Pharmacology Biochemistry & Behavior, Vol. 13, Suppl. 1, pp. 213–223. Printed in the U.S.A.

Action of Drugs of Abuse on Brain Reward Systems

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WISE, R. A. *Action of drugs on brain reward systems.* PHARMAC. BIOCHEM. BEHAV. 13: Suppl. 1, 213–223, 1980.—The finding that animals will work for electrical stimulation of some but not all parts of the brain has prompted the view that there are specialized brain circuits which subserve reward function. Two synaptic links in this circuitry have been partially identified. Studies of the effective stimulation parameters indicate that the directly activated fibers are usually high-frequency-sensitive, fast-conducting, myelinated fibers. Pharmacological studies suggest that all reward sites tested are afferent to a critical dopaminergic synapse; the myelinated, reward-relevant fiber of the medial forebrain bundle may synapse directly on the dopamine link. Dopamine blockers block self-stimulation regardless of electrode placement, and dopamine agonists are rewarding in their own right; thus the critical dopaminergic synapse plays both a necessary and (with its normal efferents) a sufficient role in reward function. Several drugs of abuse can facilitate self-stimulation, and it is hypothesized that they do so by a direct action on the same neural substrate. Amphetamine and cocaine seem to act directly in the critical dopamine synapse. Opiates might act at the dopamine synapse or cell bodies, or might act on dopamine afferents. Ethanol, barbiturates and benzodiazepines have not been extensively explored, but if their reported facilitations of self-stimulation are reliable they might be suggested to cause them by a naloxone-reversible inhibition of noradrenergic function, which disinhibits rather than directly excites the dopamine reward link. These suggestions as to the possible sites of interaction of drugs of abuse with brain stimulation reward circuitry are speculative, and are advanced as potentially heuristic working hypotheses.

Reward systems Drugs of abuse Stimulants Opiates Anxiolytics

BRAIN REWARD SYSTEMS

The notion that there are specialized neural circuits which subserve reward function derives from the discovery by Olds and Milner [67] in 1954 that rats would work to earn electrical stimulation of some but not all portions of their own brains [62]. Olds termed the sites at which stimulation is rewarding "pleasure centers" [62], but soon dropped the use of this term [65], because of two implied and subsequently challenged suggestions: the suggestion that because stimulation is rewarding it is necessarily pleasant, and the suggestion that the "center" can stand functionally separate from its afferent and efferent circuitry. The phrase "reward neuron" has also been used, but it is now fashionable to talk about reward systems or reward circuits, and its was Olds himself who began this trend in the late 1950s.

It is now clear empirically as well as logically that we must think of the reward mechanism of the brain as involving several synaptic links, and thus models of reward substrates which imply "reward neurons" or "pleasure centers" in isolation from other circuitry are misleading. However Olds' phrase "pleasure centers of the brain" caught the eye because it suggested other views of brain reward circuitry which are still held by workers in the field. The two important suggestions which still form the working hypotheses of brain stimulation reward specialists are that reward function is specialized in some definable subset of the neurons of the brain, and that a variety of natural rewards synaptically activate the same reward circuitry as is mapped out (at least in part) by brain stimulation reward studies [66]. The suggestion is that all pleasures—the pleasures of food and water for deprived animals, the pleasures of sexual activity, maternal behavior, and play, the pleasures of art and a scenic view—are felt because they somehow activate the specialized reward circuitry which we can study with the brain stimulation reward paradigm. The reason for studying the laboratory reward of brain stimulation is, for most workers, to learn about the mechanisms of natural rewards or drug rewards. The self-stimulation specialist tends to assume that the anatomical systems he studies are the systems through which flow information about all the pleasures (and perhaps some non-pleasant rewards as well) of life.

The notion that drugs of abuse have their rewarding effects and thus their abuse liability because of actions on brain stimulation reward circuits has been a central notion in the study of interactions between such drugs and intracranial self-stimulation. While different investigators have different assumptions as to what their work means, the most theoretically primal of these assumptions has been articulated by Marianne Olds: "The usefulness of this test for the study of psychotropic drugs on behavior lies in the possibility of relating the observed effects in the central nervous system, effects presumed to take place in the reward pathway itself, to the site where stimulation is applied" ([69], p. 117). While this assumption was heuristically important in the develop-

ment of pharmacological studies of self-stimulation, it is the thesis of the present paper that it is time to put it to rest. It is in only some cases at best, and perhaps in no cases at all, that drugs influencing self-stimulation do so by acting at the directly activated, reward-relevant neurons rather than at the afferents or efferents of these neurons. While it is felt that brain stimulation reward and drug reward can be used as tools to help us understand the anatomy and neurochemistry of endogenous reward substrates, it seems time that such efforts explicitly tackle the obvious fact that reward circuits and not reward neurons are the target of investigation, and that drugs might act at one synaptic link while stimulation acts at another.

