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Dopamine and Learning: Implications for Attention Deficit Disorder and Hyperkinetic Syndrome

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There is now evidence from a number of areas of research that suggests that the central neurotransmitter, dopamine (DA) may be decreased in the brains of children with attention deficit disorder and hyperkinetic syndrome (ADDH). The evidence includes the positive response to medications (e.g., amphetamine) known to enhance dopaminergic neurotransmission (see Gittelman Klein & Abikoff, this volume), the observation of decreases in biochemical markers for DA in children diagnosed with ADDH (see Shaywitz & Shaywitz, this volume) and the finding that animals undergoing neonatal DA denervation develop a hyperkinetic syndrome that is ameliorated by amphetamine (for a review see Seiden, Miller & Heffner, this volume). It is important to note that other neurotransmitters, for example norepinephrine and serotonin, may also be involved in ADDH (for a recent review, see Oades, 1987, and this volume). It is not the purpose of this chapter to review the evidence for or against the possible role for various neurotransmitters in ADDH. That has already been done, for example by Seiden et al. (this volume). The purpose of this chapter is to discuss the possible role of DA in locomotor activity and learning. To the extent that a DA decrease is found to be involved in ADDH, the present discussion may assist in understanding how a hypofunctioning of DA may lead to some of the symptoms of this disorder.

In a previous review of the role of DA in locomotor activity and learning (Beninger, 1983), it was concluded that DA may be involved in both of these phenomena. Thus, systemic treatments that led to decreases in DA neurotransmission resulted in hypoactivity whereas those that led to increases in DA neurotransmission led to increased activity or stereotypy. When specific DA terminal

regions were considered, data suggested that DA neurons projecting to basal forebrain regions including the caudate, putamen, nucleus accumbens and olfactory tubercle may enhance locomotor activity whereas mesocortical DA neurons may inhibit locomotion (but see below). Further results suggested that mesolimbic DA neurons may be primarily involved in increased locomotion produced by DA agonists whereas nigrostriatal DA neurons may be more involved in stereotypy (cf. Robbins, Jones, & Sahakian, this volume). DA was also implicated in reward-related learning, termed incentive motivational learning, but shown to be less involved in the learning of associations among stimuli.

The data supporting this general scheme have been extensively reviewed (Beninger, 1983, 1988a,b; Willner, 1983) and will not be covered again here. This chapter is concerned with new developments that further the understanding of the role of DA in locomotor activity and learning. These include studies of the possible role of DA receptor subtypes in phenomena involving DA; the subtypes are D1 receptors that are linked in an excitatory manner to the enzyme adenylate cyclase and D2 receptors that are not (Kebabian & Calne, 1979). Another approach that has yielded important new results involves the use of regional microinjections of DA agonists and antagonists. It will be shown that DA projections to the frontal cortex, like mesolimbic and nigrostriatal DA projections probably exert an excitatory influence on locomotor activity. Evidence suggests that this effect may be mediated by D2 receptors in the frontal cortex. The results of studies of place conditioning support a role for DA in this phenomenon and suggest that stimulation of D2 receptors but not D1 receptors produces the effect. The results of studies investigating the effects of DA receptor blockers on food-rewarded operant responding showed that both D1 and D2 blockers produced a gradual decline in responding. Intrasession declines in food-rewarded operant responding were seen following bilateral microinjections of a DA receptor blocker into the dorsal striatum. These findings are discussed in further detail below.

Frontocortical Dopamine and Circling

The results of previous studies have led to the conclusion that DA neurons projecting to the frontal cortex may normally inhibit locomotion. This conclusion was based on the finding that bilateral depletion of frontal cortical DA by intracortical injections of 6-hydroxydopamine (6-OHDA) led to hyperactivity after a period of 7-10 days (Carter & Pycock, 1980; Robinson & Stitt, 1981; Joyce, Stinus, & Iversen, 1983). Further support for this hypothesis was provided by the finding of a high correlation between the increase in locomotor activity and decrease in frontal cortical DA levels 30 days after bilateral electrolytic destruction of the ventral tegmental area (Tassin, Stinus, Simon, Blanc, Thierry, LeMoal, Cardo, & Glowinski, 1978). However, biochemical data demonstrated that, 4 weeks after frontal cortical DA denervation, there was an increase in DA function and utilization in subcortical areas (Pycock, Kerwin, & Carter, 1980). This result

raised the possibility that locomotor hyperactivity seen following depletions of frontal cortical DA may have been the consequence of time-dependent increases in DA function in subcortical DA-innervated regions known to contribute to the control of locomotor activity.

