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DRUGS AND REINFORCEMENT MECHANISMS: A CRITICAL REVIEW OF THE CATECHOLAMINE THEORY

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Attempts to identify and describe neuroanatomical and neurochemical substrates of central reward or reinforcement mechanisms have been the subject of a large and expanding literature during the past 20 years. The approach most often used in this endeavor has utilized the intracranial self-stimulation (ICS) paradigm first described by Olds & Milner (1), whereby an animal will perform an operant response in order to obtain electrical stimulation of the brain via a chronically implanted electrode. The predominant theory that has emerged from this body of work is the "catecholamine (CA) hypothesis," first proposed by Stein (2, 3) and later elaborated upon by Crow (4). According to this hypothesis and stated in its simplest terms, central CA-containing neurons mediate the reinforcing properties of ICS. There are several excellent reviews that summarize much of the evidence supporting this theory (3–5); therefore no attempt is made to do so again. Rather the purpose of this review is to examine critically some of the data and arguments upon which the theory rests and to discuss recent experimental results that appear to be incompatible with the CA theories, at least as originally proposed.

NORADRENALINE AND INTRACRANIAL SELF-STIMULATION

Anatomy

Since the early work of Olds & Olds (6), it has been known from mapping studies that the medial forebrain bundle (MFB) will support very high rates of ICS. This, together with the observations that ascending noradrenaline (NA) axons are located within the MFB and that *d*-amphetamine greatly facilitates the rate of responding for ICS, led Stein (2, 3) to propose that the NA axons within the MFB mediate the reinforcing properties of ICS. Since then many reports have appeared that point to

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a correlation between the location of positive self-stimulation sites and the anatomy of ascending NA projections (4, 5). The major difficulties with this approach are twofold: First, causal implications cannot be drawn from strictly correlational data, and second, given the ubiquitous distribution of NA in brain, it is hardly surprising that NA is found at many, if not all, positive self-stimulation sites. At best, therefore, the anatomical correlations can only be regarded as tentative and suggestive.

Pharmacology

The strongest early support for the NA hypothesis came from pharmacological investigations. In general, compounds believed to increase central noradrenergic tone such as monoamine oxidase inhibitors (7), *d*-amphetamine (2), and cocaine (8) increased the rate of the bar pressing response for ICS. In contrast, agents such as reserpine (9), chlorpromazine (9), and α-methyl-*p*-tyrosine (α-MT) (10), which interfere with central NA mechanisms, decreased ICS. Although these studies were interpreted as evidence for a role of central NA neurons in ICS, it is noteworthy that each of these agents influences dopaminergic (DA) as well as NA systems. Data obtained with these compounds cannot, therefore, be taken as necessarily implicating NA projections in self-stimulation behavior or in central reinforcement mechanisms.

Wise & Stein (11) provided stronger pharmacological support for the NA hypothesis in demonstrating that the dopamine-β-hydroxylase inhibitors disulfiram and diethyldithiocarbamate (DDC) decreased ICS and that this effect could be reversed by subsequent intraventricular injections of NA. A year later, Roll (12) replicated this observation with disulfiram. However, she found that the disulfiram-treated rats appeared to be asleep after the drug and that they would resume normal rates of responding for a short time if they were placed upon the ICS bar by the experimenter. Roll concluded that disulfiram had no primary effect upon brain-stimulation reward and disrupted response rates because of the induction of sedation and sleep. She also pointed out that inasmuch as her ICS tests were conducted at threshold current intensities, a drug-induced decrease in the rewarding value of the brain stimulation should have attenuated the response, whether the animals were forced to remain alert or not. Rolls et al (13) substantiated these findings by showing that disulfiram reduced arousal (as measured by locomotor activity and rearing) at doses that decreased responding for ICS. Similar effects were observed with the α-adrenergic antagonist phentolamine, and it was concluded that these agents reduced self-stimulation by nonspecific effects on behavior. As is seen below, the failure to demonstrate specific effects of drugs on the rewarding properties of ICS is a pervasive problem in this field.

The introduction of several new dopamine-β-hydroxylase inhibitors, FLA-63 and U-14,624, which are without some of the side effects of disulfiram and DDC, presented new opportunities to investigate the role of NA in ICS. Lippa et al (14) observed that injections of FLA-63 at a dose that had been shown to reduce central NA by 70% and to cause nearly complete inhibition of NA synthesis did not significantly affect ICS. In the same study, intraventricular injections of a neurotoxin for catecholamine-containing neurons, 6-hydroxydopamine (6-OHDA), which re-

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duced telencephalic NA by 90%, produced only transient (5–7 day) decreases in response rates for ICS. Furthermore, intraventricular injections of phentolamine in control or 6-OHDA–treated rats had no effect on self-stimulation. These data again cast serious doubt on the hypothesis that the mediation of positive reinforcement in ICS is somehow critically dependent upon NA. Perhaps the most devastating pharmacological evidence against the NA hypothesis has come from the laboratory of Breese and co-workers (15). In the first of these experiments it was found that selective depletion of NA by intracisternal injections of 6-OHDA did not affect self-stimulation rates in animals with lateral hypothalamic electrodes. When these animals received intraperitoneal injections of U-14,624, so that whole brain NA was reduced to 8% of control levels, no change in the self-stimulation rate was obtained. In another experiment, self-stimulating rats were pretreated with reserpine 24 hr before they received an injection of *d*-amphetamine. One hour before the amphetamine injection the animals were injected with U-14,624 or vehicle. This treatment failed to block the stimulant effect of *d*-amphetamine on ICS despite reducing whole brain NA by 99.3%. Stinus et al (16) made similar observations. They found that neither U-14,624 nor FLA-63 produced any substantial change in responding for ICS 24 hr after reserpine pretreatment, despite reducing NA synthesis to approximately 10% of control levels. Taken together these results suggest that neither ICS nor its enhancement by *d*-amphetamine is critically dependent upon central stores or de novo synthesis of NA. However, one problem with these experiments is that they utilized lateral hypothalamic or ventral tegmental electrode placements which may have stimulated ascending DA as well as NA axons. If, as has been suggested (4), DA projections are also involved in ICS, then the failure to observe effects after disruption of central NA systems may have been due to the heterogeneous nature of the electrode site. Breese & Cooper (17) subsequently tested for this possibility by implanting ICS electrodes in the locus coeruleus (LC), a pontine nucleus that contains NA perikarya but which has no known DA elements. Once again, injections of U-14,624 reduced brain NA to 27% of control levels without affecting the self-stimulation rate. Furthermore, pretreatment with reserpine and U-14,624 as described above failed to influence the stimulant effects of *d*-amphetamine on ICS obtained from the LC.

