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Behavioral Sensitization to Ethanol: Genetics and the Effects of Stress

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PHILLIPS, T. J., A. J. ROBERTS AND C. N. LESSOV. *Behavioral sensitization to ethanol: Genetics and the effects of stress.* PHARMACOL BIOCHEM BEHAV **57**(3) 487–493, 1997.—Some aspects of drug abuse syndromes may be influenced by sensitization to some drug effects. This enhancement of drug effect has been associated with prior drug exposure and with exposure to stressful stimuli. It has been postulated that sensitization to psychomotor stimulant drug effects influences sensitivity to drug reward. The drugs of abuse best characterized for sensitization phenomena include cocaine, amphetamine, and morphine. In general, ethanol's molecular mechanisms of action have been difficult to define relative to drugs with known receptor or transporter binding sites and, likewise, ethanol sensitization has been less thoroughly examined. Evidence supporting the existence of behavioral sensitization to ethanol, for genetic differences in the occurrence of ethanol sensitization, and for the influence of corticosterone on the development of ethanol sensitization is reviewed herein. There appear to be different genetic determinants of acute drug sensitivity and sensitization. Cross-sensitization between stress and ethanol suggest a potential role for hypothalamic–pituitary–adrenal (HPA) axis associated changes in ethanol sensitization, consistent with mechanisms likely contributing to sensitization to other abused drugs. Furthermore, glucocorticoid receptors appear to mediate both ethanol- and stress-induced sensitization to ethanol. A biological link between drug reward and drug sensitization involving HPA axis hormones may exist and, thus, study of the sensitization process may elucidate mechanisms relevant to drug abuse. © 1997 Elsevier Science Inc.

Cross-sensitization Dopamine Drug abuse Ethanol Genetics Glucocorticoid Locomotion Sensitization

MOST if not all drugs with abuse potential stimulate locomotion in rodents. It is, in part, the commonality of this effect among abused drugs that has led to the detailed investigation of drug-induced psychomotor stimulation. It has been hoped that animal models of drug-induced locomotor stimulation would model human drug-induced euphoria, and that the study of locomotion would provide enlightenment with respect to neurochemical mechanisms involved in determining such euphoric and rewarding drug effects. In fact, mouse lines insensitive (SLOW) and sensitive (FAST) to the stimulant effects of ethanol have been bred to permit the direct genetic study of ethanol-induced stimulation (15,80,102). They have been used to examine the neurochemical determinants of ethanol stimulation (101) and to explore the existence of common genetic determinants of sensitivity to the stimulant effects of other abused drugs (79).

Over several years of study, a great deal of progress has been made in identifying the underlying biology of acute drug-induced activation and drug reward. Although complicated "reinforcement circuits" likely exist in the brain (29), much evidence points to the importance of the mesoaccumbens dopamine pathway, with projections from the ventral tegmental area to the nucleus accumbens, in both drug stimulation and reward (26,38,53,77,98,114). However, some reinforcing drug effects likely occur via pathways independent of dopamine neurons [see (98)]. Consensus does not currently exist concerning whether or not identical mechanisms determine the intensity of drug reward/euphoria and locomotor stimulation. That is a topic for another review. Rather, to be addressed here is the recent focus on drug-induced behavioral sensitization, the augmentation of a response to a drug with repeated exposures, which may or may not be a determinant factor in addictive behavior (117). Hunt and Lands (41) have suggested that sensitization may increase the probability of the development of uncontrolled ethanol intake, and Newlin and Thomson (67) have asserted that sensitization to alcohol might reflect greater reward value of the drug. It is our view that this has yet to be conclusively demonstrated.

The primary goal of this paper is to review the small literature addressing sensitization to ethanol, speak to the importance of experiments investigating ethanol sensitization that include genetic manipulations, and focus on the potential in-

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volvement of the hypothalamic–pituitary–adrenal (HPA) axis hormone corticosterone in ethanol sensitization. In addition to summarizing these issues, some of the work on sensitization to other drugs of abuse that provides the basis for the ethanol work is presented to demonstrate their similarities.

