Pharmacology Biochemistry & Behavior, Vol. 17, pp. 239–243, 1982. Printed in the U.S.A.

Action of Drugs of Abuse on Brain Reward Systems: An Update with Specific Attention to Opiates

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Received 26 January 1982

WISE, R. A. AND M. A. BOZARTH. *Action of drugs of abuse on brain reward systems: An update with specific attention to opiates.* PHARMAC. BIOCHEM. BEHAV. 17(2) 239–243, 1982.—In addressing the role that the substrate of brain stimulation reward might play in drug abuse, Wise [47] reviewed evidence relating brain stimulation and psychomotor stimulant reward to dopaminergic but not noradrenergic elements identified with brain reward circuitry. He then speculated that one possible mechanism of opiate, ethanol, barbiturate or benzodiazepine reward might involve a specified disinhibition of the dopaminergic element. He suggested that these drugs might have inhibitory actions on locus coeruleus, which in turn might send an inhibitory projection to the dopaminergic link in reward circuitry. This speculation is challenged with respect to ethanol in the companion article [1] and with respect to opiates in the present article. Recent evidence indicates that the rewarding action of opiates is mediated in the region of the dopaminergic cells of the ventral tegmentum and not in the region of the noradrenergic cells of locus coeruleus. Rewarding opiate injections appear to activate the same or a similar dopaminergic link in brain reward circuitry as that thought to be activated through its afferent inputs in the case of brain stimulation reward and activated at its synaptic terminals in the case of psychomotor stimulant reward. Whether other drugs of abuse activate links in brain reward circuitry which function in parallel or in series with the dopaminergic link identified with opiates and stimulants remains an open question.

Drugs of abuse Brain reward systems Opiates

THIS paper and the companion piece by Amit and Brown [1] represent comments on an earlier paper [47] which was based on an invited address to the 5th Biennial International Symposium on Alcoholism; its topic was the action of drugs of abuse on brain reward systems. The talk focused on the assumptions and heuristic potential of experiments in which the interactions of rewarding brain stimulation and drugs of abuse are studied. While raising several cautionary notes on the one hand, the paper raised several speculative working hypotheses on the other. These hypotheses were outlined to illustrate various models of possible interaction of drugs of abuse with brain stimulation reward substrates and were not intended as serious suggestions as to how things actually work; however, the speculations have attracted considerable interest and are now the subject of careful scrutiny.

The present paper and the companion paper [1] represent critiques and updates of the speculations as to how ethanol and opiates might interact with brain stimulation reward substrates. The present paper focuses attention on two issues. First, it makes comment on the specific speculation that ethanol, barbiturates, and benzodiazepines might have their rewarding actions by a common mechanism and that this mechanism might involve disinhibition of the reward system resulting from an inhibition of the locus coeruleus ([47], Fig. 3). It is this speculation that is a major concern of the critique by Amit and Brown [1]. Second, it makes comment on the speculation that the rewarding properties of opiates might involve the same mechanism. It is now clear that opiate reward does not involve an action at the locus coeruleus; rather it seems likely that opiate reward involves an action at the ventral tegmental dopaminergic cells identified as a component in the circuitry for brain stimulation reward [4–7, 52]. Thus, opiates seem to have a local activating effect on the substrate of brain stimulation reward, and they can be excluded from the class of drugs suggested by Wise [47] to perhaps indirectly activate intracranial self-stimulation mechanisms. The new evidence that opiates act directly at the cells of a dopaminergic link in the endogenous circuitry for reward serves as the strongest available evidence against the cautionary notes of the initial paper [47]; this evidence indicates, at least in the case of the opiates, the action to facilitate intracranial self-stimulation reflects the direct rewarding action, and not some side effect, of an abused drug class.