Self-Stimulation Substrates

Two and a half decades of research have led to only fragmentary understanding of the substrate of self-stimulation. The neuronal target of rewarding brain stimulation has not been defined as to anatomical origin or termination or as to neurotransmitter in the case of a single rewarding electrode placement, although hypotheses and speculations abound. Most attempts tend to deal with the medial forebrain bundle, where most of the best self-stimulation is found, but even here the story is more complex than recent theory would predict. The dominant theory about the substrate of brain stimulation reward is that one of the catecholamine systems is the directly stimulated reward substrate [22, 33, 41, 95, 105], but several lines of evidence now call this hypothesis into serious question. The first is that catecholamine-containing neurons are insensitive to differences in frequency of stimulation which are critical in self-stimulation [105]. Animals prefer high frequencies of stimulation (100 to 400 Hz) and generally work poorly for frequencies below 40 Hz, whereas the catecholamine systems are already maximally activated at stimulation frequencies of 20 or 30 Hz. The second is that the refractory periods for the directly-activated fibers in self-stimulation studies are short, whereas the refractory periods of catecholamine fibers are long [88, 89, 112]. The third is that the conduction velocities of the self-stimulation target fibers are considerably faster than those for catecholamine fibers [87]. All of these findings are consistent with the view that the reward-relevant fibers at the electrode tip are myelinated fibers. Thus despite the fact that catecholamine fibers are found in the medial forebrain bundle where the strongest self-stimulation sites are found, and despite the fact that catecholamines are central to the dominant theories regarding the reward substrate, it appears that self-stimulation does not result from the direct activation of these fibers by the stimulating current. If, as will be argued, catecholamine fibers are critical for brain stimulation reward, then they must be efferent to the myelinated fiber path which appears to be the directly activated substrate in the medial forebrain bundle.

The hypothesized myelinated bundle directly links self-stimulation sites in the lateral hypothalamic area with sites in the ventral tegmental area. When stimulation pulses are alternated between lateral hypothalamic and ventral tegmental electrodes, evidence of axonal collision is seen. That is, if the pulses to the lateral hypothalamus are given too closely in time to the ventral tegmental pulses, the effects of one of the sets of pulses are blocked. It is assumed that this is due to collision of orthodromic action potentials generated at one of the sites with antidromic potentials generated at the other, and in fact it is an analysis of the critical interval at which pulses must be spaced which provides estimates of the conduction velocity of the fibers assumed to connect these regions [87]. While it is thus known that the directly activated medial forebrain bundle substrate is at least in part a myelinated system of fibers which stretches without synapse between the lateral hypothalamus and the ventral tegmental area, it is not known in which direction the system projects.

A very strong possibility is that the system projects caudally, to terminate on dopaminergic cells of the ventral tegmentum; it is these cells which appear to form the critical catecholamine link in self-stimulation [33, 105, 107]. One reason for suggesting this role for dopaminergic cells is that pharmacological evidence clearly does implicate dopaminergic systems in reward function. Selective dopaminergic blockers attenuate brain stimulation reward, and they do so regardless of the stimulation site tested. In our hands there has been no variation in the sensitivity of self-stimulation to dopaminergic blockade, regardless of whether the stimulating electrode is within, proximal to, or distal from known dopamine systems. The fact that the dopamine blockers attenuate the rewarding impact of stimulation, and not simply the animals' ability to perform the operant response [36–38, 61, 83, 106, 117], and the fact they do so regardless of the proximity of dopamine fibers to the stimulating electrode, suggests that some dopamine synapse is critical, and that it is efferent to the activity initiated at the electrode tip. The question of how many directly-stimulated fiber systems are involved in self-stimulation with various electrode placements is open to speculation.

The myelinated medial forebrain bundle self-stimulation substrate may, of course, be linked across several synapses to the critical dopamine fibers, but one finding suggests that they make direct synaptic contact with the dopaminergic cells of the ventral tegmentum and substantia nigra. This is the fact that they do not project caudally beyond the dopamine cell bodies, yet they do take the exact dorsal-ventral and medial-lateral distribution of the dopamine cells [20]. Thus the myelinated reward substrate must originate or terminate among the dopamine cells of the ventral tegmental area and the zona compact of the substantia nigra. Since there are no non-dopaminergic cell bodies in the zona compacta, and since self-stimulation is obtained from exactly this region, it is possible that the myelinated fiber system terminates there, but it cannot originate there. Moreover, terminals on the dopaminergic cells makes sense from another perspective. The distribution of dopamine cells is distinctive, and while other systems take this same dispersion [5], it would be remarkable if the myelinated fibers were to conform exactly to the limits of the dopamine cell dispersion just by chance. The distribution of growing fibers in ontogeny is thought to depend on chemical neurotaxis, and it would make sense that the myelinated reward-relevant fibers take the pipe-shaped cross section of the dopamine cell layers because they are attracted to the cells of this layer in embryonic development. Myelinated medial forebrain bundle fibers that terminate on the dopamine cells have not as yet been anatomically demonstrated, however, so this speculation awaits empirical confirmation.

Whatever their connection, two elements in brain reward circuitry are implied by self-stimulation studies. One is a myelinated, fast-conducting, high-frequency-sensitive fiber of the medial forebrain bundle which serves as the directly stimulated, reward-relevant substrate of medial forebrain bundle self-stimulation; similarly myelinated fibers might be speculated to be the directly activated element at other

self-stimulation sites. The second element is a dopaminergic element which is efferent to the myelinated element and which may receive direct synaptic input from the myelinated element. Only one of these elements is directly implicated in the rewarding effects of abused drugs, and it is not the myelinated, directly activated element.