In view of the above results, it becomes necessary to reevaluate a number of recent observations that would appear to support the NA hypothesis. The vast majority of reports concerning experiments that have utilized compounds that affect both NA and DA mechanisms (e.g. amphetamines, α-MT, monoamine oxidase inhibitors, reserpine, chlorpromazine) are not reviewed here because they do not provide information that could directly implicate the existence of NA, as opposed to DA, in ICS. Other studies require discussion, however. For example, Franklin & Herberg (18) found that while injections of FLA-63 had no effect on ICS obtained from electrodes in the lateral hypothalamus or LC, pretreatment (3–5 days) with reserpine caused FLA-63 to decrease the self-stimulation rate. Intraventricular injections of NA reinstated ICS in these animals. The authors interpreted their data as being consistent with the NA hypothesis and suggested that the necessary NA may be derived either from ongoing synthesis or by mobilization of reserve, reserpine-

sensitive pools. Missing from these potentially important observations, however, were adequate behavioral controls showing the specificity of the treatments on ICS. Although it was stated that the animals appeared to be awake and were capable of rapid and coordinated movement, it is well known that animals can display profound drug-induced deficits in operant behavior such as bar pressing and yet appear normal and alert (19–22). Therefore, this kind of experiment must include sophisticated and sensitive behavioral procedures which can control for the possibility that changes in responding for ICS might be due to factors such as subtle motor deficits, sickness, or malaise. These factors must be ruled out before inferences can be drawn regarding drug-induced changes in the reinforcing value of the brain stimulation.

Attempts have been made to provide a control for nonspecific effects of drugs by using "rate-free" measures of ICS. For example, Hunt et al (23) recently studied the effects of the α-adrenergic agonist, clonidine, on an ICS task in which the animal was required to move to one end of a shuttle box to initiate brain stimulation and to the other end to terminate that stimulation. The latencies to initiate and escape stimulation were recorded, and if the animal failed to initiate stimulation within 60 sec, the ICS was automatically turned on. This procedure permitted recording of escape behavior under conditions where ICS initiation was eliminated. Clonidine produced a dose-related increase in the latency to initiate ICS without significantly affecting escape latencies except at the highest dose. It was suggested that a decrease in the release of NA, produced via a presynaptic action of clonidine, was responsible for the increased initiation latencies. Furthermore, the authors argued that this effect represented primary changes in brain stimulation reward processes and was not secondary to nonspecific changes in activity or reactivity because of the selective effects of the drug on initiation latencies. The difficulty with this line of reasoning lies with the assumption that the neural mechanisms and pharmacological sensitivities of operant (i.e. ICS initiation) and respondent (i.e. escape) behaviors are the same. This assumption, however, is untenable. For example, it is well established that neuroleptics interfere with avoidance or operant responses at much lower doses than are required to impair escape or respondent behavior (21). Olds & Travis (22) also made this point 17 years ago when they studied the effects of chlorpromazine on ICS and escape from experimenter-delivered brain stimulation. They found that chlorpromazine was more effective in disrupting ICS than in blocking escape from the brain stimulation and proposed that chlorpromazine acted against a neural system that controls operant or "voluntary" behavior, leaving relatively intact another system that controls respondent or "involuntary" behavior. The authors also pointed out that "the self-stimulation response, like the avoidance response, comes from the animal, as though caused by an internal program; it is not elicited by some specific change in the environmental stimulation. Escape on the other hand, is elicited by the onset of the noxious stimulus" (p. 402). Given these observations it becomes apparent that the measurement of escape latencies in the rate-free ICS paradigm is not an adequate control for drug-induced performance deficits, particularly when these may involve selective impairment of initiation of operant or "voluntary" behavior.

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Stinus & Thierry (24) implicated NA systems in the maintenance of ICS obtained from electrodes in the ventral tegmental area by showing that the reduction in self-stimulation produced by α-methyltyrosine could be reversed by oral administration of DL-threo-3,4-dihydroxyphenylserine (DOPS), a nonphysiological precursor that can be decarboxylated to form NA. These results were interpreted as strongly suggesting that a central NA pathway was activated by electrodes in this region and that this pathway was involved in ICS. However, although the DOPS did restore ICS, under the experimental conditions used it failed to restore central NA levels. This raises the possibility that the DOPS restoration of ICS was mediated by effects unrelated to NA. Alternatively, small increases in NA levels in certain critical regions of the brain may have occurred that were not detected in the whole brain assay. However, recent evidence has indicated that DOPS-induced restoration of behavior cannot be used to implicate NA as opposed to DA mediation of the behavior in α-methyltyrosine-treated animals. Specifically, Iversen (25) has shown that NA can stimulate DA receptors in the striatum. Because the striatum contains high levels of L-aromatic acid decarboxylase, DOPS could be decarboxylated to form NA which in turn could stimulate striatal DA receptors. Thus, it would appear at least theoretically possible for DOPS to restore a behavior in α-methyltyrosine-treated animals whose maintenance normally depended upon DA rather than NA.

There are a number of neurochemical and neurophysiological studies that have been interpreted as being consistent with the NA hypothesis. Stein & Wise (26) for example implanted rats with chronic push-pull cannulae in the lateral hypothalamus or amygdala and with ICS electrodes in the medial forebrain bundle. The animals were tested for ICS and rewarding sites were classified as those supporting self-stimulation at rates of 1000 or more responses per hour. Unanesthetized animals were then injected intraventricularly with ^{3}H-NA, and the effect of experimenter-delivered brain stimulation on radioactivity in the push-pull perfusate was measured. Stein & Wise found that electrical stimulation at most of the rewarding sites increased radioactivity in the perfusate whereas nonrewarding brain stimulation did not. Some sites classified as rewarding (10/34) did not increase the radioactive content of the perfusate but these sites tended to yield lower self-stimulation rates than did the positive-releasing group. In other experiments *d*-amphetamine was found to increase radioactivity in amygdaloid but not in lateral hypothalamic perfusates. The authors concluded that the release of NA is responsible, at least in part, for the facilitation of behavior caused by rewarding brain stimulation. In a similar experiment, Holloway (27) replicated these observations and also found that serotonin as well as NA was released in perfusate from amygdala by rewarding brain stimulation of the lateral hypothalamus. Nonrewarding brain stimulation tended to decrease release of NA and serotonin, while sensory stimulation had no effect. Segal & Bloom (28) found that stimulation through ICS electrodes in the LC monosynaptically inhibited the unit activity of pyramidal cells in the hippocampus, whereas electrodes in the same region that did not support ICS had a less pronounced effect. Various treatments known to disrupt ICS, including chlorpromazine, α-MT, DDC, and intracisternal 6-OHDA also blocked the effects of LC stimulation on the hip-

pocampal units. It was concluded that the reinforcing properties of LC stimulation and the inhibitory effects of this stimulation on hippocampal units were mediated by catecholamines. However, because many other stimuli (auditory, pain) also inhibited hippocampal units, the authors argued that it was unlikely that inhibition of these units, per se, exclusively mediated the reward process. Other workers have examined the effects of rewarding brain stimulation on NA utilization and metabolism. For example, Arbuthnott et al (29) found that experimenter-delivered stimulation through electrodes in the ventral NA bundle, which had previously been shown to support ICS, increased the rate of depletion of NA in the hypothalamus and preoptic area after α-MT. Similarly, Stinus et al (30) observed that imposed stimulation through ICS electrodes in the ventral tegmental area accelerated NA depletion in brain stem, hypothalamus, hippocampus, and cortex after α-MT or FLA-63. Furthermore, utilization and turnover of intracisternally administered ^{3}H-NA was increased in these same brain regions of self-stimulating animals. Anlezark et al (31) reported that self-stimulation obtained from electrodes in the LC, the origin of the dorsal NA bundle, increased ipsilateral cortical concentrations of the NA metabolite, 4-hydroxy-3-methoxy-phenylglycol. Stimulation of anesthetized animals produced similar increases but only if the electrode site had previously been shown to support ICS.

