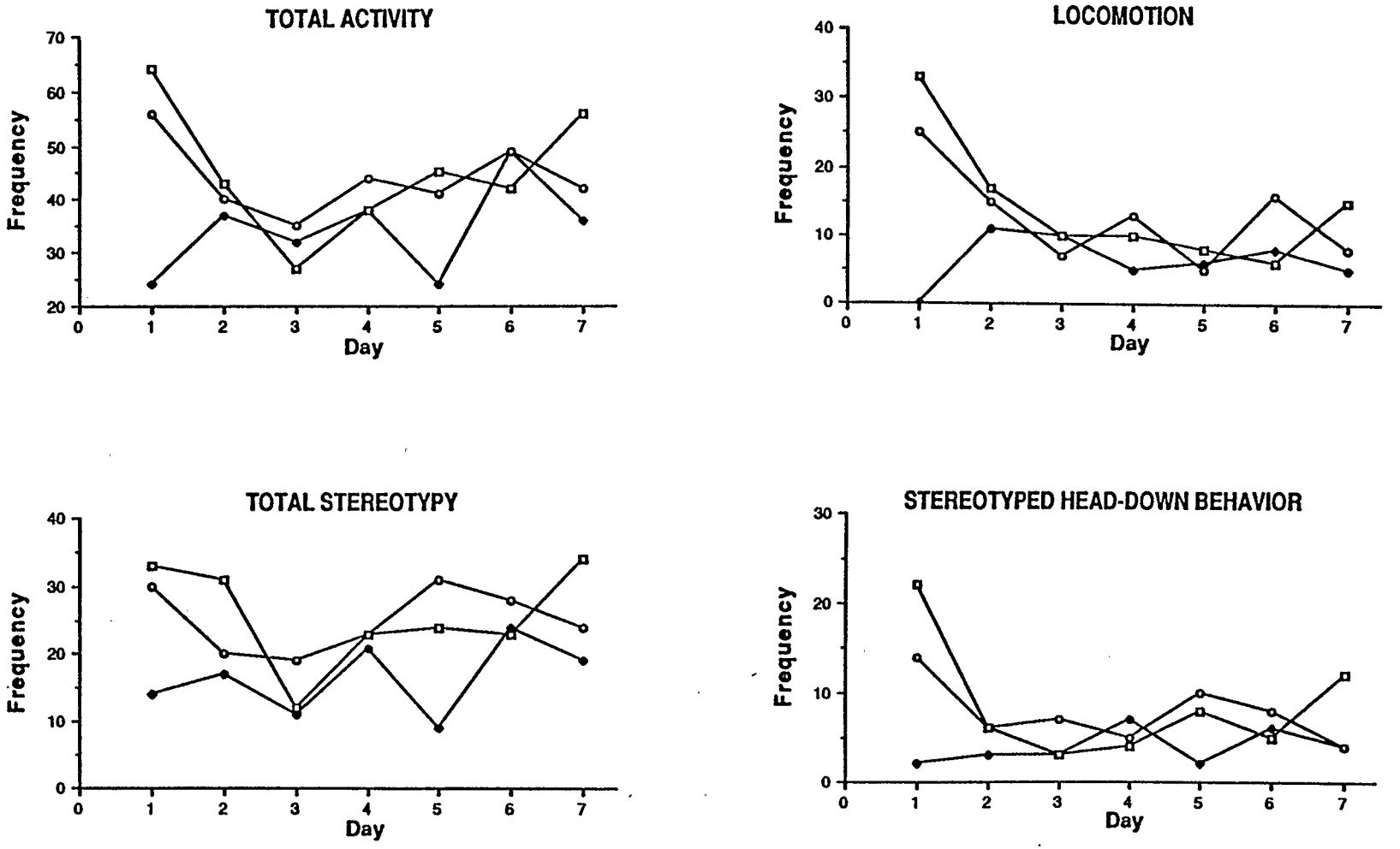
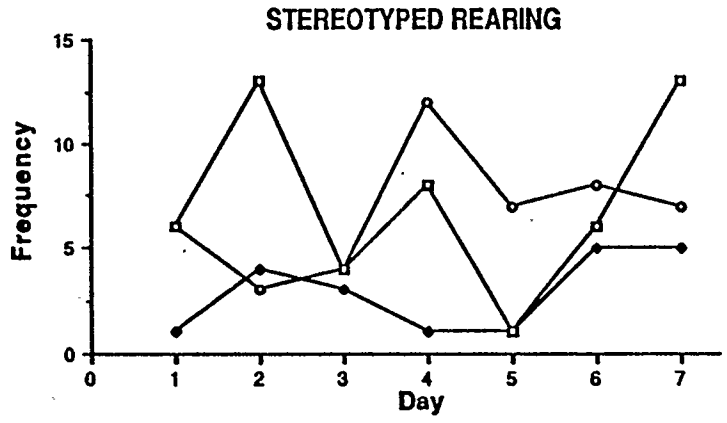
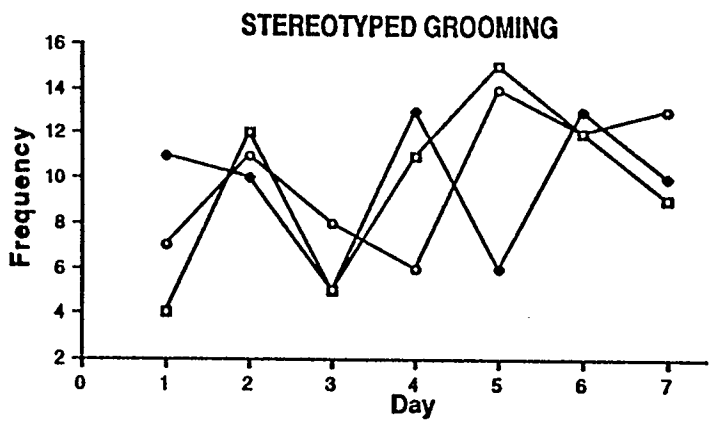
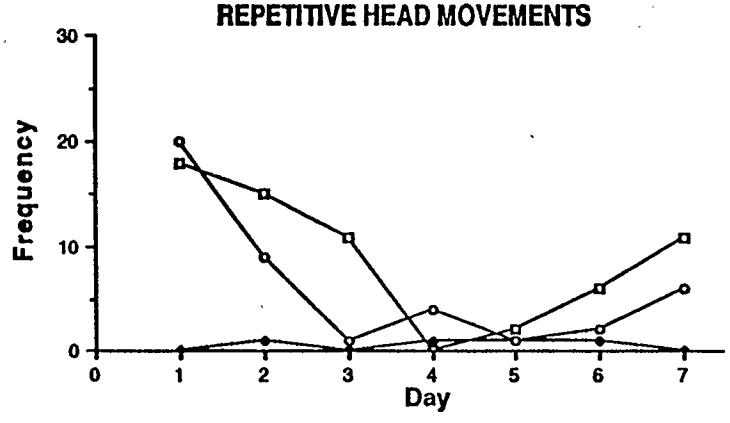
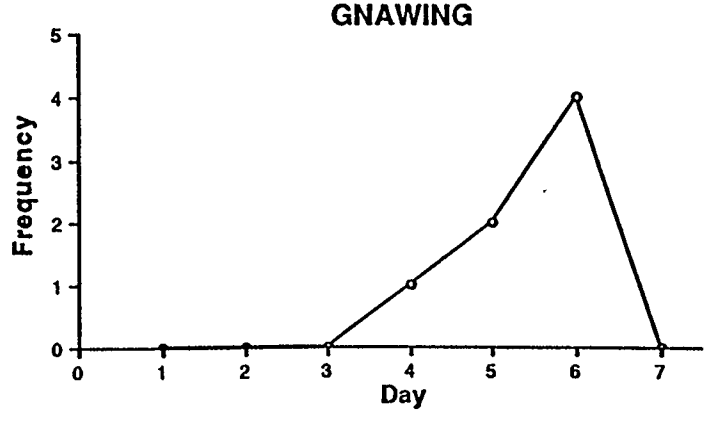