ETHANOL

Amit and Brown [1] raise several objections to the speculation that ethanol, benzodiazepines or barbiturates might be rewarding because they suppress noradrenergic systems involved in mediation of anxiety or some other function incompatible with reward. Although this speculation was not meant to serve as a theory of ethanol action, Amit and Brown have responded in detail, for the mechanism of action of ethanol is a matter central to their research [2, 10, 11]. The major point raised by Amit and Brown is well taken; it certainly remains the case that "current evidence for this particular site of anxiolytic action is suggestive at best" ([47], Fig. 3), as Amit and Brown [1] conclude. Moreover, Wise's discussion of the possible mechanisms of rewarding action of ethanol, barbiturates and benzodiazepines should not be taken as demonstrating that "dopamine is the neurotransmitter exclusively responsible for the mediation of reward," as Amit and Brown further argue. While Wise suggested this as a viable working hypothesis, it is certainly not validated by evidence which is in any way definitive. The section in which the matter was discussed was intended merely to illustrate the feasibility of the assumption that some drugs of abuse might facilitate brain stimulation reward by complex indirect mechanisms rather than by a direct rewarding action on a common substrate. Amit and Brown rightly argue that there is no good current evidence for dopaminergic mediation of ethanol, barbiturate or benzodiazepine reward. While the speculation of Wise [47] is still a logical possibility (that in our view merits consideration despite the criticisms of Amit and Brown), the present data-base is clearly inadequate to validate this speculation.

Amit and Brown argue that the rewarding effects of ethanol, opiates and fast-acting barbiturates are primarily and directly mediated by noradrenergic systems in the brain. This alternative seems also open to question, and some specific points might be made in this regard. First, Amit and Brown argue that there is still considerable controversy as to whether it is brain dopamine or brain norepinephrine that is the neurotransmitter critically involved in reward and reinforcement. In our view this controversy has not been resolved. Recent reviews have outlined in detail the evidence for dopaminergic mediation of brain stimulation reward and the evidence against noradrenergic mediation of such reward [13, 21, 46, 50, 51]. The counter-arguments cited by Amit and Brown are, in our view, no longer tenable. It has now been clearly demonstrated that dopaminergic receptor blockade and not noradrenergic receptor blockade interferes with brain stimulation reward [22–24, 55, 56], though noradrenergic receptor blockade or synthesis inhibition can impair lever-pressing capacity [22, 40, 56]. Lesions of noradrenergic pathways fail to disrupt self-stimulation with electrode placements near the relevant fibers [12, 14, 30], and the correlations between such electrode placements and the locus of nearby noradrenergic pathways is spurious [15] while the analogous correlation with dopamine pathways is strong [16]. The fact that noradrenergic pathways are not important for brain stimulation reward does not, of course, say anything critical about the question as to whether noradrenergic systems might play a role in ethanol, opiate, or barbiturate reward.

Amit and Brown argue that there is, indeed, a noradrenergic mechanism involved in ethanol, opiate and barbiturate reward. This view might yet prove correct, though we do not find present evidence convincing. If ethanol is rewarding because it activates noradrenergic systems in the brain, should it not be the case that any substance capable of noradrenergic activation would also be rewarding? This question is raised because it seems clear that the drugs of abuse that most directly influence noradrenergic synaptic output—amphetamine and cocaine—are not rewarding because of their noradrenergic actions. These agents do not lose their rewarding actions when noradrenergic systems are lesioned [38] or blocked [20, 36, 37, 53, 54], but they do lose their rewarding actions when dopaminergic systems are selectively blocked [20, 36, 37, 53, 54] or lesioned [32, 38, 39]. Why should animals not continue to lever-press for cocaine or amphetamine when the dopaminergic projections to the nucleus accumbens are lesioned or dopamine receptors are selectively blocked? If noradrenergic activation by ethanol were rewarding, then amphetamine and cocaine self-administration should be maintained in the face of selective dopaminergic challenge; the fact that it is not suggests that noradrenergic activation is not a sufficient condition for reward. The fact that noradrenergic activation by cocaine or amphetamine is not a sufficient condition for reward raises doubt in our minds as to the likelihood that noradrenergic activations by other agents, such as ethanol, is sufficient to explain the rewarding action of these agents. This argument is indirect, of course, and must be weighed against direct evidence for noradrenergic involvement in ethanol reward as marshalled by Amit and Brown [1, 2, 10, 11]. It should be noted that Wise's model is not in conflict with evidence suggesting NE involvement in ethanol reward, but merely that the action is excitation.