Many of the above, as well as other similar studies have been interpreted as showing that there are causal relationships between electrical stimulation of NA neurons, self-stimulation behavior, and central reward mechanisms. However, as was discussed with respect to the anatomical mapping studies, these kinds of data are purely correlational and hence no causal implications can logically be drawn. For example, many of the above studies utilized electrode placements directly in, or in the vicinity of the MFB. It is known that NA axons ascend in the MFB and therefore electrical stimulation of the MFB might well be expected to increase the release and utilization of NA in the terminals of these fibers. However, to ascribe the reinforcing properties of ICS to this one type of fiber system, out of all the ascending and descending systems in and around the MFB (see 32), cannot be justified on the basis of currently available information. Indeed, the lesion studies reviewed below suggest that the correlations between central NA mechanisms and ICS are spurious and lack causal significance.

Lesion Studies

If ICS electrodes are aimed at a group of NA neurons or their axons which serve essential and critical functions in ICS and reward processes, then lesions of these neurons should eliminate or greatly attenuate the self-stimulation behavior. The NA hypothesis has been evaluated in this manner on a number of occasions over the past few years and the results of adequately controlled experiments have been uniformly negative. Clavier & Routtenberg (33) trained rats to barpress for ICS from electrodes implanted in the dorsal tegmental NA projection, the major ascending NA fiber system originating in the LC. After stable baseline performance had been obtained, the animals received ipsilateral or bilateral electrolytic lesions of the LC. The lesions, w

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cortical NA by 80% or more, failed to attenuate ICS. These data argue against a necessary role of the projections of the LC in midbrain ICS. In a subsequent experiment, Clavier et al (34) implanted ICS electrodes in the locus coeruleus and then examined the effects of bilateral 6-OHDA lesions of the dorsal NA bundle on self-stimulation. Again, these lesions failed to have any effect on ICS despite reducing hippocampal and cortical NA by 97%. Nor did these lesions have any effect on the facilitation of responding for ICS produced by *d*-amphetamine. In another test of the NA hypothesis, van der Kooy et al (35) implanted ICS electrodes in the hippocampus, a structure thought to receive its NA innervation exclusively from cells in the locus coeruleus. 6-OHDA lesions of the dorsal tegmental NA bundle reduced hippocampal NA to 3% of control levels without having any significant effects on ICS or its potentiation by *d*-amphetamine (36).

The results of these experiments appear irreconcilable with the view that the ascending NA projections of the locus coeruleus serve a necessary or exclusive function in the rewarding properties of ICS. However, it could be argued that the few NA terminals that survived the lesions together with the development of postjunctional supersensitivity (37) may have been sufficient to maintain the self-stimulation behavior. This appears unlikely because similar 6-OHDA lesions of the dorsal tegmental NA bundle have been shown to produce a variety of changes in other behaviors (38, 39). It is not apparent, therefore, how denervation supersensitivity could mediate complete recovery and normal behavioral function in ICS, and yet fail to do the same for behaviors in which a role for the dorsal NA bundle has been demonstrated.

Ritter & Stein (4) and Belluzzi et al (41) have suggested that axons of the ventral NA bundle support self-stimulation. The former was a mapping study and the interpretative limitations associated with this approach have already been discussed. In the latter experiments, Belluzzi et al (41) attempted to assess the role of the ventral NA bundle in ICS obtained from electrodes in the substantia nigra, an area through which some of the axons of the ventral NA bundle are thought to pass. These authors observed that ipsilateral knife-cuts or 6-OHDA injections caudal to the nigral ICS electrodes significantly decreased self-stimulation when compared with cuts or injections contralateral to the electrodes. The knife-cuts and 6-OHDA injections reduced forebrain NA levels by 45% and 75% respectively. Nigral ICS was also disrupted by injections of DDC; this disruption could be reversed by intraventricular injections of NA. These findings suggested that NA fibers of passage play an essential role in the mediation of substantia nigra self-stimulation. However, there are experimental limitations in this study that cast doubt on this interpretation. First, knife-cuts would lesion all ascending and descending systems in the mesencephalon; therefore to ascribe special significance to the NA axons is unwarranted. Second, although intraventricular NA injections reinstated ICS after systemic injections of DDC, the experiments failed to provide evidence that this was specifically due to a restoration of the rewarding properties of ICS as opposed to a reversal of the hypoactivity and illness that this drug has been shown to produce (41, 42). Third, with respect to the finding that 6-OHDA lesions decreased nigral ICS, Belluzzi et al used very high concentrations (10 $\mu g/\mu l$) of 6-OHDA which

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almost certainly produced considerable nonspecific damage. Indeed, in an attempt to replicate this observation Clavier et al (59) also injected 6-OHDA into the ventral NA bundle of animals with nigral ICS electrodes. In this experiment, amounts of 6-OHDA (4 μg/2 μl) were injected that are thought to produce minimal nonspecific damage. These injections, which resulted in equal or greater depletions of NA than those obtained by Belluzzi et al, did not attenuate nigral ICS at any time after the lesions. These results indicate that the effects observed by Belluzzi et al after knife-cuts and 6-OHDA injections were due to the damage to non-noradrenergic elements ascending or descending in the vicinity of the lesions.

Conclusion

On the basis of the evidence reviewed above, it is evident that the hypothesis suggesting that NA neurons are the exclusive mediators of self-stimulation reward must be rejected. The anatomical data are correlative and of limited value because of the widespread distribution of NA and positive ICS sites. The behavioral pharmacological studies that have suggested an involvement of NA have failed to demonstrate specific effects on reinforcement processes as opposed to other actions such as sedation, hypoactivity, and sickness which could also impair responding for ICS. The pharmacological studies that have used DBH inhibitors with fewer side effects than disulfiram or DDC, and yet inhibit the enzyme equally well, have produced mainly negative results. Experiments that have shown changes in NA metabolism during electrical stimulation of positive ICS sites have generated interesting correlations, but there is no evidence that these correlations reflect causal and necessary relationships between ICS and stimulation of NA neurons. Indeed, lesion experiments have shown that it is possible to induce nearly complete damage to ascending and descending (17, 34) NA systems without influencing self-stimulation behavior. Finally, if central NA systems did serve some critical function in naturally occurring reinforcement processes, then damage to these systems might be expected to produce profound learning deficits. However, it is well documented that rats do not show any impairments in a wide variety of learning tasks after extensive lesions of ascending NA systems (38, 43). These observations indicate that the NA systems cannot be considered as the exclusive mediators of central reinforcement processes. It remains possible of course that these systems participate in these processes in some nonessential, nonexclusive manner; however, a demonstration of even this kind of limited involvement awaits future research.

DOPAMINE AND INTRACRANIAL SELF-STIMULATION

Anatomy

Unlike the ubiquitous presence of NA throughout most of the brain, dopamine has a more discrete distribution. Because ICS can be obtained from a number of regions that have no known dopaminergic innervation (e.g. dorsal tegmentum, hippocampus, medulla oblongata), the hypothesis that direct stimulation of DA neurons by ICS electrodes exclusively mediates the reinforcing properties of self-stimulation can

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be rejected on purely anatomical grounds. This, however, does not preclude the possibility that stimulation of central DA neurons may have reinforcing effects, and based on a correspondence between positive ICS sites and the organization of central DA perikarya, Crow (4) has suggested that self-stimulation can result from activation of DA cells in the zona compacta of the substantia nigra (SNC) and the ventral tegmental area (VTA). Cells in these two regions give rise to the two major ascending DA systems in the brain, the nigrostriatal projection (NSP) and the mesolimbic projection respectively. Although observations that ICS can be obtained in the vicinity of perikarya, axons, and terminals of these neurons are consistent with this hypothesis, these correlations can by no means be considered as proving a dopaminergic mediation (4, 44–49).

