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Actions of Drugs of Abuse on Brain Reward Systems: A Reconsideration with Specific Attention to Alcohol

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AMIT, Z. AND Z. W. Brown. *Actions of drugs of abuse on brain reward systems: A reconsideration with specific attention to alcohol.* PHARMAC. BIOCHEM. BEHAV. 17(2) 233–238, 1982.—Research in the areas of intracranial self-stimulation and drug self-administration has provided a substantial data base that has contributed to our understanding of brain reward mechanisms. In a recent article, Wise [83] argued that dopamine is the catecholamine critically involved in the central mediation of reward. The present paper attempts to examine the available data with particular reference to alcohol, but also with reference to opiates, and argues that the reinforcing effects of at least these drugs are primarily and directly mediated by noradrenergic rather than dopaminergic systems in the brain. It also argues, in direct contrast to Wise, that in the context of these drugs, dopamine seems to play a minor if not negligible role.

Drugs of abuse Brain reward systems Alcohol

TWO approaches have made unqiue and complementary contributions to our understanding of the mechanisms underlying reward and their role in positively reinforced behavior. These were the findings that animals will perform an operant response in order to receive either intracranial electrical stimulation [58] or infusions of a variety of psychoactive drugs [30,79].

Additional input has come from studies which examined the interaction between intracranial self-stimulation and drug self-administration [47, 48, 57, 76]. These studies have focused on an attempt to determine the neuroanatomical, neurochemical and neurophysiological mechanisms underlying the substrate of reinforcement. Although there has been substantial evidence implicating catecholamines (CA) in the mediation of both electrical stimulation and drug induced reward, there is still a great deal of controversy over whether it is brain dopamine (DA) or norepinephrine (NE) or both that are critically involved in reward and reinforcement [25, 34, 37, 58, 71, 81].

A DOPAMINE THEORY OF REWARD

Several investigators have espoused the position that DA is the substrate of reward [11, 34, 37, 81]. In a recent article, Wise [83] presents a theoretical framework in which he proposes that all positively reinforced behaviors are mediated by one or more of the DA systems to the exclusion of the NE system. The main interests and research efforts of the present authors are in the area of positive reinforcement and the underlying neural substrates of ethanol and opiates. While we acknowledge that DA plays a role in reinforcement of some behaviors, it is our contention that DA is not a primary agent in the mediation of ethanol and perhaps of opiate reinforcement. Consequently, we will review the literature with regard to ethanol and opiate reinforcement with particular attention to Wise's formulation.

Wise [83] argues that alcohol, barbiturates and benzodiazepines, which he classifies as "anxiolytic," may not act directly on brain reward mechanisms. These drugs are contrasted with the psychomotor stimulants which he states do act directly on DA brain reward mechanisms and the opiates whose role is unclear in that according to his formulation they may act either directly or indirectly on brain reward mechanisms. As partial support for this view, Wise suggests that these "anxiolytic" substances represent a different category of drug from the psychomotor stimulants and opiates in that they are "less readily self-administered." However, this statement is at odds with the fact that alcohol is readily self-administered not only by humans [46,74] but also by laboratory animals through intravenous [30,80], intragastric [28,29]

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and oral [4, 5, 12, 43] routes of intake. Thus in an attempt to reconcile these widely discrepant sets of data, Wise is forced to propose that if the "anxiolytics" do in fact have an effect on reward pathways, they must do so via an indirect route. Specifically, he suggests that the "anxiolytic" drug ethanol may act by inhibiting noradrenergic activity in the locus coeruleus (LC) which has been proposed as a correlate of anxiety [63]. Inhibition of LC neurons by ethanol would not only relieve anxiety but is speculated to also release DA neurons from a tonic inhibition presumably exerted by LC noradrenergic neurons. It is in this indirect manner that ethanol is proposed to activate the DA reward system.