OPIATES

Wise discussed with critical reservations the notion that opiates might be rewarding because of an interaction with the dopaminergic link in brain stimulation reward systems [47]. He suggested that opiates might, with equal probability, be suggested to directly excite the dopaminergic substrate by actions at dopamine terminal fields, cell bodies, or afferent inputs. It is now clear that opiates do excite the dopaminergic link in brain reward circuitry [5,6] and that they do so in the region of the dopaminergic cells of the ventral tegmental area [4,6]. Whereas sites of opiate, barbiturate, ethanol and benzodiazepine interaction with reward circuitry were proposed tentatively in 1980, with question marks to indicate possibilities rather than facts ([47], Fig. 3), the site of the opiate rewarding action can now be identified with some certainty.

The site of opiate rewarding action and the site of opiate facilitation of brain stimulation reward have been directly identified by central microinjection studies involving three paradigms; the same site is involved in both actions. Broekkamp [8,9] has shown that morphine and endorphin injections into the posterior lateral hypothalamus and the ventral tegmental area facilitate brain stimulation reward with no signs of the behavioral sedation that is seen with other injection sites. The shortest latencies occur with injections into the ventral tegmental region of dopaminergic cell bodies [8]. Injections into the striatum or nucleus accumbens have minor effects, and injections into sites caudal to the ventral tegmentum cause prominent inhibitory effects. Broekkamp suggests that the site of the facilitory effect is the site of the dopaminergic cells of the ventral tegmentum, and he argues that morphine injected into other positive sites diffuses to the region of dopaminergic cells [8]. Based on Broekkamp's data

and on the working hypothesis (see [47]) that opiates are rewarding because of the same action that accounts for opiate facilitation of brain stimulation reward, Bozarth [4–6] has found that rats will learn to lever-press for direct injections of morphine into the ventral tegmental area but not the nucleus accumbens or caudate nucleus. Rats will also work for posterior lateral hypothalamic morphine injections [33,42], but not, in our hands, with small injection cannulae [4,6]. Finally, rats will return to the place in their environment where opiate effects have been experienced [3,41], and this can be demonstrated with intracranial injections of morphine [6,34]. This "conditioned place preference" is established by injections of morphine into the region of the ventral tegmental dopaminergic cells, but not into the regions dorsal [34] or caudal [6] to these cells. Thus the site of rewarding opiate action and the site of reward-facilitating opiate action are both established in the ventral tegmental area. Opioid peptides similarly have reward-facilitating actions in this region [8].

The mechanism of opiate rewarding action is not so well pinned down as is the site of this action, but current evidence points to the likelihood that ventral tegmental morphine is rewarding because in activates dopaminergic cells in this region. First, morphine microinjected into this region is associated with increased locomotor activity; the mechanism of the locomotor activity appears to involve the major dopaminergic projection from the ventral tegmental area to nucleus accumbens [29]. Second, unilateral rewarding injections of morphine in the ventral tegmental area cause circling in the direction associated with dopamine release in the accumbens [4,6]. Third, conditioned place preference established with systemic heroin is blocked by dopamine receptor blockers as well as by opiate receptor blockers [6,7]. While additional work is needed and is in progress, the current data thus suggest that opiates are rewarding because of a local activation of dopaminergic cells in the ventral tegmental area; these cells are also presumed to play a critical role in brain stimulation reward, psychomotor stimulant reward and food and water reward [46–51].