BEHAVIORAL SENSITIZATION

Behavioral sensitization is the augmentation of a response to a stimulus with repeated exposures. Like initial stimulant responses, locomotor sensitization is a common response to most, if not all, drugs that are abused by humans. Drugs most commonly used to study the sensitization phenomenon have been cocaine (37,104,108), amphetamine (37,39,81,110), and morphine (46,81,110). Although knowledge of drug sensitization existed near the turn of the century [see (27,106)], the first demonstration of ethanol sensitization of which we are aware was that of Masur and Boerngen (65), who treated mice for up to 60 days, once daily, with 1–3.5 g/kg ethanol and showed increases in the initial locomotor responses to some ethanol doses.

Ethanol sensitization has been little investigated since publication of these results, but some studies do exist (16,17,66, 78,81,82). An example of sensitization to the locomotor stimulant effects of ethanol is shown in Fig. 1. The locomotor activity of genetically heterogeneous mice (HS) was measured in Omnitech (Columbus, OH, USA) digiscan activity monitors on 2 consecutive days after an IP saline injection. The first day permitted habituation to the test environment and procedures. The second day provided a measure of baseline activity in habituated mice. On day 3, half of the mice (chronic drug group; CD) were tested after an IP ethanol injection (2.5 g/kg; 20% v/v) and the other half after saline treatment (chronic saline group; CS). A stimulant response to ethanol is apparent from the mean of CD group mice on day 3 in Fig. 1. On 10 subsequent consecutive days, CD group mice were given daily injections of ethanol (2.5 g/kg), and CS group mice received saline; no activity testing was performed on these days. On day 14, both groups were tested after treatment with 2.5 g/kg of ethanol. CD mice clearly showed a sensitized response relative to their acute stimulant response on day 3. Furthermore, sensitization was evident in the comparison of CD and CS group responses on day 14.

One reason for the relative paucity of ethanol sensitization reports in the literature may be because there appears to be an important species difference in its occurrence; it can be demonstrated in mice, but has been difficult to demonstrate in rats (66), the research animal that has been most commonly used in studies of sensitization to other drugs. However, even in mice, there are strain-dependent differences in propensity toward the development of drug sensitization (7,16,64,81,82, 92,103,107,108). This variable has been considered in some recent rat studies examining sensitization (11,56) and has also proven to be important in some rat studies of acute ethanol stimulant effects (57,111). Interestingly, whereas both acute stimulation and sensitization appear to be common properties of abused drugs, several genetic analyses have now suggested that acute stimulant sensitivity to cocaine and ethanol is not genetically related to the magnitude of sensitization to either of these drugs (16,82,108). Thus, these two effects may have at least partially divergent underlying molecular determinants.

DOPAMINE, SENSITIZATION, AND DRUG ADDICTION

Evidence for a direct role of sensitization in drug addiction might come from the demonstration that similar biological