Psychomotor Stimulant Reward Substrates

Another line of evidence suggesting critical dopaminergic involvement in reward function is evidence linking intravenous stimulant reward to a dopaminergic substrate. It is now clearly established that the dopamine synapse is critical for the rewarding impact of intravenous amphetamine and cocaine. First, these agents are known to alter catecholamine synaptic activity. Amphetamine causes catecholamine release and blocks catecholamine inactivation by reuptake; it also inhibits catecholamine catabolism and it may act as an agonist at catecholamine receptors [7, 16, 32, 46]. Cocaine also inhibits catecholamine inactivation by reuptake [45]. Second, blockade of catecholamine synthesis or receptors blocks or attenuates the rewarding effects of stimulants [72,102]. When selective blockers are used it seems clear that it is the dopamine and not the norepinephrine synapse that is critical; it is dopamine blockers and not norepinephrine blockers which mimic the reward-attenuating effects of chlorpromazine [24, 26, 114, 116]. Third, dopamine agonists have amphetamine-like rewarding properties, while norepinephrine agonists do not [8, 9, 110, 116]. Finally, human subjects report reduced amphetamine euphoria when treated with dopamine blockers or non-selective catecholamine blockers or synthesis inhibitors, while amphetamine euphoria is not reduced by norepinephrine blockers [44,48]. These facts taken together indicate that the rewarding impact and thus the abuse liability of the psychomotor stimulants is due to their ability to increase dopaminergic synaptic function, and is unrelated to their ability to increase noradrenergic synaptic function.

The effects of neurlopetic drugs on stimulant self-administration provides an important check on the possibility that dopamine blockade simply causes Parkinsonian-like impairment of lever-pressing capacity. This interpretation has been advanced with some force in relation to brain stimulation reward and food reward studies, since in these cases both reward reduction and neuroleptic treatment cause decreased behavioral output. This is not the case with the intravenous stimulant rewards, however; here reducing the dose per injection of stimulant causes compensatory increases in the rate of responding, and treatment with dopamine blockers has the same effect. If low doses of dopamine blockers are given the animals simply increase their response rates, maintaining unusually high levels of stimulant in the blood, as though higher than normal level of stimulant were required to produce an equivalent rewarding effect [26, 114, 116]. Such higher response rates cannot be interpreted readily as difficulty in initiation of movement or in coordination of complex motor acts, and thus lend credence to more indirect arguments that neuroleptics block the rewarding impact of food and brain stimulation rather than impairing response capacity in such studies.

Food Reward Substrates

While the study of brain stimulation reward was expected to reveal important things about natural reward systems, it is only recently that what has been learned about the experimental reward has been applied to the study of such natural rewards as those of food and water. Here again, it seems that blockade of dopaminergic receptors antagonizes the specific reward dimension of food and water for hungry and thirsty animals ([108,109], G. J. Gerber, J. Sing and R. A. Wise, in preparation). While it is clear that neuroleptics do not merely and do not totally block the rewarding impact of food, it seems equally clear that attenuation of the rewarding quality of food is a preferential, low dose consequence of dopamine blockade. Again, the evidence converges from several lines of study.

First, neuroleptic treatment impairs the learning of lever-pressing for food reward in hungry animals [85]. This might not seem surprising, since neuroleptics cause obvious sedation at high doses, and even minimal (low dose) sedative effects might be expected to interfere with learning [3,34]. However, this is not the explanation, as is seen in tests of animals that are already well trained at the time of drug treatment.

The effects of pimozide in well trained animals' lever-pressing or alley-running for food do not always involve suppressed performance. In fact the first time that animals are tested under neuroleptic treatment they may press as much for food as do undrugged animals [108]. In our paradigm this means about 200 lever-presses in a half-hour session. Non-rewarded animals (animals tested for the first time with the food dispenser unloaded) make about the same number of responses before they give up and leave the response lever. Thus the first time well-trained animals are tested it takes non-rewarded animals as long to extinguish their non-unrewarded habit as it takes normally rewarded animals to satiate theirs; pimozide-treated animals can keep up to the pace of both comparison groups. However the willingness of non-rewarded animals to respond on the second such non-rewarded test (with two days of normally-rewarded retraining intervening) is less; with subsequent tests animals learn to cease responding earlier and earlier on non-rewarded test days. Similarly, response rates diminish with subsequent days of pimozide testing; the decrease over successive tests parallels that seen under non-reward. The high levels of performance on the first pimozide test day rule out the possibility that these doses impair the ability to initiate voluntary movement by simply sedating the animals; the poor performance seen on the fourth test day indicates that the rewarding impact of food (its ability to maintain the response habit once it has been initiated) has been attenuated by the drug. The possibility that the response decrements are an artifact of progressive drug sensitization or accumulation can be ruled out, since the same injections given in the home cage rather than the test situation have no such cumulative effects [108].

The fact that it is food's ability to sustain responding, rather than the animal's ability to initiate responding, which is blocked by neuroleptic drugs is particularly clear when discrete trials in a runway task are analyzed [108]. Response initiation here can be perfectly normal for several trials under pimozide treatment, but with successive trials response latencies and response completion times deteriorate. On the first day of testing under pimozide there was no evidence of sedation or fatigue; yet a week later, in a second test, there was a marked deterioration of performance which was not seen in the first test. The same difference in first and second test performance was seen in the non-rewarded comparison

group; it is a well-known consequence of repeated non-rewarded testing. As animals become more and more familiar with non-rewarded trials they become less and less willing to sustain responding under this condition. Similarly, as animals become more familiar with the blunted impact of food under pimozide, they become less willing to work for food under this treatment. Thus the effects of pimozide on food-rewarded behavior are consistent with the inference from brain stimulation reward and drug reward tests; pimozide seems to block the rewarding impact of a variety of rewards.