FIG. 2. Behavioral responses to continuous infusions of vehicle or amphetamine at 12 or 16 mg/kg/day. Each value represents the number of intervals daily in which that behavior was observed, summed over 5 animals per group (maximum score = 90).









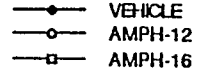


FIG. 2. . . . continued.

towards increased activity levels over the seven days, this trend is more variable across time and shows a lower rate of increase than is the case among AMPH-treated animals after day 3.

A significant locomotor activation in response to 16 mg/kg/day of AMPH was found only on day 1 (t = 4.84, p = .004, one-tailed). Stereotypy produced by this regimen of AMPH treatment, like total activity, tended to show a U-shaped function over time, with elevations generally on days 1, 2 and 7. Total stereotypy scores were significantly increased above control levels on days 1 (t = 3.21, p = .012, one-tailed) and 2 (t = 2.37, p = .012, one-tailed), subsequently declined rapidly to a low on day 3, but thereafter increased again to a level approaching statistical significance on day 7 (t = 1.83, p = .07, one-tailed). Stereotyped head-down behavior was significantly elevated on day 1 (t = 3.14, p = .012, one-tailed), declined rapidly by day 2, and was significantly increased again on day 7 (t = 2.53, p = .04, one-tailed). Stereotyped rearing similarly showed a trend towards increases on days 1 (t = 1.89, p = .083, one-tailed) and 7 (t = 1.97, p = .067, one-tailed), but this behavior generally demonstrated a more variable course over time. No significant changes in stereotyped grooming resulted, although at its highest level on day 5 there was a trend towards an increase over levels among control animals (t = 1.77, p = .083, one-tailed). The occurrence of repetitive head movements was significantly elevated on days 1 (t = 14.70, p = .004, one-tailed), 2 (t = 2.42, p = .044, one-tailed) and 7 (t = 2.75, p = .024, one-tailed), and showed a trend towards an increase on day 3 (t = 2.40, p = .083, one-tailed), dropping to a low only on day 4.

The administration of 12 mg/kg/day of AMPH, compared with the 16 mg/kg/day dose, tended to produce lower levels of total activity and of stereotyped behavior early

and late during the course of drug administration, while the reverse seemed to occur in the intermediate stage. The decline in stereotypies after the initial phase of activation tended to occur earlier and was not as severe as that seen among animals which received the higher dose. The second phase of stereotypy when present also appeared generally to occur earlier, with total stereotypy and stereotyped head-down behavior peaking on day 5, and stereotyped rearing peaking on day 4, and subsequently dropping off again. Repetitive head movements, initially at a similar level, fell off one day sooner and subsequently showed a lower and more variable rise over time. Gnawing was infrequently observed only among animals which received the lower dose of AMPH on days 4 to 6. Locomotor scores tended to be slightly lower among rats treated with 12 mg/kg/day of AMPH early during the infusions, with both groups showing a similar rate of decline. Trends occurred towards significantly lower frequencies of total stereotypy on day 2 (t = 1.62, p = .099, one-tailed) and of stereotyped head-down behavior on day 7 (t = 2.07, p = .063, one-tailed), while none of the other differences in behavioral indices were statistically significant (p > .16, one- and two-tailed). The limb flicks and wet dog shakes which have sometimes been associated with continuous AMPH treatment were never observed at either dose tested.