Pharmacology

There is a considerable pharmacological literature concerning the effects of compounds that selectively block DA receptors on self-stimulation. In an elegant series of experiments Wauquier & Niemegeers (50) showed that haloperidol, pimozide, and pipamperone decreased ICS obtained from lateral hypothalamic electrodes in a dose-related manner. Similar observations have since been made in other laboratories (19, 46, 51), and there is therefore widespread agreement that pharmacological interference with central DA mechanisms can impair self-stimulation behavior. However, the immediate question that arises from these studies is, to what extent does the reduced response rate for ICS reflect a reduction in the reinforcing value of the brain stimulation as opposed to an impaired ability to perform the operant response? This question is particularly relevant in the case of DA systems because these systems are known to serve important motor functions. Wauquier & Niemegeers (50) favored the motor-deficit interpretation because they pointed out that various learned responses are disrupted by about the same dose levels of neuroleptics. They concluded that these drugs may interfere "with a general system involved in the output of fixed learned behavior, triggered by various positive and negative reinforcements." The reinforcement vs motor-deficit question has since been investigated by several other laboratories. Rolls et al (19) examined the effects of spiroperidol on operant responding for ICS, food, or water. This drug was found to produce a dose-dependent decrease in response rate from electrodes in the VTA, hippocampus, anterior hypothalamus, septal area, and nucleus accumbens. Interestingly, spiroperidol was just as effective in decreasing the self-stimulation rate from electrodes in an area that did not contain DA neurons (hippocampus) as it was in the other areas where DA neurons were probably directly stimulated. Similarly, Phillips et al (46) have shown that pimozide and haloperidol decrease ICS from the dorsal tegmentum, a nondopaminergic site, and from the dopaminergically innervated nucleus accumbens equally well. Rolls et al (19) then showed that at the doses that impaired ICS, spiroperidol also produced severe disruptions of barpressing for food and water. These same doses had only minor effects on eating and drinking in the home cage after 24 hr of food and water deprivation, indicating that the drug did not decrease hunger or thirst. The authors concluded that an impairment of motor

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function could account for the effects of dopamine-receptor blockade on self-stimulation and that the impairment appeared to increase as a function of response complexity.

In a subsequent experiment from the same laboratory, Mora et al (51) trained rats either to barpress or lick a tube for ICS in the lateral hypothalamus. Spiroperidol produced an identical dose-related decrease in either barpressing or licking for ICS. At a dose of 0.062 mg/kg the drug reduced both kinds of response by about 90%. Previously, however, Rolls et al (19) had shown that a higher dose of the drug (0.1 mg/kg) had negligible effects on licking for water in water-deprived animals. The authors argued therefore that the decrease in licking for brain stimulation was not due to a motor impairment and that DA receptors may be involved in brain stimulation reward. However, neither Mora et al (51) nor Rolls et al (19) reported the baseline rates of licking for water or ICS, and as is discussed below, if the baselines were not the same, this could account for the differential effects of spiroperidol on responding for these two reinforcers. Even if the baseline rates were similar, other interpretative problems exist, and one of these relates to the level of motivation of the animal in response to two different reinforcers. Thus, although an animal may respond for ICS and water at similar rates, it is conceivable that the organism may be more motivated to respond for one reinforcer than the other. If a neuroleptic did produce a subtle motor deficit, then the impairment would possibly be detectable when responding for ICS but might be masked in water-reinforced responding if the organism was relatively more highly motivated for water than for ICS. Perhaps preference tests for ICS and water would serve to resolve this problem.

Fibiger et al (20) reported that pimozide and haloperidol decreased operant response rates both for ICS and food, but in these experiments the relative inhibitory effects of the neuroleptics were significantly greater on ICS than on food-reinforced behavior. At first glance, this might be taken to indicate a somewhat selective effect of these drugs on brain stimulation reward; however, as was noted by the authors, the response rate for the ICS was about 6 times higher than it was for food. Since baseline response rates are known to influence the effects of drugs markedly (50, 52), it is possible that this variable rather than a selective effect on brain stimulation reward was responsible for these observations. To establish a control for this possibility, Fibiger et al (20) trained animals to respond for brain stimulation or food on a variable interval 60 sec schedule. Rates of responding for the two reinforcers did not differ significantly on this schedule, and under these circumstances, haloperidol affected bar pressing for ICS and for food to a similar extent. The doses of pimozide and haloperidol that reduced responding for food did not affect 22-hr deprivation induced feeding in the home cage, suggesting that the impaired response was not due to decreased hunger or to decreased reinforcing properties of the food. The authors suggested that neuroleptics decrease response rates for ICS primarily by impairing the function of certain DA systems that are critically involved in the initiation or maintenance of operant behavior rather than by interfering with central reward processes.

While the above experiments are consistent with the view that central DA systems serve important functions in motor behavior, they do not of course exclude the

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possibility that these projections also play a role in brain stimulation reward. However, it has become apparent that demonstration of such a role requires techniques that clearly differentiate between the effects of drugs on motor function and central reinforcement processes. Liebman & Butcher (53, 54) attempted to resolve this problem using a number of different techniques. In the first experiments they showed that pimozide decreased barpressing for ICS obtained from electrodes in the lateral hypothalamus or mesencephalic central gray (53). These effects were observed at below maximum response rates produced by low levels of electrical stimulation. They then showed that the decrease in the rate of responding produced by the lower dose of pimozide could be reversed by increasing the electrical current, and concluded therefore that the animals were motorically capable of responding for ICS and that the effect of pimozide was due to a decrease in reward value rather than a motor deficit. However, increasing the current also increased the baseline (nondrug) rate of responding, and inasmuch as it is known that the effects of neuroleptics on ICS can vary as a function of the baseline response rate (20, 50), Liebman & Butcher's observations cannot be regarded as unequivocal evidence for a motivational deficit. In the second study by these authors (54), which used a rate-free measure of ICS, it was found that pimozide decreased the amount of time spent on the "ON" side of the apparatus significantly more in animals with electrodes in the substantia nigra than in rats with lateral hypothalamic electrodes. On the basis of these and other data obtained with apomorphine and amphetamine, it was suggested that ICS in the substantia nigra had DA substrates, whereas in the lateral hypothalamus both NA and DA substrates were involved; however, pimozide also significantly decreased the number of crossings and locomotor activity in the ICS apparatus, and as discussed above, deficits in response initiation or maintenance could also produce changes in performance in the rate-free paradigm.