One way to systematically test this possibility was to employ acute manipulations of frontal cortical DA using microinjections and thereby avoiding long term compensatory changes in the function of subcortical systems. Robert J. Stewart, Michel A. Morency and Patricia R. Dickson, working in my laboratory, have conducted an extensive series of studies investigating the effects of unilateral microinjections of dopaminergic agents into the medial prefrontal cortex on the circling behaviour of rats. As animals characteristically circle away from (contralateral to) the side of higher DA activity, results suggested that increased stimulation of DA receptors in the frontal cortex leads to increased activity. Results further suggested that this effect may have been mediated by D2 DA receptors.

The experimental protocol was as follows. Groups of rats (n = 18) were surgically prepared with chronic indwelling unilateral guide cannulae. After recovery from surgery, each rat was tested in a circular arena a total of seven times with 72 hours separating tests. The test sessions were as follows: (1) no central injection; (2) central injection of vehicle; (3), (4) and (5) each of three drug doses with order of central administration (in 0.5 or 1.0 μl) counterbalanced across rats over three sessions; (6) replication of vehicle; (7) replication of no central injection. All complete turns (360°), ipsiversive and contraversive to the side of the cannula, were counted during four observation periods that occurred at 0-5, 15-20, 30-35 and 45-50 min into the session. The following compounds were tested in separate groups of rats: the indirect-acting DA agonists (+)-amphetamine sulphate (6, 12, 25 μg) and cocaine hydrochloride (25, 50, 100 μg), the local anesthetic procaine hydrochloride (10, 100, 1000 μg), the D1 and D2 antagonist *cis* -flupenthixol (1, 10, 25 μg), the specific D1 agonist SKF 38393 (2,4,8 μg), the specific D2 agonist quinpirole (3, 6, 12 μg) and the specific D2 antagonists metoclopramide hydrochloride (6, 25, 100 μg) and sulpiride (.001, ,01, .1 μg). The ability of sulpiride (1.0 μg) to antagonize the effects of cocaine (50 μg) also was tested in a separate group. Whenever an antagonist was tested, the rats always received an intraperitoneal (ip) injection of amphetamine (1.5 mg/kg) 15 min prior to every test session to increase overall activity.

After histological verification of cannulae placements and discarding rats that had defective cannulae during the conduct of the experiments, groups numbered from 8-14 rats. For each rat the total number of ipsiversive turns was summed over the four observation periods and similarly for contraversive turns. For each rat these sums were then used to calculate a ratio of ipsiversive turns to the total number of turns (ipsiversive plus contraversive). Ratio values of 0.5 indicated equal turning in both directions; values greater or less than 0.5 indicated ipsiversive or contraversive circling, respectively. The total number of turns per session (ipsiversive plus contraversive) served as the second dependent variable.

Comparisons of the turning ratio data for the first and second no-injection sessions, as well as the first and second vehicle sessions, never revealed any significant differences in any of the experiments. Consequently, the data for the two no-injection sessions and those for the two vehicle sessions were averaged for each rat. The results from the no-injection sessions illustrate the acute nature of the manipulations being made in these experiments as the animals returned to baseline circling ratios after drug sessions. Vehicle scores were found never to differ from no-injection scores further showing that intrafrontocortical saline did not systematically produce a directional bias.