When animals are trained under partial reinforcement conditions, where a food pellet comes only after a fraction of the animal's responses, animals usually show increased willingness to sustain responding under subsequent non-reward conditions. Here the animals are habituated to non-reward (because a fraction of their responses are always non-rewarded) and because of this habituation non-reward becomes less effective in extinguishing the lever-press habit. Since considerable responding during non-reward conditions does occur, and since it occurs in the absence of the food pellet, it must be some other stimuli in the environment which elicit the habitual response; indeed, since the food pellet does not come until after the response even on rewarded trials, it must be the lever and other food-associated stimuli which always elicit responding in trained animals. The food-associated stimuli in the environment are termed "incentive motivational stimuli" or "secondary reinforcers," and it is these stimuli which provide stimulus control of behavior and maintain responding in these tasks. These stimuli (as well as the reward itself) lose their ability to elicit or sustain lever-pressing in pimozide-treated rats. This is reflected in tests where partial reinforcement is used to train animals and where testing under the influence of pimozide is compared to testing of animals given non-reward. Here the pimozide-treated animals cease responding much more quickly than the non-rewarded animals; the incentive motivational stimuli that sustain responding in the non-rewarded animals do not do so in the pimozide-treated animals [43]. Thus the drug not only blocks the rewarding impact of food, but also blocks the rewarding or incentive impact of environmental sights and sounds associated with food. In man neuroleptics seem to take all the little pleasures out of life; similarly in the Parkinsonian patient dopamine loss seems to attenuate the ability of environmental stimuli and events to elicit interest and arousal and inspiration. In rodents we can only speculate as to the subjective effects of drugs, but they appear to blunt the impact of environmental stimuli associated with rewards, as well as blunting the impact of the rewards themselves.

It should be noted that of these three classes of reward (stimulant drugs, brain stimulation, and gustatory rewards) only the stimulant rewards are thought to have a direct interface at the critical dopaminergic synapse. Both food and water reward, and in all probability brain stimulation reward, must activate dopamine neurons primarily through effects on their afferent inputs, as must reward-associated environmental stimuli.

EFFECTS OF DRUGS OF ABUSE ON BRAIN STIMULATION REWARD

If one accepts the view that brain stimulation activates an endogenous reward substrate (and that it is the likely substrate of food reward, sexual pleasure and the like) then it is easy to accept the view that drugs of abuse similarly represent potent avenues for activating this substrate. Just as morphine can be viewed as a pharmacological probe for an endogenous pain suppression mechanism, so can it be seen as a probe for an endogenous reward substrate. From this view it would be predicted that drugs of abuse should facilitate brain stimulation reward, reducing the electrophysiological input required to produce a given degree of reward. Drugs of abuse should enhance the effects of electrical stimulation, either bringing the reward system closer to its threshold for excitation, or reducing the number of neurons requiring electrophysiological activation by providing pharmacological activation of some portion of the critical neural pool. From this point of view the facilitation of self-stimulation by drugs of abuse is a necessary condition. One could not hold the view that drugs of abuse have their own rewarding action through brain stimulation reward system if these drugs did not enhance the effects of brain stimulation reward, at least over some reward-relevant dose range.

The fact that some drugs of abuse do facilitate self-stimulation has led some investigators to treat the hypothesis as though it were confirmed. This is not the case, however, since this finding is a necessary condition, but not a sufficient one. The facilitating effects of drugs of abuse on self-stimulation are generally interpreted to imply an action directly on the brain reward substrate. M. Olds suggests that these effects must be at the level of the directly stimulated neuron [69]. It is, of course, not necessary to take this view. One might suspect that anxiolytic drugs facilitate self-stimulation by rendering the animal less susceptible to situational threats or distractions and one might suspect analgesic drugs to facilitate self-stimulation by rendering the animal less susceptible to known [25] aversive side effects of stimulation. There are many ways that a drug might facilitate self-stimulation without directly activating the reward substrate.

What could constitute critical proof of the hypothesis that the facilitating effects of abused drugs on self-stimulation reflect the rewarding quality of the drugs, and reflect an action in the same substrate as is activated by stimulation? Ultimately it would be necessary to determine the mechanism of rewarding action in terms of its neuroanatomy and its neurochemistry, and show its identity with the similarly-determined mechanism of self-stimulation. At present, available evidence approaches this state only in the case of the psychomotor stimulants. In the absence of detailed knowledge as to the mechanisms of the rewarding and self-stimulation-facilitating effects of drugs of abuse, and of the rewarding effects of brain stimulation, the notion that common mechanisms are involved must rest on inference and correlative data. The impact of the hypothesis will be proportional to the number of necessary but individually ambiguous conditions that can be validated. The most important fact to establish is that a drug in question does facilitate self-stimulation; next it must be established that it does so at doses and with time courses which correspond to its rewarding actions and not to its side effects (such as sedation or analgesia). Even when such findings are available, the notion that it is the rewarding effects of the drug that are reflected in the facilitation of brain stimulation reward will still need direct support. This can only come from a complete understanding of the mechanisms of rewarding brain stimulation and of each of the various effects and side effects of the drug in question. For this reason the brain stimulation paradigm might suggest fruitful lines of investigation regarding mechanisms of action of drugs of abuse, but it will never itself serve as evidence supporting these mechanisms.

Psychomotor Stimulants

Amphetamine and cocaine are generally viewed as drugs which simply and directly facilitate self-stimulation. This is in contrast to the general view of the actions of other drugs of abuse, which have more ambivalent effects. In fact, amphetamine can facilitate or inhibit self-stimulation depending on a number of parameters [101]. Generally, low doses of amphetamine facilitate self-stimulation, increasing rates of responding at a fixed stimulation intensity, or decreasing the stimulation intensity needed to produce a given level of responding [21, 97, 101, 104]. However, high doses of amphetamine can inhibit self-stimulation, and lower doses can also be inhibitory with some electrode placements, or if stimulation currents or baseline rates are high [14, 53, 94, 101].