The data showing the ventral tegmental area to be the site of both the rewarding action of opiates and the facilitating actions of opiates on brain stimulation reward reflect a test of the working hypothesis discussed in Wise's paper [47]. This working hypothesis is that the facilitation of self-stimulation by drugs of abuse is a behavioral end point reflecting the direct rewarding actions of the drugs in their own right and that this behavioral action can be used to study drug reward mechanisms. While the demonstration of direct central morphine self-administration at the particular opiate receptor population predicted by self-stimulation studies is not proof of this working hypothesis, it strongly supports it and demonstrates its heuristic value. In the case of opiates it now seems very likely that the facilitation of self-stimulation is an index of the direct rewarding action of the drugs, and the mechanisms of the reward-facilitating action and the direct rewarding action are the dopaminergic cells of the ventral tegmentum (or the terminals of their immediate afferents).

PARALLEL OR SEQUENTIAL REWARD SYSTEMS?

Amit and Brown's [1] position is fundamentally at odds with the present position only on the question of whether there are multiple, parallel reward mechanisms, each mediating a specific rewarding action, or whether there is one general system (or at best only a few such systems) through which the reward messages relevant to a number of different drug and other rewards all funnel across sequential elements. Amit and Brown argue for multiple, parallel systems, arguing that the concept of a "single brain system responsible for all reinforcement is neither parsimonious nor defensible." We see it as parsimonious, but the data-base for such a view is admittedly minimal at present. Wise [47] did not argue the validity of this hypothesis on existing data, though he certainly advanced it as an interesting and important possibility. The alternate view is that there are multiple reward systems in the brain, involving dopamine, norepinephrine and enkephalin as their neurotransmitters, and that they are associated with incentive, reinforcement, and gratification aspects of reward, respectively [43]. This line of thought was first developed by Herberg *et al.* [28,44] and by Crow [18], though enkephalin did not yet figure in their views. Several earlier authors considered the possibility that there were multiple catecholaminergic reward systems ascending the medial forebrain bundle in parallel (see, e.g., [27]). The possibility that different classes of drugs of abuse might activate different reward substrates, as might different natural rewards like those of food and water, is a possibility with every bit as much logical attraction as the possibility that all rewards activate a single common substrate. Indeed, Wise himself has argued for separate motivational systems in the medial forebrain bundle in a somewhat different context and with regard to a different motivational function [45]. Thus there is not more logical appeal to the notion of a single reward system than to the notion of multiple parallel systems.

The empirical support for the notion of multiple parallel systems now seems to show signs of deterioration, however. First, the notion that rewarding brain stimulation usually activates catecholamine systems directly is no longer viable [26,47]. Rewarding brain stimulation would rather seem to be dependent on dopamine because the stimulated substrate is afferent to a critical dopaminergic link in the system [47,49]; while dopaminergic neurons do not have the properties associated with the directly stimulated element in brain stimulation reward, they do have properties that would fit with the next stage of processing of the reward message [26]. Second, the evidence against the view that electrophysiological activation (either directly or trans-synaptically) or noradrenergic systems is rewarding is strong, as already mentioned. Third, the specific notion that enkephalinergic reward systems function in parallel to dopaminergic reward mechanisms [43] now seems untenable. The fact that ventral tegmental morphine actions account for opiate reward seems to link enkephalinergic involvement in reward to interneurons that are in series rather than in parallel with the dopaminergic link. The opiate receptor population in the ventral tegmental area is in all likelihood on the dopaminergic cell bodies, their afferents, or both [29, 31, 35]. The fact that a rewarding action of opiates can be blocked by dopaminergic blockers in a situation where motor side effects of the blocker could not play any significant role [6,7] supports this view. Thus the enkephalinergic and dopaminergic reward substrates seem not to be parallel systems with different reward functions but seem rather to be sequential links in a common system with a single reward function. Whether ethanol, barbiturates or benzodiazepines act in series with or in parallel to this system remains, in our view, a question for further research.

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