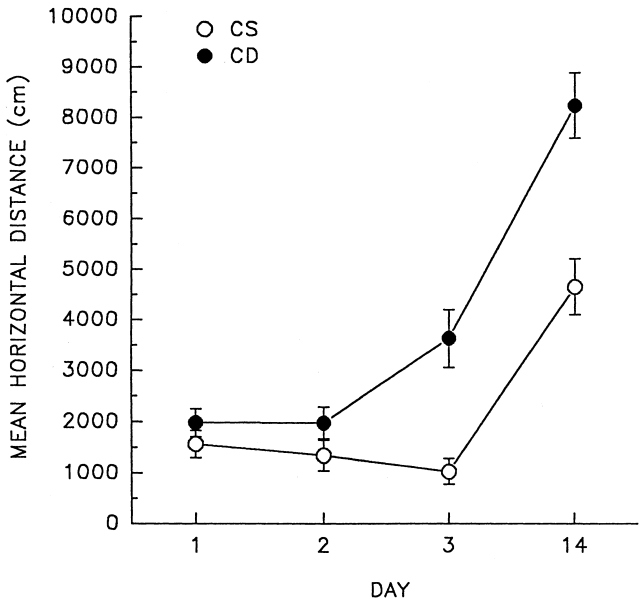

FIG. 1. Mean horizontal distance (cm) traveled ± SEM by genetically heterogeneous female mice on four open-field locomotor activity test days. On days 1 and 2, mice of both the chronic saline (CS) and chronic drug (CD) groups were tested for 10 min beginning immediately after an IP saline (0.9%) injection. On day 3, CS mice were again tested after saline, and CD mice were tested after a 2.5-g/kg ethanol injection. On days 4–13, mice were injected once daily with saline (CS) or 2.5 g/kg ethanol (CD) and were returned to their home cages without testing. On day 14, mice of both groups were tested after a 2.5-g/kg ethanol injection.

systems underlie both sensitization and vulnerability to drug self-administration or reinforcement. Dopamine systems have been widely investigated and have received prodigious support for their involvement in drug reward, most commonly measured by analysis of their involvement in proclivity toward drug self-administration (5,10,40,55,63,68,88) or by determining dopaminergic changes associated with drug self-administration (35,58,115). Enduring changes in mesoaccumbens dopamine transmission have also been postulated to be involved in drug sensitization (6,49,72,75,94,97,98,109). However, projections involving other pathways and neurotransmitters interacting with the dopamine system (45,49,116), as well as effects independent of the dopamine system, should not be ignored (54).

THE HPA AXIS, SENSITIZATION, AND DRUG ADDICTION

The HPA axis also appears to play an important role in drug reward and drug sensitization. For example, it has been shown that stressful environmental conditions or exposure to known stressors can enhance the propensity toward self-administration of drugs with abuse potential (19,62,83,99,100). Furthermore, a specific role for corticosterone in vulnerability to amphetamine and cocaine self-administration has been suggested (62,85,86), and evidence that corticosterone itself can support self-administration behavior exists (84). Finally, individual variability in propensity toward amphetamine self-administration was associated with larger and longer stress-induced increases in dopamine concentrations in the nucleus accumbens, suggesting a link between HPA axis activity and dopamine systems in the determination of drug proclivity (95).

In addition to an involvement of the HPA axis in drug self-administration behavior, there is strong evidence supporting involvement of the HPA axis in drug sensitization. Behaviorally sensitizing drugs have been demonstrated to increase HPA axis activity or affect neural corticosteroid receptor levels (50,61). Repeated or chronic exposure to stressors has been shown to result in sensitized responses to drugs with stimulant effects (23,52,83,93), and vice versa (1). In other words, there is cross-sensitization between stressors and drugs. In addition to repeated stressors, repeated corticosterone administration has been shown to produce or enhance amphetamine and cocaine sensitization (24,69,73). Adrenalectomy reduced amphetamine (89) and nicotine (43) sensitization, and there is some evidence suggesting that sensitization to morphine and amphetamine is dependent specifically upon corticosterone secretion, when sensitization was induced by exposure to stressors (21,22). On the other hand, some results have appeared suggesting that circulating adrenal hormones are not necessary for the development of amphetamine-induced sensitization, because both sham-treated and adrenalectomized rats exhibited sensitization (2). Corticotropin-releasing factor (CRF) may also play a role in the sensitization process, because treatment with an antiserum to CRF was effective in attenuating the development of sensitization to amphetamine (14), and repeated central, but not subcutaneous, application of CRF induced amphetamine sensitization (9).