Little interest has focussed on the reasons for high-dose inhibition of self-stimulation; it is generally assumed that stereotypy or locomotor activity induced by high doses of amphetamine may interfere with lever-pressing. This explanation is not very satisfactory, however, since it can be demonstrated that animals can lever-press at high rates even during intense stereotypy [111]. Another suggestion is that at high doses, amphetamine activates the reward substrate so strongly as to render lever-pressing for stimulation redundant [21, 86, 104]. This view, too, is unsatisfactory, for amphetamine does not inhibit self-stimulation at doses that are rewarding in their own right; the doses of amphetamine which inhibit self-stimulation are well above the dose that is rewarding and satiating [111].

While little attention has been devoted to the high-dose effects of amphetamine and cocaine, a good deal has been focused on the low dose effects. The facilitating effects of low doses of amphetamine are generally taken to mean that the stimulant potentiates activity in the brain stimulation reward system [21,104]. The fact that amphetamine acts in the catecholamine synapse fits well with the view that rewarding brain stimulation directly activates a catecholamine reward substrate. If the rewarding effects of amphetamine are due to pharmacological activation of a dopamine synapse, and if the rewarding effects of brain stimulation are due to the direct electrophysiological (or the evoked, trans-synaptic) activation of a dopamine synapse, then amphetamine serves as an interesting model for the interface of drugs of abuse with an endogenous reward substrate. Amphetamine facilitation of self-stimulation is, in fact, the implicit model for theories of brain reward mechanisms as the substrates of drug self-administration.

Even the amphetamine model, however, is not without its problems. There is the question of the mechanism by which high doses inhibit self-stimulation. Further, there is the more difficult question of why lower doses do not inhibit self-stimulation. If amphetamine activates the reward system directly, why does this pharmacological activation not reduce rather than enhance the animal's willingness to lever-press for stimulation? In the typical intravenous self-administration paradigm rats are usually satisfied for periods of half an hour by a single amphetamine injection [113]. Why shouldn't the same injections similarly satisfy the motivation to self-stimulate? In fact when animals are given concurrent access to amphetamine and brain stimulation rewards they increase their response rates from the single-reward baseline in both cases [111]. One possibility is that amphetamine's effects are less due to the direct release of dopamine by the drug than to the potentiation by the drug of stimulation-induced dopamine release [104]. It is known that amphetamine potentiates catecholamine release to a greater degree in active rather than inactive fibers [99]. In some way amphetamine could thus increase the impact of brain stimulation reward even at doses that are rewarding in their own right. While there are such hypotheses for future exploration, it should be clear from this discussion that even in the case of amphetamine (the most clear-cut case for the argument that drugs of abuse facilitate brain stimulation reward because they activate the same reward substrate), a good deal of further work is needed before the situation is clearly understood. It remains unclear for example why amphetamine reward does not substitute for brain stimulation reward if it redundantly activates the same reward substrate.

Opiates

Opiates also facilitate self-stimulation, and they also have effects in dopaminergic systems. In this case, however, the site of action of the drug is not so well established as in the case with psychomotor stimulants. Some authors have regarded opiates as dopamine agonists [29,51], while others consider them to be dopamine antagonists [27, 28, 76]. Opiate receptors are found in the region of dopamine cell bodies and also in the region of dopamine synaptic terminals [50, 57, 73, 74, 90]. It is not known whether they are presynaptic, post-synaptic or both. Opiate receptors are also found in non-dopamine areas and have been theoretically linked to other transmitters (e.g. [2, 39, 47]). Thus there is no compelling neurochemical or neuroanatomical evidence which would suggest that opiate actions must be restricted to catecholamine systems. Rather opioid transmitter systems would seem to synaptically interact with a wide range of other transmitters; thus, unlike the case for psychomotor stimulants, there is no reason to link opiates exclusively to catecholamine mechanisms of action.

Neither is there any established link of opiates to an identified reward mechanism. Some authors have argued that enkephalin neurons may be involved in their own distinct reward phenomena [10]. That naloxone can impair self-stimulation and at least in some hands ([10,93], but see [98]) has been taken as evidence for such a view. Nevertheless it is attractive to consider the possibility that opiate reward, like brain stimulation, food and stimulant reward, ultimately activates a common dopaminergic reward substrate. Intravenous opiate self-administration is disrupted by pimozide as well as naloxone (G. Gerber and R. A. Wise, in preparation), and this suggests that a critical dopaminergic synapse is efferent to the receptor at which opiates initiate their rewarding neural effects. The fact that pimozide does not cause compensatory increases in opiate intake, as it does with stimulant intake, and as do opiate antagonists in the case of opiates [42], reduces the force of this argument, but may be explained by synaptic links between the opiate receptor and the dopaminergic neuron in question, as suggested in Fig. 1.

The effects of opiates on self-stimulation have been taken to imply a common mechanism despite the absence of direct independent evidence. The effects of opiates on self-stimulation are dual; opiates both inhibit and facilitate self-stimulation. In most cases, there is a period of inhibition seen at the beginning of the session, lasting as long as a few hours [1, 31, 54, 68, 101]. After the inhibitory effects wear off facilitation is seen [1]. The facilitatory effects are seen even during the period of response suppression. This is best seen from comparison of rate and threshold measures. Morphine