Effect of SCH 23390 Alone and in Combination with AMPH. The behavioral responses to continuous infusions of vehicle, SCH 23390, AMPH or a combination of the latter two are presented in Fig. 3, as in the previous section. Gnawing was not observed among these groups.

SCH 23390 (0.5 mg/kg/day) administered alone tended to depress most behavioral indices somewhat in comparison with vehicle-treated controls, with these changes occasionally reaching statistical significance. Thus total activity was

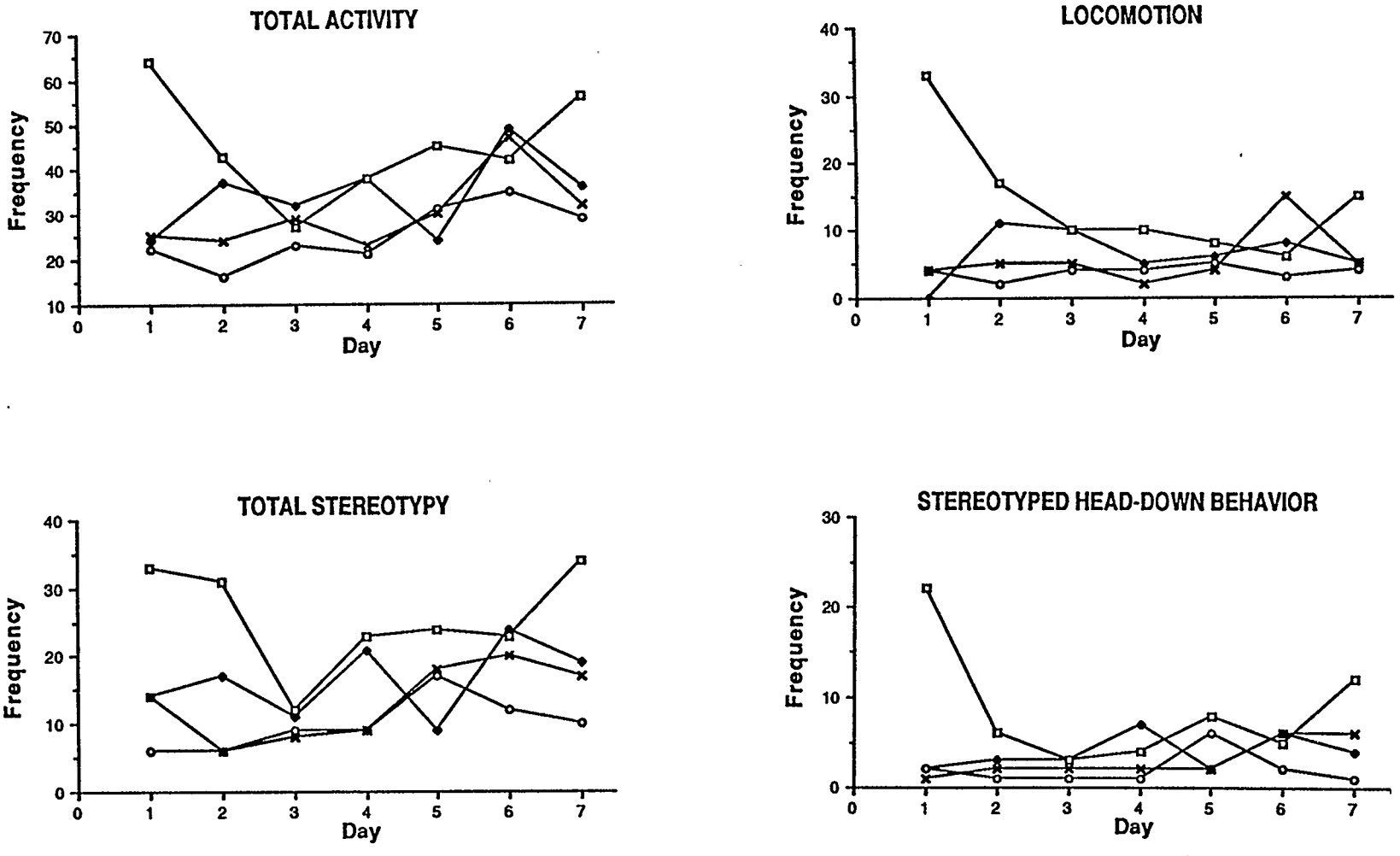
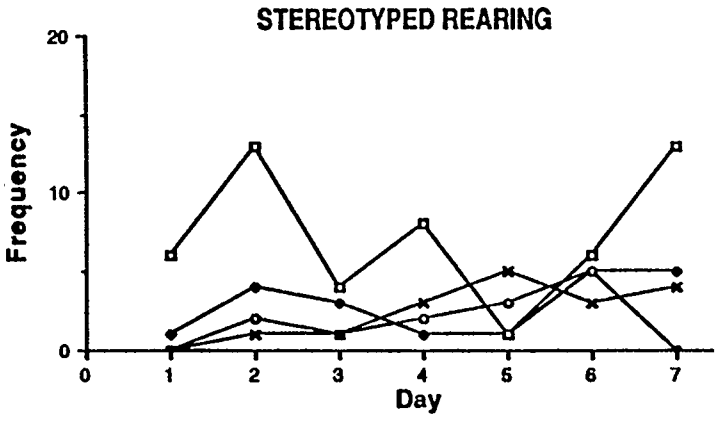
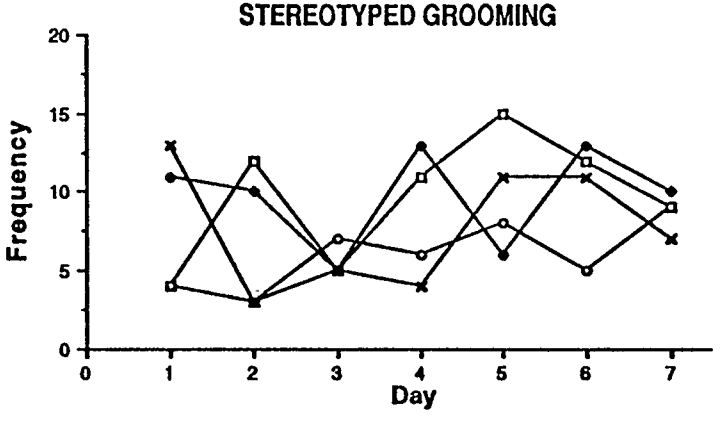
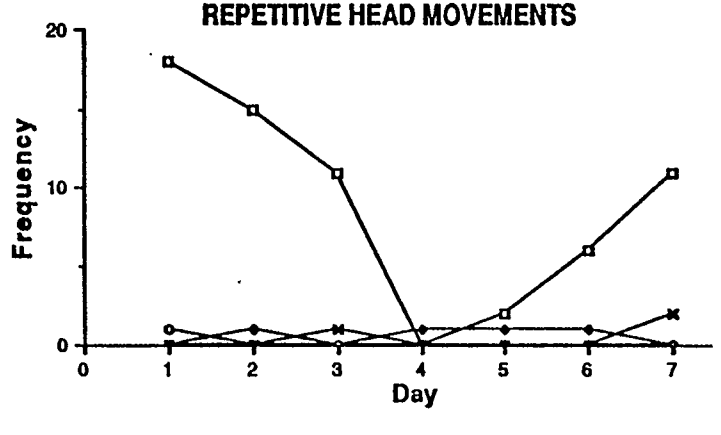