In a novel and ingenious approach to the problem of discriminating between motor and reinforcement variables in interpreting the effects of neuroleptics on ICS, Fouriezos & Wise (55) reasoned that if these drugs blocked the reinforcing value of the brain stimulation they should produce an extinction curve, similar to that seen when the electrical current is turned off in a well-trained animal. Under this condition, animals initially respond at normal rates, and only after several responses fail to be reinforced does the response rate decline. Thus, it was argued that a drug that attenuates the reward value of stimulation would cause a reduced response rate only after an initial period of normal responding, whereas a drug that produced motor deficits would result in a reduced but steady response rate throughout the session. The authors found that in 5 out of the 7 rats, pimozide resulted in an initially normal rate of responding that was followed by a rapid decline in response rate. These data led the authors to conclude that pimozide decreases ICS by blocking the reinforcing value of the stimulation rather than by producing motor impairment. An alternate explanation might be that pimozide increased motor fatigue in these animals and this caused the animals to cease responding after a short time. In this regard, it is of considerable interest that parkinsonian patients, in whom the DA nigrostriatal projection has degenerated, often report increased motor fatigability (56). Fouriezos and Wise attempted to set up a control for this possibility by blocking access to the

ICS lever for 10 min in one rat that had ceased responding after pimozide. On removing the barrier, this animal briefly resumed responding at a high initial rate. The authors inferred that the animals were capable of responding in the latter part of the session and that motor deficits therefore could not explain the lack of responding during that period. However, it would also seem possible that the auditory and visual stimuli associated with the removal of the barrier may have aroused the animal sufficiently to resume responding for a short period of time until motor fatigue again disrupted responding. Although these results are of considerable interest, further work appears necessary before the effects of neuroleptics on the pattern of responding for ICS can confidently be ascribed to a block in the reward value of the brain stimulation.

A new approach in examining the effects of neuroleptics on ICS has been to administer these compounds directly into discrete regions of brain via intracerebral cannulae. In one such study, Broekkamp & van Rossum (57) implanted rats with ICS electrodes in the VTA. Injections of haloperidol into the neostriatum ipsilateral or contralateral to the ICS electrode reduced ICS by 30% and 38% respectively. Although the authors ascribed the effects of the contralateral injections to a "general motivational depression," these findings would appear to be more compatible with a motor-deficit hypothesis. That is, if the neuroleptic specifically blocked the reinforcing properties of brain stimulation, injections ipsilateral to the electrode would be expected to have greater effects on ICS than contralateral injections. If, however, these treatments simply impaired the operant response, contralateral and ipsilateral injections would be expected to have similar effects. In another study, Mora and co-workers (51) found that intracerebral injections of spiroperidol had greater effects on lateral hypothalamic ICS after injection into the ipsilateral nucleus accumbens when compared with globus pallidus injections. The pallidal injections produced greater motor deficits, as assessed by a battery of simple neurological tests; therefore, the authors suggested that DA receptors in the nucleus accumbens are involved in ICS in a way that is due not just to their role in motor behavior. It remains possible of course that injections into these different regions produced qualitatively different motor impairments from those measured in the neurological test battery, and the authors conceded that a different and subtle type of motor deficit might account for the effects of spiroperidol on ICS. Unfortunately, the ipsilateral-contralateral paradigm was not utilized in this study. In a subsequent paper, Mora et al (58) examined the effects of intracerebral injections of spiroperidol on ICS obtained from a number of brain regions in monkeys. The effects of spiroperidol varied with injection and ICS sites. Generally, amygdala ICS seemed most sensitive and the locus coeruleus ICS least sensitive to the effects of spiroperidol regardless of the injection site. The response rate for glucose was not affected by any of the intracerebral spiroperidol injections. Again the authors concluded that decreased self-stimulation found at some sites could not be explained by a single effect such as motor impairment or sedation. While this conclusion may be justified, it is difficult to comment further on this work because all of the drug effects were reported as a percentage of the control response rate and the baseline rates were not stated. If, however, the response rates varied at the different ICS sites, this would complicate the interpretation of these findings.

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Recent lesion studies have demonstrated that the stimulant effects of *d*-amphetamine on ICS are mediated by central DA neurons (15, 59). If future research confirms these observations, a considerable body of evidence on the effects of amphetamines on ICS can be viewed as supporting a role for DA in self-stimulation. Whether the amphetamine-induced facilitation in responding for ICS is due to a potentiation of the reinforcing properties of the brain stimulation, or whether it is due to a more general activation of motor output cannot be answered by most studies. However, some early experiments on the effects of amphetamine on ICS suggest that this drug does in fact have direct effects on the brain stimulation reward. Stein & Ray (60) tested rats in a situation in which each response produced a stepwise decrease in ICS current. By pressing a second lever the animals could reset the current to the highest level. The authors found that *d,l*-amphetamine decreased the current at which animals would press the reset lever. These data suggest that the drug decreased the brain stimulation reward thresholds. In a subsequent study, Stein (2) obtained very low response rates for ICS by using current intensities well below those producing maximal rates of responding. In this situation *d*-methamphetamine greatly facilitated the response rate. If, however, the ICS current was turned off at the time of the methamphetamine injection, no increase in rate occurred. These results clearly show that the facilitation in responding produced by methamphetamine cannot be explained in terms of a nonspecific increase in operant response rate. Rather, the data are consistent with the hypothesis that amphetamine can decrease ICS reward thresholds. Using a rate-free paradigm, Poschel & Ninteman (61) found that the amount of time spent in the part of the apparatus in which brain stimulation was delivered increased as a function of ICS current intensity. They then demonstrated that methamphetamine significantly increased the amount of time spent in that part of the apparatus during low current stimulation. It is difficult to imagine how an increase in motor activity could account for these observations, and the authors' conclusion that methamphetamine increased the rewarding value of brain stimulation appears well justified.

The differential effects of *d*- and *l*-amphetamine on ICS have been taken to implicate DA and NA neurons in self-stimulation.
that *d*- and *l*-amphetamine were approximately equipotent at increasing ICS response rates when electrodes were aimed at a "dopaminergic" site such as the SNC, whereas the *d*-isomer was much more effective than *l*-amphetamine at increasing ICS from a "noradrenergic" site in the lateral hypothalamus. These observations have since been confirmed and extended by other laboratories (62–64). The behavioral results appeared to correlate remarkably well with initial neurochemical findings which indicated that the two isomers were approximately equally effective in inhibiting DA uptake by DA neurons, while *d*- was substantially more potent than *l*-amphetamine in inhibiting NA uptake into NA neurons (65). However, three other laboratories failed to confirm these neurochemical observations (see 46), and in fact found exactly opposite effects, i.e. equipotentiality of the isomers on NA uptake, and more potent effects of *d*- than of *l*-amphetamine on DA uptake. These latter findings, together with the lack of unequivocal evidence for any involvement of NA systems in ICS (see above), leaves the significance of the differential effects of *d*- and *l*-amphetamine unknown. It is noteworthy, however, that many other

drugs and treatments, including tranylcypromine, chlorpromazine, apomorphine, thymoxamine, chlordiazepoxide, hormones, and food deprivation are known to have different effects on ICS obtained from different regions of the brain (7, 62, 63, 65). As with the amphetamine isomers, the significance of these observations with respect to the neural substrates of brain stimulation reward await future research.

Lesion Studies

Inasmuch as the pharmacological literature has provided a degree of support for a role of DA systems in brain stimulation reward, the question arises as to whether stimulation of these systems exclusively mediates reward when electrodes are implanted in their vicinity. Breese et al (67) first showed that intraventricular injections of 6-OHDA, which produced extensive lesions of central DA neurons, resulted in long-term reductions in ICS. These observations were subsequently confirmed and extended by others (15, 68). Although these studies implicate DA systems in some aspects of ICS behavior, they do not permit a distinction to be made between lesion-induced motor impairments and possible changes in the reinforcing value of the brain stimulation. Phillips et al (47) attempted to address this question by implanting ICS electrodes in the striatum of rats. After ICS rates had stabilized, 6-OHDA lesions were placed in the SNC either ipsilaterally or contralaterally to the striatal electrodes. The contralateral lesions were used to control for possible motor impairments. The lesions reduced striatal DA by approximately 95%. ICS remained at less than 10% of prelesion rates in the ipsilateral group, whereas responding in the contralateral group gradually recovered to reach 72% of control values 28 days postoperatively. The differential effects of ipsilateral and contralateral SNC lesions were interpreted to indicate that in addition to producing motor deficits in operant responding, reduction of striatal DA was accompanied by a loss of brain stimulation reward obtained from this structure.