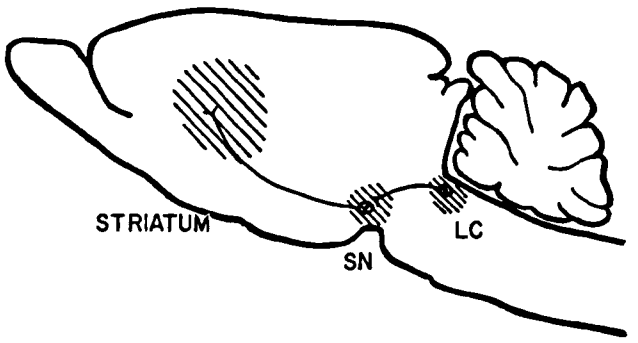

FIG. 1. Suggested sites of potential interaction of opiates with brain reward circuitry. Opiate receptor fields are cross-hatched in the region of the striatal dopamine terminal field, the tegmental dopamine cell region, and the region of locus coeruleus (LC), which is thought to inhibit reward circuitry, perhaps by an inhibitory synapse on the dopamine cells themselves. Opiates inhibit locus coeruleus firing; their actions in the tegmentum and striatum are not yet understood, and may be either pre- or post-synaptic in either region. Thus opiates may act on, or either afferent or efferent to, the dopamine cells implicated in reward function.

causes a biphasic effect when rate is considered, first slowing and then speeding responding. If, however, thresholds are considered, a simple facilitation is reflected in threshold reduction, and this is seen immediately, during the period when response rates are slowed [31]. Thus even when animals are responding minimally, right after a morphine injection, they are willing to work for lower stimulation currents than would normally sustain responding. As mentioned in the case of amphetamine effects, however, it appears that reliable opiate effects are seen only with some electrode placements [53].

When they are seen, the independence of facilitating and inhibiting effects of morphine can be demonstrated in several additional ways [31]. With repeated testing there is tolerance to the inhibiting effects but not the facilitating effects; as tolerance develops the facilitating effects are unmasked, and expressed more fully [13]. Facilitation without signs of response suppression can be seen if morphine is microinjected into the ventral tegmental area: suppression without facilitation is seen if the drug is injected into the dorsal tegmental area [12]. Pure facilitation can be seen in a shuttle-box task [52]. Finally, pure facilitation can be seen in response to very low doses of opiates; these facilitations are immediate and have dose-dependent durations ([81], G. J. Gerber, M. A. Bozarth and R. A. Wise, in preparation). Thus opiates can cause an immediate facilitation of self-stimulation. However it must be noted that this effect is seen in only some animals and the possibility that it is uniquely associated with some self-stimulation sites and not others is a possibility that needs further attention.

Anxiolytics

Other, but not all, drugs of human abuse also facilitate self-stimulation [101]. Current evidence suggests that the probability of a drug reliably facilitating self-stimulation is generally proportional to the propensity of lower animals to self-administer the drug in question, but problems of scaling self-administration propensity are virtually insurmountable. How can one know which routes of administration, which doses or concentration, and which parameters of taste masking, work requirements and accessibility are appropriate for comparison?

Ethanol, benzodiazpines and barbiturates have been reported to facilitate self-stimulation. These effects are not as reliably demonstrated as those of stimulants and opiates, and are apparently not nearly as robust. One report makes it attractive to link ethanol, benzodiazepines and barbiturates together and to consider them in possible relation to opiates; each was found to facilitate self-stimulation in a naloxone-reversible manner [55,56]. Thus they may all share access to brain reward circuitry, through a link involving an opiate receptor. Where in the network they might act to ultimately influence activity at the opiate receptor in question is a matter for speculation, but the fact that their effects are not nearly so robust as those of morphine might suggest a distant or indirect influence.

That these drugs act by brain reward mechanisms at all requires a good deal of further demonstration. Ethanol, for example, has been reported by some workers [55, 56, 84] to facilitate self-stimulation, and by others [15, 58, 84, 100] to inhibit it. The facilitation of self-stimulation which is readily demonstrated (in some animals) with opites has not been clearly demonstrated with ethanol, although the suppressive effects (and tolerance to them) have been [58]. Benzodiazepines facilitate self-stimulation in some animals but impair it in others [64,71]. Barbiturate effects are similarly ambiguous since the line between behavior-enhancing and sedating actions seems particularly sharp with these drugs [60,80]. Any serious attempt to relate these drugs to rewarding actions in self-stimulation systems will require a good deal of parametric work delineating the conditions under which reliable facilitations can be demonstrated.

The lack of confirmed and reliable effects of these drugs, however, may well be due to the fact that they have not yet received much experimental attention. The finding of Olds and Travis [68] that morphine inhibits self-stimulation in the hour or two after injection may have put off for a decade further work which was to reveal morphine's masked facilitatory effects [1]. It may well be the case that robust facilitations will be seen with ethanol, benzodiazepines and barbiturates as more work is done with these agents. If the naloxone-reversible facilitations reported by Lorens and Sainati [55,56] can be confirmed, then these agents may well be found to derive their abuse liability from actions on brain reward mechanisms. The facts that their actions are less robust than those of amphetamine or morphine, and that they are less readily self-administered in their own right, may reflect a more indirect access to brain pathways than is the case with stimulants and opiates.

MECHANISMS AND MODELS

The Reward Neuron

Self-stimulation specialists frequently discuss, among themselves, the "reward neuron" as they variously conceive it at the time. In such discussions one of two defining features of the "reward neuron" is usually implicit. Some use the term to denote the elements at the electrode tip which are activated by rewarding stimulation and which (among the number of systems so activated) carry the reward-relevant message to the next synaptic link in the reared circuitry.

Others use the term to denote the elements in the brain where incoming sensory messages from reward stimuli take on motivational significance—the site at which the subjective experience in Olds' phrase "pleasure center" arises [107]. In the simplest models of drug-self-stimulation interactions, such as that of Marianne Olds ([69] quoted earlier), these two defining features are assumed to apply to the same neuron. In the M. Olds conception the "reward neuron" has its soma in the bed nucleus of the lateral hypothalamus, where it can be activated directly by either electrical stimulation or by morphine [70].