FIG. 3. Behavioral responses to continuous infusions of vehicle, SCH 23390 (0.5 mg/kg/day), amphetamine (16 mg/kg/day), or a combination of SCH 23390 and amphetamine. Each value represents the number of intervals daily in which that behavior was observed, summed over 5 animals per group (maximum score = 90).







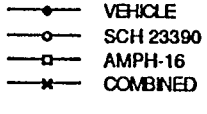


FIG. 3 . . . continued.

significantly lower among rats which received the blocker on days 2 (t = 2.13, p = .032, one-tailed), 4 (t = 2.07, p = .052, one-tailed) and 6 (t = 2.62, p = .028, one-tailed), while lower scores were found for locomotion on day 2 (t = 2.85, p = .02, one-tailed), and for total stereotypy on days 2 (t = 2.46, p = .028, one-tailed) and 6 (t = 3.10, p = .02, one-tailed). In contrast, a small increase in locomotion was found on day 1 (t = -4.00, p = .024, one-tailed).

SCH 23390 appeared to at least partially suppress the activation induced by AMPH. The combined infusion of SCH 23390 and AMPH (16 mg/kg/day) actually produced a trend towards a decrease in total stereotypy compared with vehicle-treated animals on days 2 (t = 2.20, p = .087, two-tailed) and 4 (t = 2.56, p = .06, two-tailed), while no other differences between these two groups proved to be significant ($p > .12$, two-tailed).

However, some behavioral activation appeared to occur during the period of combined drug administration, most apparent in the marked increase in locomotor scores on day 6, which are significantly above levels found in animals treated with blocker alone (t = 4.00, p = .004, one-tailed). Similarly, total activity shows a rise on day 6, with this increase over levels among blocker-treated rats approaching significance (t = 2.06, p = .06, one-tailed). Total stereotypy scores are increased on day 1 (t = 3.02, p = .024, one-tailed) and show a trend towards increases compared with blocker-treated animals on days 6 (t = 1.84, p = .083, one-tailed) and 7 (t = 1.30, p = .087, one-tailed). Stereotyped grooming was significantly increased among animals receiving combined treatment relative to blocker-treated rats on day 1 (t = 3.29, p = .016, one-tailed), while stereotyped rearing was significantly elevated on day 7 (t = 4.00, p = .024, one-tailed). Consistent with indications of behavioral

stimulation late over the course of the infusions, subjective observations at the end of the experiment suggested that rats which received combined treatment were markedly hyperresponsive to handling.

CHAPTER 4

DISCUSSION AND CONCLUSIONS

Metabolic Effects of Continuous Amphetamine

This study failed to replicate the increases in glucose utilization found previously in nucleus accumbens with continuous AMPH infusion (Eison et al, 1981; Orzi et al, 1983), although a trend consistent with these earlier results appeared. Instead, enhancements were observed in several dopaminergic extrapyramidal structures, including subthalamic nucleus, globus pallidus, substantia nigra pars compacta and substantia nigra pars reticulata, whereas increased glucose utilization was previously reported only in the latter structure. The reasons for these discrepancies are not clear. The metabolic activation noted previously in nucleus accumbens was not of a large magnitude, and it is possible that the semi-quantitative 2-DG technique used in this study simply lacked sufficient sensitivity to detect such an effect, if present. However, even if this were the case, this would obviously not account for the more widespread activation found within the nigrostriatal system. The absence of elevated ^{14}C ratio scores in the medial habenula, employed as a control structure, suggests that the increases in nigrostriatal nuclei do not merely reflect reduced glucose metabolism in the corpus callosum, which provided the ^{14}C values for the denominator of the ratio scores.