The results for the combined no-injection sessions, combined vehicle sessions and each of the three doses of each drug are shown in Figure 1. Both amphetamine (Fig. 1A) and cocaine (Fig. 1B), but not procaine (Fig. 1C), dose-dependently produced contraversive circling, suggesting that stimulation of DA neurotransmission in the frontal cortex led to an enhancement of motor activity (Morency, Stewart, & Beninger, 1987; Stewart, Morency, & Beninger, 1985). The cocaine effect could not be attributed to a local anesthetic effect of the drug as procaine was without significant effect (Morency et al., 1987). The expected opposite effect of a DA receptor blocker was produced by *cis*-flupenthixol (Fig. 1D) that resulted in dose-dependent ipsiversive circling (Beninger & Dickson, 1987). The D1 agonist SKF 38393 (Fig. 1E) was without significant effect (Beninger & Dickson, 1987) whereas the D2 agonist quinpirole (Fig. 1F) produced contraversive circling (Beninger & Dickson, 1987) and the D2 antagonists metoclopramide (Fig. 1G) and sulpiride (Fig. 1H) produced ipsiversive circling (Morency et al., 1987; Stewart et al., 1985). Finally, the contraversive circling produced by cocaine was blocked by co-injection of sulpiride (Fig. 1I) further suggesting that the cocaine effect was a result of its action at DA synapses (Morency et al., 1987).

Total turns for each group are shown in Table 1. The much higher total turns of the groups given ip amphetamine can be seen clearly. With the exception of flupenthixol and quinpirole, all groups showing significant dose effects on turning ratios also showed significant changes in total turns over doses. In general, with increasing drug dose there was an increase in total turns. This might indicate the increase in directional bias, whether ipsiversive or contraversive, leading to more completed turns and fewer partial turns in either direction (only total turns were counted). The quinpirole group was an exception, showing a non-significant decrease in total turns with increasing dose. The explanation of this effect awaits further study, however, it is noteworthy that in spite of this drug's opposite effect on total turns, it, like amphetamine and cocaine, produced a dose-dependent increase in the proportion of contraversive circling.

The results of these and related studies (Morency, Stewart, & Beninger, 1985) suggest that DA in the frontal cortex, like DA in the dorsal and ventral striatum, may be excitatory in its influence on motor behaviour. If this hypothesis is supported by further research, it would suggest that DA in all of the terminal regions

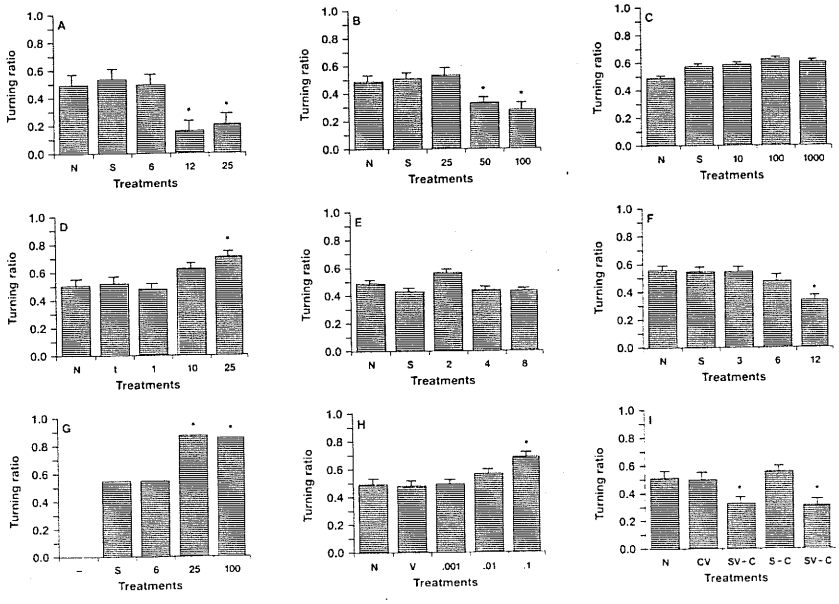

FIG. 1. Effects of pharmacological manipulations of frontocortical dopamine on circling behavior of rats. Each bar graph shows the mean (± SEM) turning ratios [total ipsiversive turns/(total ipsiversive + contraversive turns)] for one experiment for the combined no-injection sessions (N), the combined saline sessions (S), and each of the three doses of each drug. A: (+)-amphetamine; B: cocaine; C: procaine; D: *cis*-flupenthixol; note that the inactive geometric isomer, *trans*-flupenthixol (t), instead of saline, was used for control injections; E: SKF 38393; F: quinpirole; G: metoclopramide; H: sulpiride; I: sulpiride vehicle and cocaine (SV+C) or sulpiride and cocaine (S+C). Asterisks indicate doses that differed significantly from their respective saline conditions. (Adapted from Beninger & Dickson, 1987; Morency et al., 1987; Stewart et al., 1985.)

tested is similarly involved in the control of motor activity, increases in DA neurotransmission leading to increases in locomotor activity and decreases in DA neurotransmission leading to decreases in locomotor activity.