A similar approach has been used to determine the role of the dopaminergic NSP in brain stimulation reward obtained from electrodes in the SNC (59). In these experiments, ipsilateral 6-OHDA lesions of the NSP resulted in large but temporary reductions in ICS which returned to preoperative rates 8–10 days after the lesions. In this instance, however, NSP lesions contralateral to the electrodes had effects identical with the ipsilateral lesions. It was concluded therefore that the deficits in responding for ICS produced by unilateral NSP lesions could be accounted for in terms of transient motor deficits produced by these lesions and that this dopaminergic projection was not the exclusive or essential neuronal substrate mediating the reinforcing properties of nigral ICS. The observation that nigral ICS could still be obtained despite nearly complete destruction of the ascending DA projections implicates other presently unspecified neuronal systems in the vicinity of the SNC. However, Clavier & Fibiger (59) also noted that it would be incorrect to conclude that the dopaminergic projections are irrelevant to nigral ICS. This conclusion was based on the observation that facilitation of nigral ICS by *d*-amphetamine was abolished by the ipsilateral but not the contralateral NSP lesions. It was therefore suggested that this facilitation of responding was due to the additive effect of electrical stimulation and *d*-amphetamine on the release of DA in the terminal

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regions of the ascending DA systems. In a similar vein, Cooper et al (15) have shown that selective depletion of brain DA by intraventricular 6-OHDA injections significantly reduces the rate-increasing effects of *d*-amphetamine on lateral hypothalamic ICS. In another study, Ornstein & Huston (69) found that unilateral injections of 6-OHDA into the substantia nigra disrupted ICS equally in the ipsilateral and contralateral lateral hypothalamus. Furthermore, bilateral 6-OHDA injections abolished ICS when lever-pressing was the criterion but not when more simple motor responses were used as operants. The authors concluded that the NSP is not critically involved in the reward process, and that attenuation of ICS by the 6-OHDA lesions was most likely due to disruption of operant performance.

Conclusion

Anatomical considerations preclude the possibility that direct stimulation of DA systems exclusively mediates ICS. This does not rule out an involvement of these systems under some circumstances, and there exist pharmacological data that are consistent with such a role. However, interpretation of these data is difficult because of the well-established involvement of DA projections in motor output. In attempting to evaluate drug-induced changes in brain stimulation reward, it therefore becomes necessary to provide rigorous controls for possible modifications in motor performance. To date, experiments utilizing specific DA receptor blocking agents have not provided unequivocal evidence that supports a dopaminergic mediation of ICS reward. However, certain amphetamine-induced changes in ICS are most likely due to direct effects on brain stimulation reward, and it is probable that these actions of amphetamine have dopaminergic substrates. Lesion studies have shown that DA may mediate the reinforcing properties of ICS in some structures (e.g. striatum). In other regions such as the lateral hypothalamus and SNC, DA projections appear to serve a nonessential, perhaps modulatory function in ICS, and other noncatecholaminergic systems are almost certainly involved. In summary then, there is preliminary evidence for a limited role of DA systems in brain stimulation reward. Much additional work is required to define the nature and extent of this involvement.

OTHER EXPERIMENTAL PARADIGMS

On reviewing the above evidence, it is possible to argue that the problem with the CA hypothesis is not so much with the hypothesis itself but rather with the experimental technique that has most often been used to examine it, namely ICS. Stimulating electrodes will influence many of the neural elements in their vicinity and if, as appears to be the case, there exist multiple and perhaps redundant pathways which can mediate ICS, then it is not surprising that researchers have experienced considerable difficulty in defining the role of specific CA systems. An alternative to this approach has recently been developed that appears to provide strong support for a role of DA in at least some central reinforcement processes. It has been known for some time that animals will self-administer certain psychoactive drugs, but only recently have attempts been made to define the pharmacological substrates of this

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behavior. While space does not permit a detailed review of this emerging field, a few observations require comment. Yokel & Wise (70) demonstrated that low doses of specific DA receptor blocking agents such as pimozide and (+)-butaclamol increased the rate of responding for intravenous *d*-amphetamine in rats. The results suggested that low doses of the neuroleptics reduced the reinforcing properties of amphetamine by partial blockade of DA receptors, so that higher doses of amphetamine were required to maintain the same reinforcing effects. Injections of phentolamine, phenoxybenzamine, or propanolol had variable effects on responding and these effects did not appear to be due to blockade in the reinforcing properties of amphetamine. Rather, when effective, these drugs produced performance deficits. These results suggest that DA but not NA mechanisms are involved in the reinforcing effects of amphetamine. Roberts et al (71) subsequently reported similar findings for intravenous self-administration of cocaine. Furthermore, these authors reported that 6-OHDA lesions of the nucleus accumbens produced long-term decreases in cocaine self-administration while lesions of the ascending NA projections were without effect. These data again point to an involvement of central DA but not of NA neurons in the reinforcing properties of these stimulant drugs.

Further preliminary, but no less intriguing evidence can be found in human psychopharmacological studies. It is well known that drugs such as amphetamine and cocaine are capable of producing global euphoric sensations in man. On this basis it can be hypothesized that these agents may have effects on neuronal systems that may normally be involved in primary positive reinforcement mechanisms. It is of considerable interest therefore that α-MT pretreatment has been reported to block the euphoric effects of amphetamine in man (72). While the α-MT study could not discriminate between a possible DA or NA mediation of this effect, in a subsequent study by Gunne et al (73) pimozide pretreatment reduced amphetamine euphoria whereas neither phenoxybenzamine nor propranolol had this effect. The human studies, like ICS and intravenous self-administration experiments in animals, therefore point to an involvement of central DA but not of NA systems in reward. Given some of the limitations of the ICS technique, it is hoped that future research using these other paradigms may further delineate the role of central DA projections in positive reinforcement.

CONCLUSION

Recent data and the issues raised in this review indicate that the NA hypothesis of brain stimulation reward is untenable. It remains possible that central NA neurons participate in certain reinforcement processes in a nonessential and nonexclusive manner, but there is currently no evidence to support even such a limited role. A better case can be made for an involvement of central DA neurons in reinforcement. However, ICS studies clearly argue that brain stimulation reward is not exclusively dependent upon these DA systems and that noncatecholaminergic systems exist that can maintain this behavior. It will be the task of future research to identify the relevant noncatecholaminergic systems and to delineate the precise role of central DA systems in positive reinforcement.