It is our contention that Wise's attempt to incorporate ethanol into the DA theory of reward is faced with considerable difficulties. An examination of Wise's position reveals four necessary conditions without which his hypothetical model becomes untenable. The first condition is that alcohol is an "anxiolytic" presumably meaning that it is capable of reducing anxiety. The second condition is that activation of the noradrenergic system and in particular the LC is "the correlate of anxiety." The third condition requires the inference that there is an inhibitory link between the LC and DA reward neurons. The fourth condition is that ethanol inhibits noradrenergic activity in the LC thereby relieving anxiety and concommitantly leading to a disinhibition of DA neurons which constitutes activation of the brain reward mechanisms. Although it follows logically that a refutation of any one of these necessary conditions would negate Wise's hypothesis, with regard to alcohol none of these four conditions stands up to close scrutiny.

THE ISSUE OF "ANXIOLYTICS"

The classification of alcohol, barbiturates and benzodiazepines as "anxiolytics" is an unusual way of classifying drugs. Traditionally, barbiturates and ethanol are classified as sedative-hypnotics, while the benzodiazepines are considered minor tranquilizers [39]. With regard to alcohol in particular, the suggestion that this drug is an anti-anxiety agent has long been the subject of controversy. Ever since and, in fact, even before Masserman and Yum [51] reported that cats with induced experimental neurosis increased their intake of milk adulterated with ethanol, researchers have explored the possibility that there is a direct relationship between anxiety and alcohol consumption. Some earlier studies have shown that experimental stress induced by expsoure to a regime of intermittent, inescapable application of foot-shock tended to produce fluctuating and transitory increases in alcohol intake. However, when interpreting these data, it must be remembered that in most cases the increases in alcohol intake occurred not during exposure to shock—when anxiety would presumably be greatest—but quite some time following termination of the stress when anxiety would presumably be decreasing or be completely terminated [21, 44, 75]. Later reports revealed that ethanol consumption was unrelated to exposure to stress [23], and, in fact, under most conditions of induced anxiety, animals tended to reduce rather than increase their consumption of alcohol [40, 54, 60, 65, 73]. Unfortunately, the data with regard to animal studies are confusing at best. The picture with regard to human studies on anxiolytic properties of alcohol is best summarized by Nathan and O'Brien [55] who state "One wonders, on reviewing these data, how the common view of beverage alcohol as an anxiety reducer came into being."

In view of the recent interest in stress-induced activation of endogenous opiate system [2], we have attempted to reexamine the relationship between alcohol consumption and experimentally induced stress. Daily exposure to stressors such as foot-shock, cold-water swim or immobilization failed to produce any significant alteration in voluntary ethanol intake in rats (Ng Cheong Ton, Brown, Amit, manuscript in preparation). The only noticeable trend was a slight reduction in drinking by rats in the foot-shock group.

Another line of evidence shedding some additional light on the possible involvement of alcohol on extinction of avoidance [3, 6, 7, 8]. In the typical one-way active avoidance paradigm, the animal is presumed to have learned to avoid the part of the apparatus in which an electric shock was inflicted on him by moving to the safe side of the apparatus. The rate with which the animal extinguishes the avoidance response is considered to be a function of the anxiety that was generated during avoidance training; thus a drug which has anxiety reducing properties should act to hasten the extinction process. Paradoxically, the effect of ethanol has been found to increase resistance rather than facilitate extinction of avoidance [3, 7, 8]. In light of this evidence, it would therefore be more parsimonious to assume that alcohol has no role in anxiety reduction.

THE ROLE OF THE LOCUS COERULEUS IN ANXIETY

With regard to the second condition proposed by Wise, namely that the LC is involved in anxiety, support for this notion is based on a single theoretical report [63]. In fact, Wise references two additional reports that contradict rather than support his position in that they argue against any role for NE or the LC in anxiety [25,50]. It would seem, therefore, in an area where the data are meager the weight of the evidence rests contrary to the suggestion that activation of the LC is the correlate of anxiety.