Dopamine and Place Conditioning

Besides being involved in the control of locomotor activity, DA also appears to be involved in reward related incentive motivational learning (Beninger, 1983). The place conditioning task provides one paradigm for studying this type of learning. In one version of this task, rats receive several daily exposures to a rectangular box, the stimuli associated with the two sides differing (e.g., floor texture, pattern on the walls, odour and/or illumination). The time spent on each side is recorded. A partition is then installed between the two sides and over a series of conditioning days, the rats consistently receive a rewarding stimulus (e. g., food) in one side and an equal amount of exposure to the other side but reward

TABLE 1
Total Number of Turns for Each Group of Rats Included in the Frontocortical Dopamine and Circling Section

		Phase				
Drug	*n*	*no-injection*	*vehicle*	*low*	*medium*	*high*
(+)-amphetamine	13	14.3 ± 1.5	14.4 ± 1.6	17.6 ± 1.6	21.2 ± 2.2	20.9 ± 2.4
cocaine	12	10.5 ± 1.1	13.8 ± 0.6	14.3 ± 1.1	20.7 ± 1.1	21.1 ± 1.6
procaine	12	14.5 ± 1.4	16.8 ± 2.4	15.6 ± 2.0	15.9 ± 1.7	15.6 ± 2.4
cis-flupenthixol	10	20.2 ± 2.5	22.2 ± 2.0	23.7 ± 4.4	24.6 ± 4.0	28.0 ± 4.0
SKF 38393	8	13.6 ± 1.3	12.8 ± 2.2	10.1 ± 1.3	10.3 ± 1.9	12.4 ± 1.9
quinpirole	10	10.4 ± 1.4	9.9 ± 1.4	9.2 ± 1.3	8.9 ± 1.3	8.6 ± 2.1
metoclopramide	12		76.7 ± 7.0	88.4 ± 6.2	102.0 ± 8.8	98.6 ± 6.1
sulpiride	11	58.6 ± 6.3	56.4 ± 5.8	56.6 ± 4.2	61.0 ± 7.3	74.4 ± 6.6
cocaine & sulpiride	14	13.8 ± 1.5	14.9 ± 1.3	20.1 ± 1.6	13.6 ± 1.7	19.1 ± 2.3

Doses corresponding to "low", "medium" and "high" were different for different drugs as indicated in the text. Also indicated in the text is the protocol for the cocaine & sulpiride experiment which differed from the others.

is never presented there. On subsequent test days with the partition again removed and no reward given on either side, animals are observed to spend significantly more time on the side previously associated with reward (Spyraki, Fibiger, & Phillips, 1982a). A role for DA in this type of learning was suggested by the finding that treatment with the DA receptor blocker haloperidol on conditioning days, although not affecting feeding, led to a significant attenuation of place conditioning based on food (Spyraki et al., 1982a).

A number of related studies have shown that place conditioning can be established with the stimulant drugs amphetamine (Spyraki et al., 1982b) and cocaine (Spyraki et al., 1982c) and with the opiate compound heroin (Spyraki et al., 1983). DA was implicated in the effects of amphetamine and heroin by the finding that DA receptor blockers or destruction of the mesolimbic DA system blocked place conditioning in these groups (Spyraki et al., 1982b, 1983) but, surprisingly, neither the DA antagonists pimozide and haloperidol nor 6-OHDA lesions of the DA terminal region, nucleus accumbens, blocked cocaine produced place conditioning (Spyraki et al., 1982c). One possibility suggested by Spyraki et al. (1982c) was that cocaine might have a peripheral local anesthetic effect (Bedford, Turner, & Elsohly, 1984) that in some way resulted in place conditioning, a suggestion that was supported by the observation that the local anesthetic procaine also produced place conditioning.