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Literature Cited

1. Olds, J., Milner, P. 1954. Positive reinforcement produced by electrical stimulation of septal area and other regions of rat brain. *J. Comp. Physiol. Psychol.* 47:419–27
2. Stein, L. 1964. Self-stimulation of the brain and the central stimulant action of amphetamine. *Fed. Proc.* 23:836–50
3. Stein, L. 1968. Chemistry of reward and punishment. In *Psychopharmacology. A Review of Progress,* ed. D. H. Efron, pp. 105–23. Washington DC: GPO
4. Crow, T. J. 1972. Catecholamine-containing neurons and electrical self-stimulation. I. A review of some data. *Psychol. Med.* 2:414–21
5. German, D. C., Bowden, D. M. 1974. Catecholamine systems as the neural substrate for intracranial self-stimulation: A hypothesis. *Brain Res.* 73:381–419
6. Olds, M. E., Olds, J. 1963. Approach-avoidance analysis of rat diencephalon. *J. Comp. Neurol.* 120:259–95
7. Poschel, B. P. H. 1969. Mapping of rat brain for self-stimulation under monamine oxidase blockade. *Physiol. Behav.* 4:325–31
8. Crow, T. J. 1970. Enhancement by cocaine of intra-cranial self-stimulation in the rat. *Life Sci.* 9:375–81
9. Stein, L. 1962. Effects and interactions of imipramine, chlorpromazine, reserpine and amphetamine on self-stimulation: Possible neurophysiological basis of depression. In *Recent Advances in Biological Psychiatry,* ed. J. Wortis, pp. 288–308. New York: Plenum
10. Cooper, B. R., Black, W. C., Paolino, R. M. 1971. Decreased septal-forebrain and lateral hypothalamic reward after alpha methyl-p-tyrosine. *Physiol. Behav.* 6:425–29
11. Wise, C. D., Stein, L. 1969. Facilitation of brain self-stimulation by central administration of norepinephrine. *Science* 163:299–301
12. Roll, S. K. 1970. Intracranial self-stimulation and wakefulness: Effect of manipulating ambient brain catecholamines. *Science* 168:1370–72
13. Rolls, E. T., Kelly, P. H., Shaw, S. G. 1974. Noradrenaline, dopamine and brain stimulation reward. *Pharmacol. Biochem. Behav.* 2:735–40
14. Lippa, A. S., Antelman, S. M., Fisher, A. E., Canfield, D. R. 1973. Neurochemical mediation of reward: A significant role for dopamine? *Pharmacol. Biochem. Behav.* 1:23–28
15. Cooper, B. R., Cott, J. M., Breese, G. R. 1974. Effects of catecholamine-depleting drugs and amphetamine on self-stimulation of brain following various 6-hydroxydopamine treatments. *Psychopharmacologia* 37:235–48
16. Stinus, L., Thierry, A. M., Cardo, B. 1976. Effects of various inhibitors of tyrosine hydroxylase and dopamine beta-hydroxylase on rat self-stimulation after reserpine treatment. *Psychopharmacologia* 45:287–94
17. Breese, G. R., Cooper, B. R. 1975. Relationship of dopamine neural systems to the maintenance of self-stimulation. In *Neurotransmitter Balances Regulating Behavior,* ed. E. F. Domino, J. M. Davis, pp. 37–56. Ann Arbor
18. Franklin, K. B. J., Herberg, L. J. 1975. Self-stimulation and noradrenaline: Evidence that inhibition of synthesis abolishes responding only if the 'reserve' pool is dispersed first. *Brain Res.* 97:127–32
19. Rolls, E. T., Rolls, B. J., Kelly, P. H., Shaw, S. G., Wood, R. J., Dale, R. 1974. The relative attenuation of self-stimulation, eating and drinking produced by dopamine-receptor blockade. *Psychopharmacologia* 38:219–30
20. Fibiger, H. C., Carter, D. A., Phillips, A. G. 1976. Decreased intracranial self-stimulation after neuroleptics or 6-hydroxydopamine: Evidence for mediation by motor deficits rather than by reduced reward. *Psychopharmacology* 47:21–27
21. Herz, A. 1960. Drugs and the condi-

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tioned avoidance response. *Int. Rev. Neurobiol.* 2:229–77
22. Olds, J., Travis, R. P. 1960. Effects of chlorpromazine, meprobamate, pentobarbital and morphine on self-stimulation. *J. Pharmacol. Exp. Ther.* 128: 397–404
23. Hunt, G. E., Atrens, D. M., Chesher, G. B., Becker, F. T. 1976. α-Noradrenergic modulation of hypothalamic self-stimulation: Studies employing clonidine, L-phenylephrine and α-methyl-p-tyrosine. *Eur. J. Pharmacol.* 37:105–11
24. Stinus, L., Thierry, A. M. 1973. Self-stimulation and catecholamines. II. Blockade of self-stimulation by treatment with alpha-methylparatyrosine and the reinstatement by catecholamine precursor administration. *Brain Res.* 64:189–98
25. Iversen, L. L. 1975. Dopamine receptors in the brain. *Science* 188:1084–89
26. Stein, L., Wise, C. D. 1969. Release of norepinephrine from hypothalamus and amygdala by rewarding medial forebrain bundle stimulation and amphetamine. *J. Comp. Physiol. Psychol.* 67: 189–98
27. Holloway, J. A. 1975. Norepinephrine and serotonin: Specificity of release with rewarding electrical stimulation of the brain. *Psychopharmacologia* 42:127–34
28. Segal, M., Bloom, F. E. 1976. The action of norepinephrine in the rat hippocampus. III. Hippocampal cellular responses to locus coeruleus stimulation in the awake rat. *Brain Res.* 107:499–511
29. Arbuthnott, G., Fuxe, K., Ungerstedt, U. 1971. Central catecholamine turnover and self-stimulation behavior. *Brain Res.* 27:406–13
30. Stinus, L., Thierry, A. M., Blanc, G., Glowinski, J., Cardo, B. 1973. Self-stimulation and catecholamines. III. Effect of imposed or self-stimulation in the area ventralis tegmenti on catecholamine utilization in the rat brain. *Brain Res.* 64:199–210
31. Anlezark, G. M., Walter, D. S., Arbuthnott, G. W., Crow, T. J., Eccleston, D. 1975. The relationship between noradrenaline turnover in cerebral cortex and electrical self-stimulation through electrodes in the region of locus coeruleus. *J. Neurochem.* 24:677–81
32. Millhouse, O. E. 1969. A golgi study of the descending medial forebrain bundle. *Brain Res.* 15:341–63
33. Clavier, R. M., Routtenberg, A. 1976. Brain stem self-stimulation attenuated by lesions of medial forebrain bundle but not by lesions of locus coeruleus or the caudal ventral norepinephrine bundle. *Brain Res.* 101:251–71
34. Clavier, R. M., Fibiger, H. C., Phillips, A. G. 1976. Evidence that self-stimulation of the region of the locus coeruleus in rats does not depend upon noradrenergic projections to telencephalon. *Brain Res.* 113:71–81
35. van der Kooy, D., Fibiger, H. C., Phillips, A. G. 1977. Monoamine involvement in hippocampal self-stimulation. *Brain Res.* 136:119–30
36. Phillips, A. G., van der Kooy, D., Fibiger, H. C. 1977. Maintenance of intracranial self-stimulation in hippocampus and olfactory bulb following regional depletion of noradrenaline. *Neurosci. Lett.* 4:77–84
37. Zis, A. P., Fibiger, H. C. 1975. Functional evidence for postsynaptic supersensitivity of central noradrenergic receptors after denervation. *Nature* 256:659–61
38. Mason, S. T., Iversen, S. D. 1975. Learning in the absence of forebrain noradrenaline. *Nature* 258:422–24
39. Price, M. T. C., Fibiger, H. C. 1975. Ascending catecholamine systems and morphine analgesia. *Brain Res.* 99: 189–93
40. Ritter, S., Stein, L. 1974. Self-stimulation in the mesencephalic trajectory of the ventral noradrenergic bundle. *Brain Res.* 81:145–87
41. Belluzzi, J. D., Ritter, S., Wise, C. D., Stein, L. 1975. Substantia nigra self-stimulation: Dependence on noradrenergic reward pathways. *Behav. Biol.* 13:103–11
42. Roberts, D. C. S., Fibiger, H. C. 1976. Conditioned taste aversion induced by diethyldithiocarbamate (DDC). *Neurosci. Lett.* 2:339–42
43. Fibiger, H. C., Roberts, D. C. S., Price, M. T. C. 1975. In *Chemical Tools in Catecholamine Research*, ed. G. Jonsson, T. Malmfors, C. Sachs, I:349–56. Amsterdam: North-Holland
44. Prado-Alcala, R. A., Kent, E. W., Reid, L. D. 1975. Intracranial self-stimulation effects along the route of the nigrostriatal bundle. *Brain Res.* 84:531–40
45. Phillips, A. G., Filbiger, H. C. 1973. Dopaminergic and noradrenergic substrates of positive reinforcement: Differential effects of d- and l-amphetamine. *Science* 179:575–77
46. Phillips, A. G., Brooke, S. M., Fibiger, H. C. 1975. Effects of amphetamine iso-