Differences in experimental procedures may have contributed to the discrepancies noted. It is possible that the declining rate of AMPH delivery associated with the pellet infusions employed by Eison et al (1981) results in a pattern of metabolic activation which is different from that produced by pump infusions. Orzi et al

(1983) employed pumps to deliver AMPH, but these infusions were continued over a slightly longer period, 7 days, compared with the 5- to 6-day infusions in the present study. The effect of this additional treatment time is unclear, however it would seem somewhat surprising that this would have as large an impact on the metabolic outcome as is observed here.

The technique employed by Orzi et al (1983) involved partial restraint of the animals during the 2-DG experiments, preventing locomotion. There is some evidence suggesting a complex interactive effect of locomotion and drug dose on single unit activity in the striatum with acute AMPH administration (Gardiner et al, 1988), and it is thus conceivable that AMPH administered either acutely or continuously may differentially affect glucose utilization in the striatum, and therefore in striatal output nuclei, in freely moving vs. restrained rats. However, acutely administered AMPH has produced extensive metabolic increases in extrapyramidal structures among partially restrained rats (Porrino et al, 1984; Orzi et al, 1983), indicating that it is possible to obtain this pattern of stimulation in response to AMPH in restrained animals, at least with acute treatment.

Apparently on the basis of brief, informal observation periods, Orzi et al (1983) noted mild, continuous and essentially unchanged hyperactivity, but no stereotypy, in their AMPH-treated animals over the course of the drug infusions and during the 2-DG experiments. These observations are somewhat puzzling, since the dose of AMPH given (12 - 15 mg/kg/day) typically produces stereotypic behaviors. This stereotypy, particularly after the first several days, may be more subtle than that produced by acute AMPH administration, and it is possible that the observational procedure described by Orzi et al (1983) may have failed to detect any stereotypy

which was actually present. Alternatively, there may be differences among strains of rats in responsiveness to continuous AMPH, or perhaps a lower effective dose of AMPH was actually administered, resulting in a behavioral pattern which actually did consist primarily of hyperactivity.

At any rate, in the present study both informal observation of the animals during the 2-DG experiments and the behavioral ratings performed among separate groups of rats suggested the presence of stereotypy, in addition to some hyperactivity, in animals receiving 12 or 16 mg/kg/day of AMPH. The relatively selective metabolic activation in nucleus accumbens found by Orzi et al (1983) among rats which were described as hyperactive, and the more extensive activation in extrapyramidal motor structures reported here, is consistent with the importance generally ascribed to the mesolimbic and nigrostriatal DA systems in the mediation of hyperactivity and stereotypy, respectively. While the behavioral ratings performed in the current study suggested that the higher dose of AMPH may produce a somewhat greater maximal level of stereotypic behaviors, a trend in the reverse direction was generally found on days 5 and 6, the time of the 2-DG experiments here. Thus the trend towards increased metabolic activity observed in the subthalamic nucleus and anterior substantia nigra pars compacta among rats which received 16 mg/kg/day of AMPH does not correlate in any simple manner with the behavioral data collected.

While the absence of an extensive metabolic stimulation in extrapyramidal motor structures following continuous AMPH treatment found previously has been attributed to the mode of AMPH treatment (i.e. continuous vs. acute), the results of the present experiment suggest that the appearance of widespread metabolic activation within these structures is not restricted to the acute regimen of AMPH administration. It is

interesting that a fairly selective activation of metabolic activity in nucleus accumbens has been found with acute administration of low doses of AMPH, which stimulated locomotion, while prominent increases in glucose utilization were found throughout the dopaminergic extrapyramidal system with higher doses of acute AMPH, which produced stereotypy (Porrino et al, 1984). It is possible that drug dose is an important parameter in the metabolic effects of continuously administered AMPH as well, and one might speculate that a dose-response curve may be present which is similar to that seen with the administration of acute AMPH, with metabolic stimulation primarily of nucleus accumbens at low doses of continuous AMPH, but with activation of nigrostriatal structures appearing at higher doses. However, even if this were the case, it does not follow that the processes underlying the similar patterns of 2-DG uptake would necessarily be the same.

The absence of a significant elevation in 2-DG uptake in caudate in the context of increases in the other dopaminergic extrapyramidal structures and the presence of stereotypy in response to continuous AMPH in the present study represents a discrepancy from most previous results employing high doses of acute AMPH or other DA agonists (Orzi et al, 1983; Porrino et al, 1984; McCulloch et al, 1982a). Porrino & Lucignani (1987) reported no alterations in overall glucose utilization within caudate in response to acute administration of the DA agonist methylphenidate, although a dark band in a restricted portion of caudate was noted in the autoradiographs. However, it may be recalled that continuous AMPH has been reported to produce selective neurotoxic effects within caudate, with damage to striatal DA terminals found in rats which received 16 mg/kg/day for 3 days (Ellison et al, 1978b; Ricaurte et al, 1984). It is therefore possible that the absence of a significant metabolic activation

found in caudate in the present study is related to DA terminal damage, which would be expected at least at the higher dose of AMPH administered. The impact of the damage to striatal DA terminals is difficult to estimate, in part because the extent of such damage is unclear.