Recently, Michel A. Morency, working in my laboratory, replicated the Spyraki et al. (1982c) finding of cocaine-produced place conditioning and also found that pimozide failed to block the effect (see Fig. 2A). He reasoned that if conditioning based on cocaine was attributable to its peripheral local anesthetic effects as Spyraki et al. (1982c) suggested, it might be possible to establish place condi-

tioning following intracerebroventricular (icv) administration of cocaine that did not have a local anesthetic effect and that, therefore, could be blocked by pimozide. Results supported this hypothesis. Thus, icv cocaine produced place conditioning that was blocked by pimozide (Fig 2B). In addition, icv administration of procaine produced no significant effect on place learning (Morency & Beninger, 1986).

These results provide further support for the hypothesis that DA plays a role in mediating reward-related learning. They provide no clear basis for understanding the apparent reward effect following peripheral injections of procaine or cocaine in animals with central DA function reduced. One intriguing possibility is that the local anesthetic properties of cocaine or procaine reduced the putative discomfort resulting from the ip injection. As the animals were always injected with saline on control days when they were placed into the opposite side of the place conditioning chamber, the two sides may have had different levels of peripheral discomfort associated with them. On test sessions, animals may then have been seen to spend significantly more time in the side associated with the

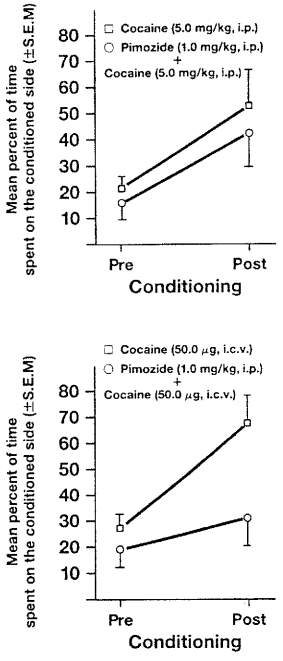

FIG. 2. Effects of pimozide on cocaine-produced place conditioning. Mean (±SEM) percent of time spent on the conditioning side by cocaine and pimozide + cocaine groups during pre- and postconditioning test sessions following intraperitoneal (i.p.) cocaine (upper panel) or intracerebroventricular (i.c.v.) cocaine (lower panel). Both i.p. and i.c.v. cocaine produced significant place conditioning but pimozide only blocked the latter effect. (From Morency & Beninger, 1986.)

(putative discomfort-reducing) local anesthetic. Although this account is speculative, the observation that icv administrations of procaine failed to lead to place conditioning and that icv cocaine-produced place conditioning was blocked by pimozide can be seen to be consistent with it (Morency & Beninger, 1986).

A new line of investigation concerns the possible differential involvement of D1 and D2 DA receptors in place conditioning. Diane C. Hoffman and Patricia R. Dickson have investigated the effects of the D1 agonist SKF 38393 (0.01, 0.1, 1.0 and 10.0 mg/kg ip) and the D2 agonists quinpirole (0.01, 0.025, 0.05, 0.1, 0.25, 1.0 and 5.0 mg/kg ip) or bromocriptine (0.01, 0.1, 0.5, 1.0, 5.0 and 10.0 mg/kg ip) in place conditioning. Results (Fig. 3) revealed that both quinpirole and bromocriptine but not SKF 38393 produced a significant place preference. In fact, the highest dose of SKF 38393 was seen to produce a place aversion (Hoffman, Dickson, & Beninger, 1988; Hoffman & Beninger, 1987). These results continue to support the hypothesis that DA is involved in reward-related learning and provide preliminary evidence that stimulation of D2 receptors may be important for this effect; a similar conclusion has been reached by others studying different reward paradigms, e.g., drug self-administration (Woolverton, Goldberg, & Ginos, 1984).

Dopamine and Food-Rewarded Operant Responding

Some of the earliest work that formed the foundation of the hypothesis that DA may form a critical link in the neurocircuitry that mediates the effects of reward on behaviour involved the observation that operant responding for rewarding