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mers and neuroleptics on self-stimulation from the nucleus accumbens and dorsal noradrenergic bundle. *Brain Res.* 85:13–22

47. Phillips, A. G., Carter, D. A., Fibiger, H. C. 1976. Dopaminergic substrates of intracranial self-stimulation in the caudate-putamen. *Brain Res.* 104:221–32
48. Routtenberg, A. 1971. Forebrain pathways of reward in Rattus Norvegicus. *J. Comp. Physiol. Psychol.* 75:269–76
49. Routtenberg, A., Malsbury, C. 1969. Brainstem pathways of reward. *J. Comp. Physiol. Psychol.* 68:22–30
50. Wauquier, A., Niemegeers, C. J. E. 1972. Intracranial self-stimulation in rats as a function of various stimulus parameters. II. Influence of haloperidol, pimozide and pipamperone on medial forebrain bundle stimulation with monopolar electrodes. *Psychopharmacologia* 27:191–202
51. Mora, F., Sanguinetti, A. M., Rolls, E. T., Shaw, S. G. 1975. Differential effects on self-stimulation and motor behavior produced by microintracranial injections of a dopamine-receptor blocking agent. *Neurosci. Lett.* 1:179–84
52. Kelleher, R. T., Morse, W. H. 1968. Determinants of the specificity of behavioral effects of drugs. *Ergeb. Physiol.* 60:1–56
53. Liebman, J. M., Butcher, L. L. 1973. Effects on self-stimulation behavior of drugs influencing dopaminergic neurotransmission mechanisms. *Naunyn-Schmiedebergs Arch. Pharmacol.* 277: 305–18
54. Liebman, J. M., Butcher, L. L. 1974. Comparative involvement of dopamine and noradrenaline in rate-free self-stimulation in substantia nigra, lateral hypothalamus, and mesencephalic central gray. *Naunyn-Schmiedebergs Arch. Pharmacol.* 284:167–94
55. Fouriezos, G., Wise, R. A. 1976. Pimozide-induced extinction of intracranial self-stimulation: Response patterns rule out motor or performance deficits. *Brain Res.* 103:377–80
56. Selby, G. 1968. In *Handbook of Clinical Neurology,* ed. P. J. Vinken, G. W. Bruyn, 6:173–211. Amsterdam: North-Holland
57. Broekkamp, C. L. E., van Rossum, J. M. 1975. The effect of microinjections of morphine and haloperidol into the neostriatum and the nucleus accumbens on self-stimulation behavior. *Arch. Int. Pharmacodyn.* 217:110–17
58. Mora, F., Rolls, E. T., Burton, M. J., Shaw, S. G. 1976. Effects of dopamine-receptor blockade on self-stimulation in the monkey. *Pharmacol. Biochem. Behav.* 4:211–16
59. Clavier, R. M., Fibiger, H. C. 1977. On the role of ascending catecholaminergic projections in intracranial self-stimulation of the substantia nigra. *Brain Res.* 131:271–86
60. Stein, L., Ray, O. S. 1960. Brain stimulation reward "thresholds" self-determined in rat. *Psychopharmacologia* 1: 251–56
61. Poschel, B. P. H., Ninteman, F. W. 1966. Psychotropic drug effects on self-stimulation of the brain: A control for motor output. *Psychol. Rep.* 19: 79–82
62. Goodall, E. B., Carey, R. J. 1975. Effects of d- versus l-amphetamine, food deprivation, or current intensity on self-stimulation of the lateral hypothalamus, substantia nigra, and medial frontal cortex of the rat. *J. Comp. Physiol. Psychol.* 89:1029–45
63. Herberg, L. J., Stephens, D. N., Franklin, K. B. J. 1976. Catecholamines and self-stimulation: Evidence suggesting a reinforcing role for noradrenaline and a motivating role for dopamine. *Pharmacol. Biochem. Behav.* 4:575–82
64. Stephens, D. N., Herberg, L. J. 1975. Catecholamines and self-stimulation: Pharmacological differences between near- and far-lateral hypothalamic sites. *Brain Res.* 90:348–51
65. Coyle, J. T., Snyder, S. H. 1968. Catecholamine uptake by synaptosomes in homogenates of rat brain: Stereospecificity in different areas. *J. Pharmacol. Exp. Ther.* 170:221–31
66. Stark, P., Turk, J. A., Redman, C. E., Henderson, J. K. 1969. Sensitivity and specificity of positive reinforcing areas to neurosedatives, antidepresents and stimulants. *J. Pharmacol. Exp. Ther.* 166:163–69
67. Breese, G. R., Howard, J. L., Leahy, J. P. 1971. Effect of 6-hydroxydopamine on electrical self-stimulation of the brain. *Br. J. Pharmacol.* 43:255–57
68. Phillips, A. G., Fibiger, H. C. 1976. Long-term deficits in stimulation-induced behaviors and self-stimulation after 6-hydroxydopamine administration in rats. *Behav. Biol.* 16:127–43
69. Ornstein, K., Huston, J. P. 1975. Influence of 6-hydroxydopamine injections in the substantia nigra on lateral hypo-

thalamic reinforcement. *Neurosci. Lett.* 1:339–42
70. Yokel, R. A., Wise, R. A. 1976. Attenuation of intravenous amphetamine reinforcement by central dopamine blockade in rats. *Psychopharmacology* 48:311–18
71. Roberts, D. C. S., Corcoran, M. E., Fibiger, H. C. 1977. On the role of ascending catecholaminergic systems in intravenous self-administration of cocaine. *Pharmacol. Biochem. Behav.* 6:615–20
72. Jönsson, L. E., Anggard, E., Gunne, L. M. 1971. Blockade of intravenous amphetamine euphoria in man. *Clin. Pharmacol. Ther.* 12:889–96
73. Gunne, L. M., Anggard, E., Jönsson, L. E. 1972. Clinical trials with amphetamine blocking drugs. *Psychiatr. Neurol. Neurochir.* 75:225–26

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