Further, the possible effect of striatal terminal damage on glucose metabolism in striatal efferent structures, including globus pallidus, subthalamic nucleus and substantia nigra, is extremely difficult to assess. Metabolic activation after intrastriatal DA injection has previously been demonstrated in each of these nuclei (Brown & Wolfson, 1983), while the acute systemic administration of apomorphine in rats with unilateral electrolytic lesions of the striatum has suggested that DA agonist-induced increases in glucose utilization in globus pallidus and substantia nigra pars reticulata result primarily from alterations of striatal output rather than from direct actions on DA receptors in these structures (Hosokawa et al, 1984). Thus it is possible that striatal DA terminal damage could produce complex effects on functional activity, particularly in globus pallidus and substantia nigra pars reticulata, and could contribute to the increases found in these structures via disinhibition due to the reduced striatal input, although Hosokawa et al (1984) found that striatal lesions tended to largely abolish the increases normally induced by apomorphine in these regions.

The limitations of the 2-DG technique should be considered in the interpretation of the results of the present and earlier studies. It cannot be concluded from observations of unaltered 2-DG uptake that the experimental manipulation had no effect on neuronal activity in that structure, since for example, opposing influences from different afferents or opposing actions within different neurotransmitter systems in a given structure could cancel each other out, or an effect could be too small to be detected

even with the fully-quantitative 2-DG method. The 2-DG technique does not permit the direct identification of the transmitter system involved in any observed changes in metabolic activity. Previous studies involving extensive mapping of regional alterations in cerebral glucose utilization resulting from the administration of AMPH and other DA agonists have found relatively selective effects in structures which are components of DA pathways, while DA antagonists have been shown to prevent these effects (McCulloch et al, 1982a, b; Orzi et al, 1983; Porrino & Lucignani, 1987; Porrino et al, 1984). There is thus considerable evidence suggesting that AMPH produces its metabolic effects predominantly through an interaction with DA systems, however the contribution of other transmitter systems known to be affected by AMPH cannot be determined. Further, as implied in the previous paragraph, it is impossible to distinguish changes in glucose utilization occurring as a direct result of drug actions within a particular structure from those representing secondary effects at other sites. The strength of the 2-DG technique, given its present degree of resolution, thus lies in its ability to map functional activity in many brain structures simultaneously, rather than to precisely define the nature of neuronal events in a particular region.

The relatively small number of animals included in this study, in conjunction with the high inter-animal variability frequently observed in ratio scores within treatment groups, as indicated by the standard deviations, emphasize the need to treat these results with caution. This may be especially applicable to the comparisons between the two doses of AMPH, given the smaller group sizes in these cases. It is not clear to what extent simply increasing the group sizes might overcome the limitations in sensitivity associated with the 2-DG technique used here, particularly in the context of the relatively small effect expected in nucleus accumbens. Even if a reliable increase

in 2-DG uptake could be shown in nucleus accumbens using larger numbers of animals, it seems unlikely that the degree of antagonism, if any, of AMPH effects by SCH 23390 could be readily assessed with any degree of sensitivity. This technique appears to be less than ideal for this application, and it may be preferable to adopt a more sensitive approach. A 2-DG study of the effects of combined administration of AMPH and SCH 23390 was therefore not attempted.

Behavioral Effects of Continuous AMPH.

The results of the behavioral ratings indicate that continuous infusions of AMPH (12 and 16 mg/kg/day) via osmotic pumps produce high initial levels of stereotypy followed by a rapid decline, in agreement with previous studies which used either pumps or pellets to administer AMPH (Gately et al, 1987; Nielsen, 1981; Eison et al, 1983; Ellison et al, 1978a; Huberman et al, 1977). A second phase of stereotypy emerged as well, which is particularly evident at the higher dose of AMPH. Locomotor activity tended to be markedly elevated only on day 1, while a longer period of drug infusion than employed here would be necessary to determine whether the small upturn appearing late in the period of drug treatment may represent the beginning of an upward trend, since a biphasic locomotor response has been found with 2-week intra-accumbens infusions of DA (Costall et al, 1982).

Thus a second phase of stereotypy which has sometimes been noted late in the course of pellet infusions of AMPH (within days 4-7), primarily involving prolonged grooming (Huberman et al, 1977) or a relatively small increase in head-down behaviors as defined in the current study (Ellison et al, 1978a), does not appear to be dependent on the pattern of declining drug output associated with pellet infusions, as has sometimes been suspected. The present study can obviously not address the question of

whether the altered social behaviors (social stereotypies) observed by Ellison et al (1978a) during this late phase would also occur with pump infusions among rats housed in social colonies. However, it appears that a pronounced biphasic response, at least in some forms of stereotypy, can be observed over 7 days of AMPH infusion via pumps, with the magnitude and timing of these phases perhaps partially determined by the dose administered, as discussed further below.

A second phase of stereotypy during 7 days of pump-based AMPH infusions has not been reported previously even with apparently large doses of AMPH (Nielsen, 1981), which may in part reflect the limitations of the stereotypy rating scale used. Conventional rating scales typically involve subjective judgements of the intensity of stereotypy, with certain response categories often considered to be ordered along a continuum. Stereotypy induced by continuous AMPH can be fairly subtle, especially later in the course of treatment, sometimes consisting of prolonged bouts of behaviors which can seem relatively normal in other respects and might not be detected by traditional rating scales. This may reinforce recent criticisms of these scales (Fray et al, 1980; Rebec & Bashore, 1984), and suggests that it may be particularly important with continuous AMPH administration to quantify the resulting behaviors more precisely than global rating scales allow.