In the catecholamine theories of reward the "reward neuron" would be a noradrenergic [23, 82, 95, 103] or a dopaminergic [20, 22, 109, 114] cell with soma in the brainstem and terminals in the forebrain, and with a fiber projection through the medial forebrain bundle. Considering the dopamine neuron as the reward substrate illustrates the inadequacy of a single-neuron model of reward function. The dopamine neuron (and its efferents) can account for the rewarding effects of the psychomotor stimulants, and might conceivably account for the rewarding effects of opiates as well (since there are opiate receptors at both the cell bodies and the terminal fields of the dopaminergic neuron), but cannot itself account for brain stimulation reward, since the frequency responses, refractory periods and conduction velocities of the catecholamine systems are incompatible with those which characterize the directly stimulated fibers in self-stimulation [40,105].

The Two-Neuron, Excitatory Model

A more complex model is clearly required, and since dopamine receptor blockade interferes with all rewards thus far tested, the model should, for now, have as a central element the dopamine neuron and its efferents. In addition at least one afferent link must be added to illustrate how the target neurons for brain stimulation reward and for psychomotor stimulant reward are linked. The most attractive possibility is that there is an excitatory afferent to the dopamine neuron, and that this afferent is the myelinated, fast-conducting, high-frequency-following neuron which is directly activated by rewarding stimulation of the medial forebrain bundle. Neither the anatomy nor the neurochemistry of such a neuron can be suggested on present evidence, however; the myelinated link in self-stimulation is inferred solely from behavioral data [40,105]. Moreover the wealth of sites which support self-stimulation make it obvious that if the directly-stimulated fibers in each instance synapse on a dopaminergic efferent, then there must be several such stimulated systems. Since the frequency response is similar for a variety of sites thus far examined, it seems likely that in most cases the refractory periods will prove to be short and the conduction velocities fast; if so, myelinated fibers will be implicated as the directly-stimulated link to the dopamine element in a variety of electrode placements. Whether these hypothesized elements will all project directly on dopaminergic neurons, or whether any of them will have directly excitatory connections is an open question.

Other variations on the two-neuron, excitatory model might be suggested; Poschel favored the view that the catecholamine link in reward function was an arousal link which synapsed upon and activated the reward neuron [75]. However, if this were the case we would expect to find some self-stimulation sites at which dopamine blockade is ineffective; thus it seems likely that the dopaminergic link in the reward substrate is efferent to, not afferent to, the directly activated, reward-relevant fibers of self-stimulation.

The Two-Neuron, Disinhibitory Model

Other models can be put forward; one will serve to illustrate the degrees of freedom open when the single neuron model is set aside. James Olds anticipated the complexity of the reward system as we currently understand it and suggested from an early vantage point that one-neuron models would be inadequate for even the early self-stimulation data [63]. The prevalence of one-neuron conceptions might fit with the fact that the noradrenergic substrate once thought to subserve self-stimulation [23,82] diverges anatomically to reach an impressive number of self-stimulation sites. Self-stimulation with electrodes in the region of locus coeruleus, brachium conjunctivum, ventrolateral central gray, zona incerta, medial forebrain bundle, septal area, olfactory bulb, frontal and cingulate cortex, hippocampus, and cerebellum in each case must activate fibers of the dorsal tegmental noradrenergic bundle. It was clear from J. Olds' early studies, however, that self-stimulation of different regions had different characteristics, and Olds [63] first suggested that brain stimulation reward might involve direct activation of reward neurons in some cases while involving disinhibition of such neurons in other cases. It is particularly interesting to think of such an arrangement in relation to the facilitation of self-stimulation by anxiolytic drugs, since they are thought to suppress activity of a system which itself appears to suppress self-stimulation.

The dorsal noradrenergic bundle was initially offered as a reward neuron candidate [23,82]. Norepinephrine was considered a likely candidate for the reward transmitter because of early pharmacological studies, with the dorsal noradrenergic bundle as the likely substrate because of its mentioned projections to multiple self-stimulation sites. Recent evidence, however, suggests just the opposite view; the dorsal noradrenergic bundle is now argued not to support self-stimulation, and activity in this bundle may well antagonize reward function.

Evidence for this position stems from two types of study, mapping studies and lesion studies. Early mapping work suggested that self-stimulation could be obtained with electrodes in the noradrenergic nucleus locus coeruleus [23,82]. More recent work shows that the positive site in this region are not directly in the noradrenergic cell group proper, but rather are clustered anterolateral to it, perhaps more closely associated with the mesencephalic nucleus of the trigeminal system [4, 19, 91]. Lesion studies now show that self-stimulation with locus coeruleus or medial forebrain bundle stimulation sites is not dependent upon the fibers of the dorsal noradrenergic bundle. Indeed, dorsal bundle and locus coeruleus lesions improve rather than disrupt self-stimulation [17, 18, 49]. Since there is evidence of a projection from the locus coeruleus to the region of the tegmental dopamine cell bodies [92], and since the usual action of norepinephrine is inhibitory [11], an inhibitory link between the locus coeruleus and the dopamine element in reward function stands as a viable possibility.