THE INHIBITORY ACTION OF NE ON DA

The next component of Wise's model requires that "the usual action of NE" be inhibitory on DA neurons. While there is some evidence supporting the notion that the role of NE neurons is primarily inhibitory on some brain structures (e.g., Purkinje cells in the cerebellum [9]), Wise does not cite, nor are we aware of any supportive data for the inference that DA neurons are tonically inhibited by the NE neurons of the LC. Moreover, the proposition that the NE neurons of the LC exert such an inhibitory action would require that any potential reinforcer acting through the NE system must be capable of inhibiting the NE system and thereby releasing the DA system from its tonic inhibition. In other words, if in fact tonic inhibition of the DA system by NE does exist, then it would follow logically and necessarily that chronic inhibition or suppression of the NE system by electrolytic or neurochemical lesions or by dopamine-beta-hydroxylase inhibition or by receptor blockade should result in spontaneous reward and euphoria. No such phenomena has every been reported despite the common usage of these procedures (e.g., [5, 7, 12, 28, 29, 34, 43, 49, 70].

INHIBITION OF NE BY ANXIOLYTICS

The fourth necessary condition needed for Wise's hypothesis to be viable is that "anxiolytics" must exert an inhibitory effect on NE neurons of the LC. While the evi-

dence to support such a statement is minimal and, even as such, indirect [52,61], there are substantial research data that indicate the contrary. Ethanol has been shown to stimulate neuronal activity and, in particular, to increase noradrenergic functioning. For example, single cell recording studies have shown that peripheral injections of ethanol increase the rate of firing have shown that peripheral injections of ethanol increase the rate of firing of cerebellar Purkinje cells [66,68] or neurons of the lateral hypothalamus within the medial forebrain bundle [77]. In addition, electrophoretic applications of ethanol directly to neurons of the lateral hypothalamus, zona inserta, and thalamus also resulted in increased discharge frequency [78].

Ethanol has also been shown to alter neurochemical functioning in various brain structures and systems. Of particular interest for the present discussion are the studies which have demonstrated that ethanol injections tend to increase the turnover of brain NE in laboratory animals [19, 20, 24, 41, 45].

Acetaldehyde, the primary metabolite of ethanol has been shown to be a positive reinforcer and to be readily self-administered both by animals [15,17] and possibly even by humans [13]; Brown *et al.*, paper submitted for publication). Acetaldehyde has also been shown to exert even greater effects in increasing the turnover of NE than has ethanol [31, 59, 72]. From this evidence it would appear that ethanol and its active reinforcing metabolite has an excitatory rather than an inhibitory effect on noradrenergic neurons.

This issue is further strengthened by a set of independent yet related experiments. These experiments demonstrate that an intact noradrenergic system is a prerequisite for ethanol self-administration in laboratory animals. One example of this is that lesions to central CA neurons produced by treatment with the neurotoxin 6-hydroxydopamine reduces voluntary ethanol consumption except in animals where noradrenergic neurons were protected by pretreatment with desmethylimpramine [12]. Neurochemical lesions specifically in the dorsal noradrenergic bundle were also shown to produce significant reductions in voluntary ethanol consumption in rats [43] or to prevent the acquisition of ethanol preference in rats [49]. We have also reported that the administration of FLA-57 (a dopamine beta-hydroxylase inhibitor) which blocks the conversion of DA to NE results in a marked suppression of ethanol intake in rats which were previously alcohol-preferring [4]. We have also shown that this suppression of ethanol intake persists long after FLA-57 injections are terminated [14]. FLA-57 reduces brain levels of NE and turnover of NE without affecting levels of DA [16,36] thereby precluding the possibility that the suppression of ethanol intake may be related to DA. These results have been confirmed by other investigators who have demonstrated that intragastric self-administration of ethanol in rats was reduced by treatment with the dopamine-beta-hydroxylase inhibitors U14, 624 [28], and FLA-57 [29]. On the other hand, haloperidol, a DA receptor blocker, was shown to have no effect on ethanol self-administration [5,28]. Furthermore, we have found that the reduction of synthesis of DA by treatment with RO4-4602 (an inhibitor of aromatic dopa-decarboxylase) did not alter ethanol intake in rats (unpublished observations).