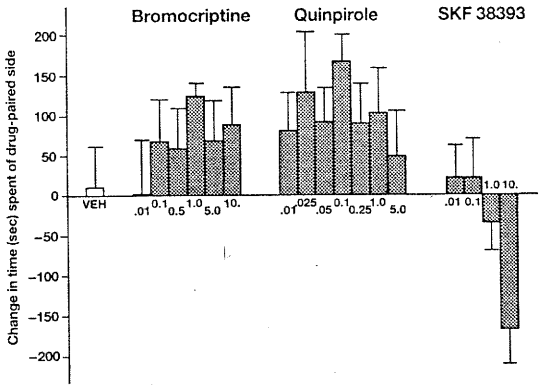

FIG. 3. Ability of the D1 agonist SKF 38393 or the D2 agonists bromocriptine and quinpirole to produce place conditioning. Each bar indicates the mean (±SEM) change in time spent on the drug-paired side from pre- to postconditioning for vehicle (VEH) or one dose (mg/kg) of the drug. Both bromocriptine (1.0 mg/kg) and quinpirole (0.1 mg/kg) produced a significant place preference and SKF 38393 (10.0 mg/kg) produced an aversion. (Adapted from Hoffman & Beninger, 1987; Hoffman et al., 1988.)

stimulation of the brain was significantly reduced by manipulations that decreased central DA neurotransmission (see reviews by Fibiger & Phillips, 1979; Wise, 1982). It was subsequently reported that DA receptor blockade also affected responding for food, pimozide producing an extinction-like day-to-day decline (Wise, Spindler, deWit, & Gerber, 1978). Although this has been a highly controversial area of research, the basic finding has often been replicated (cf., Beninger, 1983, 1988a,b).

One approach to the question concerning the possible role of D1 and D2 receptors in reward-related learning has been to investigate the effects of receptor-subtype specific DA antagonists on operant responding for food. In a recent study the effects of the D1 antagonist SCH 23390 (0.01, 0.05 and 0.1 mg/kg ip) and the D2 antagonist metoclopramide (1.0, 5.0 and 10.0 mg/kg ip) were tested. Rats were trained to lever-press on a variable interval (VI) 30-sec schedule for food for 10 training days. Groups then received one of the doses of the drug or saline or extinction for 5 consecutive sessions. Results revealed that the highest doses of SCH 23390 (Fig. 4C) and metoclopramide (Fig. 4D) produced a significant day-to-day decline in responding similar to that seen in extinction (Beninger, Cheng, Hahn, Hoffman, Mazurski, Morency, Ramm, & Stewart, 1987). Others have similarly found that appetitive operant responding underwent an extinction-like decline following treatment with SCH 23390 (Nakajima & McKenzie, 1986) or D2 blockers (Gallistel & Davis, 1983). These data suggested that both D1 and D2 receptors may participate in the control of behaviour by food reward.

It has also been possible to seek the DA terminal region that may participate in food reward by locally administering microinjections of DA receptor blockers to animals trained to lever-press for food. Catherine M. D'Amico and Laura Suzuki have investigated the effects of bilateral microinjections of the DA receptor blocker *cis*-flupenthixol into the dorsal striatum on rats trained to lever-press on a VI 30-sec schedule of food reward. Results (Fig. 5) revealed that *cis*-flupenthixol (25.0 μg in 1.0 μl on each side) produced a significant intrasession decline in responding. No significant effect was seen following saline or the inactive geometric isomer, *trans*-flupenthixol (Beninger & D'Amico, 1986). Spread of the drug to other regions was unlikely (cf. Ahlenius, Hillegaart, Thorell, Magnusson, & Fowler, 1987) and control studies have shown no significant effects with injections into the cortex dorsal to the striatum or into the amygdala (Beninger & Suzuki, in preparation). Although this work is preliminary and other structures and drugs will be tested, results suggest that regional microinjections of DA antagonists to animals lever-pressing for food may eventually reveal the sites in the brain that mediate this type of reward-related learning.

Dopamine and Learning: Implications for ADDH

As already discussed, there is some evidence suggesting that DA may hypofunction in the brains of children with ADDH. This includes the positive response to amphetamine, a drug that enhances DA neurotransmission (see Gittelman Klein