This is an interesting possibility because the locus coeruleus is also a proposed target for opiates and other anxiolytics [78] and it is a region of heavy opiate receptor density (Fig. 1). Opiates suppress locus coeruleus cell firing [2], as do other anxiolytics [78], and it has been suggested that this is the site of anxiolytic action. Stimulation of the

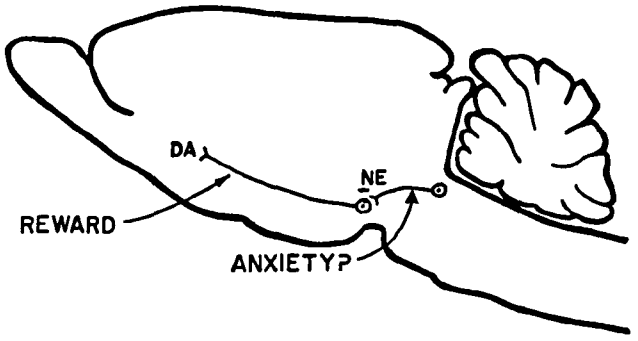

FIG. 2. A speculative model of possible noradrenergic-dopaminergic interaction. The noradrenergic element is viewed as suppressing reward function when it is activated as a correlate of anxiety. Anxiolytic drugs are suggested to disinhibit the reward system in this model. Whether or not the inhibitory element is noradrenergic or involves the locus coeruleus, as shown, disinhibitory modulation of the reward system is an important possible mode of action of anxiolytic drugs which have abuse liability.

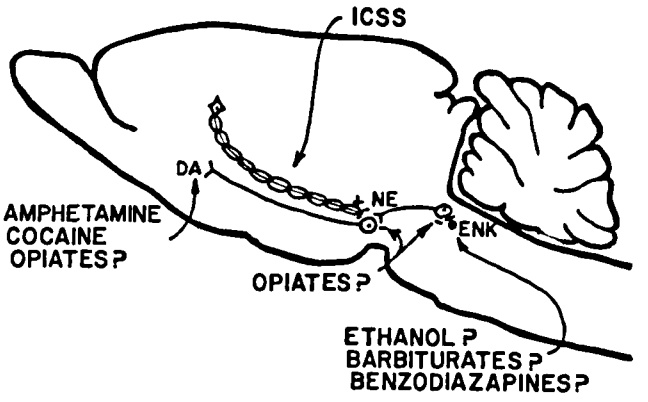

FIG. 3. Summary model of current candidates for brain reward circuitry. The dopamine neuron is thought to be at least one synapse efferent to the directly activated fiber system in brain stimulation reward, which is shown as myelinated. Amphetamine and cocaine are known to act at the dopamine link, presumably in the synapse though perhaps at tegmental autoreceptors. Opiates might act at any level of the diagrammed model. Ethanol, barbiturates and benzodiazepines are speculated to link through inputs to an opiate receptor to a noradrenergic inhibitory control over the dopamine cells; current evidence for this particular site of anxiolytic action is suggestive at best, but some disinhibitory links with the reward system must be taken as a serious possibility in current models of reward circuitry.

locus coeruleus induces postural responses associated with response to threat, and locus coeruleus neurons are activated by threat in monkeys, while lesions of locus coeruleus eliminate sensitivity to threat [77,79]. Activation of the locus coeruleus has thus been suggested as a correlate of anxiety, and inhibition of locus coeruleus activity has been suggested as the mechanism of anxiolytic action ([78] but see [35,59]).

Inhibition of locus coeruleus firing could account for facilitation of self-stimulation by opiates and other anxiolytic drugs, if, in fact, the locus coeruleus normally exerts inhibitory control over the activity in the dopaminergic link in the reward system as suggested in Fig. 2. The anxiolytic actions of these drugs would then be responsible for their interaction with self-stimulation, and these actions might account for their abuse liability. That is, these drugs might be abused not because they directly activate a reward system in the brain, but rather because they release such a system from tonic inhibition. This notion is a focus of current investigation. Regardless of its yet-to-be-tested validity, it provides a concrete example of the more complex models toward which this field is moving.

SUMMARY AND CONCLUSIONS

A variety of positive rewards appear to depend upon the normal function of a dopaminergic system in the brain. This dopaminergic system and its efferents are directly activated by the drug rewards of amphetamine, cocaine, apomorphine and piribedil, and may be directly activated by opiates as well, at the level of either the dopamine cell body or the dopamine synapse. Since opiate reward is blocked by dopamine receptor blockade it does not seem likely that opiates act efferent to this dopamine link in brain reward circuitry. Other rewards also appear to activate the dopamine elements through their synaptic afferents. Food and water must do so, and brain stimulation must do so in most instances, since only a fraction of brain stimulation reward sites are in the proximity of dopamine projections. The estimated frequency response, refractory periods and conduction velocities for the fibers directly activated in intracranial self-stimulation all suggest that dopamine fibers are not directly activated by the standard intensities of rewarding stimulation (although it should be possible to activate them with high intensity stimulation), but rather that a fast myelinated fiber system is usually the directly-activated system at the electrode tip, even in cases where dopaminergic fibers course through the stimulation field. While the rewarding and reward-facilitating effects of opiates, benzodiazepines, ethanol and barbiturates might be mediated at the level of the dopamine neuron, it seems more likely that these agents interact with the dopamine link in reward circuitry through its afferents, either by exciting dopaminergic activity directly or by causing its disinhibition. The working hypothesis that various rewards, including various classes of drug reward, might activate a common reward substrate in the brain, and that this substrate can be localized, at least in part, by brain stimulation reward studies, is an hypothesis with considerable promise, but one which requires critical evaluation before it can be accepted as valid. The working models which appear to have the most heuristic value at the present time are summarized in Fig. 3.

ACKNOWLEDGEMENTS

Preparation of this manuscript was supported in part by NIDA grant DA-01720. I thank Michael Bozarth, Cynthia Jordan and Peter Shizgal for their critical comments on an earlier draft.

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