There appeared to be a trend, consistent with predictions, towards flatter response curves over time for most behavioral indices, including total activity and most forms of stereotypy, and lower maximal levels of stimulation, at the lower dose of AMPH (12 mg/kg/day), although very few differences compared with effects at the 16 mg/kg/day dose approached statistical significance. A differential temporal pattern of behavioral effects was also observed, supporting predictions of an earlier occurrence at

the lower dose level of both the decline in the initial phase of stereotypy and the subsequent resurgence, although the second phase of stereotypy is less clearly defined.

It appears that it may not be accurate to associate the continuous infusion paradigm exclusively with the development of tolerance to AMPH-induced stereotypy, since there appear to be phasic increases and decreases in these behaviors. Further, if the initial tolerance to AMPH-induced stereotypies and the emergence of a late stage of altered behaviors were primarily a result of the DA depletions and other neurotoxic consequences of this treatment regimen, as has sometimes been suggested, it is not clear why the higher dose of AMPH, which is presumably associated with a greater neurotoxic effect, would result in a slower development of tolerance during the initial phase of stereotypy, or result in a more pronounced second peak in stereotypy, although the more severe decline after the first phase of stereotypy might be expected. The sizable effect seen during the second phase of stereotypy at the higher dose is consistent with the possibility that dopaminergic systems may show considerable sparing of function and/or compensation for damage resulting under a high level of challenge.

Gnawing in conjunction with rearing was reported only among rats receiving the lower dose of AMPH, although these differences were not statistically significant. It is interesting that prolonged gnawing of a wire grid on the cage floor was noted in pilot work only at higher doses of continuous AMPH (20 mg/kg/day) than were employed in the present study, suggesting that the direction of gnawing could potentially be useful in discriminating between certain doses of continuous AMPH. This again points to the importance of adopting precise measures of behaviors produced by continuous AMPH, since gnawing per se is generally considered to be an intense form of stereotypy which emerges only at high doses of AMPH, and traditional rating scales, in particular, would

fail to distinguish between these two forms of gnawing.

Overall, the differences resulting from the administration of 12 vs. 16 mg/kg/day of AMPH were not large, which is not surprising given the fairly small range separating these two doses, and it may be of interest to examine the behavioral consequences of a larger range of doses of continuous AMPH in order to better define the dose-response curve resulting from this treatment mode. It appears that there are quantifiable differences in the behavioral effects at varying doses of continuous AMPH, and thus dose may be an important parameter in this paradigm, as with acute AMPH. We might prefer to speak of the behavioral effects of continuous AMPH in relation to particular doses, rather than in general terms or only in relation to the mode of administration (i.e. pump vs. pellet).

The reduced level of stereotyped grooming on day 1 among AMPH-treated rats compared with controls, although not significant, is consistent with Eison et al's (1983) finding of suppressed grooming early in the course of AMPH administration. In contrast to previous studies which quantified grooming in response to continuous AMPH, with the exception of Eison et al (1983), there was no clear finding of increased stereotyped grooming over the course of treatment in the present study, although there was a trend towards enhanced grooming on day 5 among animals which received the higher dose. Lengthy informal observations during pilot experiments suggested that very prolonged bouts of grooming which can otherwise appear normal are in fact often present with this regimen, while undrugged rats also tend to show a high frequency of grooming but of somewhat shorter durations. Thus it is possible that the behavioral sampling technique used in this study was not effective in detecting AMPH-induced increases in grooming, which if present might emerge more clearly if duration rather

than frequency of grooming were measured over longer observation intervals.

Certain other limitations inherent in the behavioral assessment method employed, in addition to the small sample sizes and liberal approach to statistical analysis, suggest that the results of the present study should be treated with caution. Any analysis of the behavioral effects of continuous AMPH is complicated by what appears to be a high degree of variation across animals in responsiveness to AMPH treatment, as has been noted with acute administration (Segal & Kuczenski, 1987), as well as considerable variability in baseline activity levels. In addition, the variability in behavior displayed by any given animal over a short space of time can be very high, with periods of fairly normal activity sometimes alternating with bouts of extreme hyperactivity or intense stereotypy. Therefore, while larger sample sizes would likely improve the reliability of the data, it seems that some refinements in the behavioral assessment procedures would markedly improve the quality of the information obtained.

As discussed above in the case of grooming behavior, it may be preferable to measure the duration rather than frequency of occurrence of the other behaviors as well, over intervals longer than the 10 s used here, thereby perhaps providing a more precise basis for the comparison of behaviors produced by AMPH against baseline or control levels. More frequent daily sampling of behaviors might help to overcome the error in the present method associated with fluctuations which appear from day to day in the timing of activity cycles. Observation conditions which allow for better discrimination of certain components of behavior, for example, of oral behaviors vs. sniffing, may be useful in providing more detailed desciptions of AMPH-induced effects at various doses. The use of objective criteria in defining behavioral response categories in the present study led to the exclusion of some aspects of behavior from the

data, such as intensity of repetitive behaviors, or prevalence of discontinuous stereotypy, typically involving certain combinations of repetitive behaviors, or repetitive behaviors interrupted by locomotion.