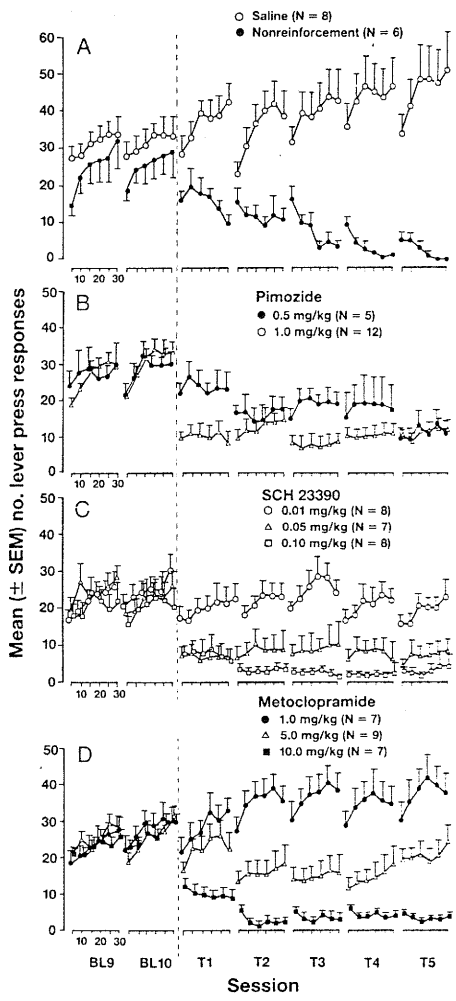

FIG. 4. Effects of D1 and D2 dopamine receptor blockers on food-rewarded variable interval operant responding. Each panel shows the mean (±SEM) responses per min for each 5-min segment of two 30-min baseline sessions (BL9 and BL10) and five test days (T1-T5) for groups treated with saline or receiving nonreinforcement (A), groups receiving the D1 and D2 blocker pimozide during the test (B), groups receiving the D1 blocker SCH 23390 in the test (C), and groups receiving the D2 blocker metoclopramide in the test (D). (From Beninger et al., 1987.)

& Abikoff, this volume) and decreased biochemical markers for DA in children with ADDH (see Shaywitz & Shaywitz, this volume). It has been found that neonatal rats subjected to treatments that significantly reduce central DA levels show a hyperkinetic response that is ameliorated by amphetamine, providing an animal model, with some similarities to ADDH, that results from decreased DA (see Seiden et al., this volume). As reviewed elsewhere (Beninger, 1983, 1988a, b), there is good evidence that DA is involved in the control of locomotor activity and reward-related learning. The present chapter has provided an update of this position including the possible excitatory influence of frontal cortical DA on locomotor activity, the possibility that D2 receptors in the frontal cortex mediate this effect, the role of DA in cocaine reward in place conditioning, the possibility that D2 receptors are primarily involved in place conditioning, the possible role of striatal DA in food-rewarded operant responding and the possibility that both D1 and D2 receptors are involved in this phenomenon. For the purposes of this section, the most relevant aspect of DA's role in behaviour is that there is good evidence that DA participates in two separable phenomena: (1) the control of locomotor activity and (2) reward-related learning.

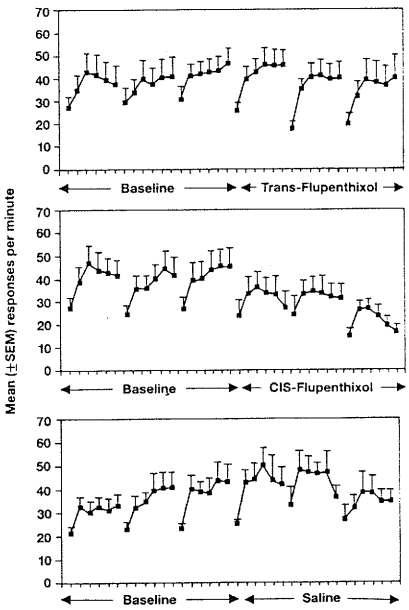

FIG. 5. Effects of intrastriatal microinjections of the dopamine receptor blocker *cis*-flupenthixol (25.0 μg in 1.0 μl on each side) on operant variable interval responding for food. Baseline sessions were the last three 30-min sessions prior to the three test sessions that were separated by 72 hours. Mean (+SEM) responses per min for each 5-min segment of each session are shown. *cis*-flupenthixol but not saline or the inactive geometric isomer *trans*-flupenthixol produced a significant intrasession decline. (Adapted from Beninger & D'Amico, 1986.)