These studies confirm the necessity of an intact NE system for the direct mediation of ethanol reinforcement. The results of the above studies could not conceivably be attributed to any involvement of the DA system. If one were to argue that DA is involved via release from inhibition by NE following ethanol exposure, then the pharmacological manipulations which destroy or inhibit NE should also result in a disinhibition of DA and evoke an increase rather than the observed decrease in ethanol intake.

THE ROLE OF THE OPIATE RECEPTOR IN ETHANOL REWARD

An additional link in Wise's proposed schema [83,84] is the possibility that ethanol may exert its inhibitory effect on the noradrenergic control system via an opiate receptor system. In order for this hypothesis to be viable, it must be reversible by opiate receptor antagonists. To the best of our knowledge, there is only one report in the literature [1] providing data which can be interpreted as support for the involvement of opiate receptors in ethanol positive reinforcement. In fact, several attempts in different laboratories to demonstrate some involvement of the opiate system in the actions of ethanol have consistently failed [22, 42, 53, 56].

OPIATE REWARD MECHANISMS

Wise [83] initially suggested that opiates may function either directly on the DA system or indirectly by NE inhibition via the opiate receptor mechanism. Subsequently, Wise and Bozarth [84] have modified this position and presented data in support of a direct rather than an indirect mechanism of action of opiates. Based on their own recent work [11], they argue that the neuroanatomical locus of opiate reward is the ventral tegmental area and the neurotransmitter mediating this phenomenon is DA. In contrast to the proposed role of DA, either direct or indirect, in opiate reinforcement, there is a rather substantial body of evidence which implicates noradrenergic systems in opiate reward. For example, animal studies have shown that self-administration of opiates can be blocked by inhibition of NE synthesis [16, 26, 27] and unexpectedly even by serotonin receptor blockade [64]. More interestingly, it has been reported that the administration of the DBH inhibitor fusaric acid reduced morphine-induced euphoria and cravings in opiate-dependent human beings [62]. On the other hand, there is accumulating evidence that argues against the involvement of DA in opiate reinforcement. Davis and Smith [26] have argued that although the DA receptor blocker haloperidol reduced morphine self-administration in rats, the effect was attributable to a non-specific motor artifact. More recently, Ettenberg *et al.* [33] demonstrated that treatment with alpha-flupenthixol, a DA receptor antagonist, failed to cause compensatory increases in intravenous self-administration of heroin as it does in the case of cocaine self-administration. Ettenberg *et al.* argue that opiate reinforcement must be mediated by some neural substrate other than DA. Thus the relative involvement of NE and DA in mediation of opiate reinforcement is, at best, unsettled.

SUMMARY AND CONCLUSIONS

In summary, we identified in Wise's "two neuron, disinhibitory" model four necessary conditions for ethanol reward and a suggestion concerning opiate reinforcement. In the present paper we have presented extensive evidence which we feel argues convincingly that none of the four conditions are defensible. The attempt to explain positive reinforcement of drugs such as ethanol through inhibition of NE and subsequent disinhibition of DA must therefore be rejected. Furthermore, the mechanism of morphine action

either directly via DA or indirectly via opiate-NE systems remains unclear. In conclusion, the fields of intracranial self-stimulation and drug self-administration research have yielded an enormous amount of data which have enriched immeasurably our conceptions and ideas about reinforcement mechanisms, in particular, and motivated behavior, in general. It would have been extremely elegant if this large body of evidence had led to one uniform, comprehensive, and simple theory of reward. Unfortunately, a survey of the relevant data reveals that the concept of a single brain system responsible for all reinforcement is neither parsimonious nor defensible on present evidence.

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