The replication of this study with a larger sample, more sophisticated method of behavioral quantification, and more rigorous statistical analysis, would be useful in drawing more definitive conclusions regarding the behavioral effects of continuous AMPH administration. However, the question of the validity of this paradigm as a model of AMPH psychosis, and in turn of paranoid schizophrenia, appears to remain a more fundamental issue in the present context. Thus the concurrent measurement of alterations in neurochemical indices, receptor populations and functional activity in relevant structures at different times over the course of AMPH infusions will be vital in attempting to identify the physiological mechanisms underlying the observed behavioral alterations, and ultimately in examining the relationship between AMPH-induced effects in experimental animals and the changes observed in human populations during AMPH psychosis and/or schizophrenia.

Antagonism of the Behavioral Effects of Amphetamine by SCH 23390

Continuous administration of the D1 antagonist SCH 23390 (0.5 mg/kg/day) alone appeared to produce a trend towards a relatively small, non-specific depression of behavior, as has been noted previously with measures of locomotor activity (Martin-Iverson et al, 1988b). This effect creates some difficulty in assessing the ability of SCH 23390 to antagonize the behavioral consequences of AMPH (16 mg/kg/day) infusion. While animals treated continuously with SCH 23390 in combination with AMPH showed no significant increases in any behavioral measures compared with those which received vehicle, the data suggested the presence of

behavioral activation among the former group compared with rats which received SCH 23390 alone.

The most prominent effect observed with combined treatment was a significant increase in locomotion on day 6 over levels seen among animals infused with SCH 23390 only, accompanied by an increase in total activity on that day, in addition to subjective reports of marked hyperactivity in response to approach and handling at the end of the experiment. This seems consistent with the previous finding that SCH 23390 was able to block the locomotor stimulant effect of continuous infusions of the D2 agonist PHNO only over the first several days, after which locomotor activity increased gradually over successive nights but showed large increases only on alternate days (Martin-Iverson et al, 1988b), although no differential effects during the dark and light periods are apparent in the present results. It is not clear whether the increases in total stereotypy and especially in stereotyped rearing found late in the course of the infusions compared with blocker-treated animals are meaningful, given the variations across time seen in these scores among the blocker-treated rats, however it seems that there may be a tendency towards an increase in a number of indices of stereotypy during the last several days of combined treatment.

The elevation in total stereotypy observed on day 1 seems to derive primarily from a significant increase in stereotyped grooming. D1 receptors have been particularly implicated in the mediation of grooming behavior, and enhanced grooming has been reported with acute administration of the D1 agonist SKF 38393 as well as of very low doses of SCH 23390 (Molloy & Waddington, 1987; Starr & Starr, 1986). However, if the present effect was a direct consequence of the actions of SCH 23390 on D1 receptors, one would obviously expect to observe increases in grooming among

animals treated with the antagonist alone as well, which is not the case here. It seems more likely that this increase in grooming may reflect an interaction of SCH 23390 with AMPH, perhaps as an incomplete suppression of the initial phase of intense stereotypy normally induced by AMPH which could potentially lead to the unmasking of a grooming response.

Although there are no clear indications in the present data of differential effects among groups receiving vehicle or combined treatment, the constellation of behavioral responses to the various treatments employed nonetheless seems to suggest an inability of SCH 23390 to completely block the behavioral stimulation produced by continuous AMPH administration, particularly during the initial and late phases of treatment which are typically associated with high levels of AMPH-induced stimulation. While the nature of the interaction between AMPH and SCH 23390 in this paradigm is unclear, it is consistent with the possibility of a partial antagonism of AMPH-induced effects, but with a residual stimulation remaining which counteracts to varying degrees the dampening effects on behavior produced by SCH 23390 alone.

While it is possible that the dose of SCH 23390 employed here was too low to provide adequate blockade of D1 receptors, this dose was expected to be relatively high under conditions of continuous administration, and one would be more likely to question the resulting selectivity for D1 receptors. Assays to provide a measure of the brain concentrations of SCH 23390 resulting from administration at this dose would be useful in addressing this issue. In addition, the caveats discussed in the previous section in regards to sample size, behavioral assessment procedures and statistical analysis apply equally here. The locomotor effect observed as a result of combined treatment with AMPH and SCH 23390, and the possible importance of the antagonism of DA-agonist

induced locomotion as a predictor of antipsychotic activity (Ljungberg & Ungerstedt,1978; Ogren et al, 1978), suggest that one might particularly wish to include automated monitoring of locomotor activity in future work to provide a more sensitive measure of this behavior.

Although the effects of concurrent infusion of a D2 blocker with AMPH at the dose employed in the present study are unclear, the concurrent administration of the D2 antagonist sulpiride has been shown to completely prevent the hyperactivity associated with intra-accumbens infusions of DA (Costall et al, 1985). Thus it is possible that there are differences between the actions of selective D1 and D2 antagonists which emerge with continuous administration. In light of the considerable literature in support of the ability of SCH 23390 to prevent the consequences of acute injections of AMPH and other DA agonists, the present results emphasize the importance of considering chronic paradigms, which may uncover effects not observed with acute administration. While the results of this study seem to call into question the effectiveness of D1 receptor blockade in preventing the long-term consequences of AMPH administration, it is apparent that SCH 23390 did have a substantial impact on the behavioral outcome of continuous AMPH infusion, supporting the notion that D1 receptors may participate in the expression of numerous behaviors which are mediated by DA systems. Further, several authors have pointed out the relevance of the ratio of D1 to D2 receptor stimulation in determining the nature of the response to acutely administered DA agonists (Arnt et al, 1988; Braun et al, 1986), suggesting another avenue which might be profitably explored within a chronic paradigm.

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