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With regards to the involvement of DA in the control of locomotor activity, there is good evidence that in adult animals there is a positive correlation between the level of DA neurotransmission and the level of locomotor activity. There is also good evidence that in *neonatal* animals, this positive correlation is not found. To the contrary, it appears that neonatal animals depleted of DA are hyperactive (see Seiden et al., this volume). How can this empirical difference in the role of DA in adult versus neonatal locomotor activity be understood? In answering this question, only speculation is possible at present. It is well known that novel stimuli have an unconditioned ability to elicit approach responses. Perhaps the mechanism by which novel stimuli produce this effect is independent of DA. According to this speculation, locomotor activity in neonatal animals depleted of DA might fail to decrease because of the activating effects of relatively novel stimuli. In adult animals with a history of learning about a variety of stimuli in different environments, the relative novelty of most stimuli would be reduced. In the absence of the putative activating effects of novel stimuli, the reliance of locomotor activity on DA can be seen clearly. Of course, this speculation does not explain why animals neonatally depleted of DA are seen to be more active than controls. However, it may be possible to understand the hyperactivity with reference to the other phenomenon that may involve DA, reward-related learning.

Rewarding stimuli, often biologically important stimuli including, for example, food, water, thermal comfort, sexual contact and other social stimuli, produce learning. Empirically, they change behaviour by leading to an increase in the frequency of responses that preceded their presentation in a particular environment. Theoretically, they change neutral environmental stimuli associated with reward into conditioned incentive motivational stimuli that, by definition, acquire an enhanced ability to elicit approach and transactional responses (cf. Beninger, 1983; Bindra, 1978). It is well documented that this type of learning is impaired by treatments that reduce DA neurotransmission. For example, in place conditioning, stimuli on the side associated with food would be said to become conditioned incentive stimuli, leading to an increase in time spent in their presence. As already discussed, treatment with DA antagonists during conditioning trials, while not affecting eating, blocks learning. The acquisition of a lever press response for food can be understood as another example of incentive learning and it has similarly been shown to be impaired by DA antagonists (Wise & Schwartz, 1981). Animals undergoing neonatal DA depletions may show a similar impairment in incentive learning. Thus, Seiden (personal communication) has shown that water-rewarded lever press acquisition was significantly impaired in animals receiving neonatal DA depletions.

The effects of reward on behaviour could be said to change attention. A rat that has been rewarded for pressing a lever spends a great deal of time interacting with (paying attention to) the lever in comparison to a rat with a similar history of being fed in the test chamber independently of lever pressing. A rat in a place conditioning study is seen to spend significantly more time in the presence

of (paying attention to) environmental stimuli signalling reward. Following this line of reasoning, rats undergoing lever press acquisition training or place conditioning while treated with DA receptor blockers and observed to be impaired in learning, could be said to have an attentional deficit.

The following speculation is an attempt to understand ADDH and its response to amphetamine as a consequence of DA hypofunction in the light of what is known about the role of DA in locomotor activity and learning. Thus, the child with ADDH, although possibly having reduced DA, may not be hypoactive because of the activating effects of novel environmental stimuli. The child may show an attention deficit because of an impairment in reward-related learning. The usual effects of reward on behaviour are to increase the incentive properties of environmental stimuli that signal reward leading to an increase in the ability of those stimuli to produce approach and transactional responses or, for present purposes, to command attention. As a result of the putative impairment of this usual learning process, the child with ADDH may move more frequently from stimulus to stimulus leading to an apparent *hyper*activity. It is perhaps worth adding that there is at least one other type of learning, the learning of associations among stimuli, which has been shown to be relatively independent of DA (cf., Beninger, 1983, 1988a, b). This finding might suggest that children with ADDH may show intact associative learning but impaired incentive learning. Finally, treatment with amphetamine would lead to enhanced DA neurotransmission which might, in turn, lead to better incentive learning, more attention to stimuli signalling reward and a resultant reduction in activity.

In conclusion, there is now an extensive literature suggesting an involvement of DA in the control of locomotor activity and incentive learning. Current studies seek to identify the possible involvement of DA terminal regions and receptor subtypes. There is some evidence that ADDH may result from a hypofunction of DA neurotransmission. It may, therefore, follow that children with ADDH are impaired in incentive learning. The development of these relationships requires considerable speculation and existing uncertainties about the etiology of ADDH (see Rutter, this volume) only make this task more difficult. However, the treacherous waters between basic research and clinical phenomena must be forded if the former is to contribute to an understanding of the latter.

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