DOPAMINE/HPA AXIS INTERACTION

In part, the involvement of the HPA axis appears to be tied to interactions with monoamine systems, particularly dopaminergic systems. Lesions of dopaminergic neurons in the ventral tegmental area have been found to alter corticosteroid receptor affinity in the ventral striatum (13) and to reduce basal and stress-induced corticosterone secretion (12). Some effects consequent to alteration of HPA axis activity appear to be mediated by enhancement of dopamine neurotransmission (52,71,118). Stressful manipulations modified locomotor responses to catecholamine receptor agonists (70,120); however, the direction of change appeared to be dependent upon the stress-induction procedures used. Exposure to stress produced changes in the dopamine system similar to those seen with repeated drug exposures (3,8,47,48). Reserpine-induced depletion of monoamines decreased corticosteroid receptors (60). Blockade of monoamine uptake with antidepressant drugs has been shown in several studies to increase corticosteroid receptor mRNA (4,74,96). Corticosterone administration has been found to upregulate tyrosine hydroxylase immunoreactivity in the ventral tegmental area (69). Finally, some recent results indicated that the stress-induced sensitization of the locomotor stimulant effects of drugs injected directly into key components of the mesoaccumbens dopamine pathway were dependent upon corticosterone secretion (20). Clearly, changes in HPA axis activity have been associated with alterations in dopaminergic function and vice versa.

ETHANOL, DOPAMINE, AND HPA AXIS HORMONES

There are several similarities between the effects of ethanol and other stimulant drugs on dopamine systems and the HPA axis. For example, experimenter-administered ethanol as well as ethanol self-administration have been shown to increase dopaminergic neurotransmission (25,36,42,114,115,119). In rats, this increase in dopamine release in the nucleus accumbens appears to be coincident with ethanol's acute stimulant effects (25,42). However, sensitivity of the nucleus accumbens dopamine system to acute ethanol administration was not related to genetically determined alcohol preference (119). The acute stimulant effects of ethanol in mice can be attenuated by dopamine receptor antagonists (51,59,101). Moderate acute doses of ethanol have been shown to increase plasma corticosterone levels (30,44,90). Ethanol drinking has also been associated with increased corticosterone secretion (105) and with alterations in brain CRF levels (34). In addition, adrenal hormones have been implicated in the control of acute ethanol stimulation (112) and ethanol consumption (87). For example, adrenalectomy was shown to reduce the ethanol intake of rats, and intake was restored by corticosterone in their drinking water (31) or by subcutaneous implantation of corticosterone pellets (32). Ethanol intake could also be suppressed by the corticosterone synthesis inhibitor metyrapone, with some blockade of this effect by prior corticosterone treatment (33).

ETHANOL SENSITIZATION, GENETICS, AND STRESS

Our work on the genetics of ethanol sensitization, and the involvement of HPA axis hormones, particularly corticosterone, has been published recently (82,91), as has a review of the behavioral genetics of drug sensitization (76). We had previously shown that FAST and SLOW mice, selectively bred for differential sensitivity to the acute activating effects of ethanol, also differed with respect to their latency to develop ethanol sensitization (78). FAST mice developed a sensitized response more quickly than SLOW mice. However, when given additional ethanol exposure, SLOW mice did develop sensitization. Subsequent work compared C57BL/6J and DBA/2J inbred strain mice, which are known to differ in sensitivity to the acute stimulant effects of ethanol [e.g., (28)]. DBA/2J mice showed sensitization to ethanol [(81); also shown by (16,17)], whereas C57BL/6J mice were resistant to the development of sensitization (81). However, studies using recombinant inbred strains tentatively mapped acute ethanol sensitivity and sensitization to different chromosomal regions of the mouse and found no significant genetic correlation between initial ethanol response and degree of sensitization (16,82). Interestingly, two tentative map locations for acute sensitivity to ethanol's stimulant effects were near the genes *Adh-1*and *Adh-3*, which code for alcohol dehydrogenase enzymes; these areas were not associated with ethanol sensitization (82). These two rigorous data sets, involving over 20 strains each, suggest that differences in the molecular biology of acute ethanol stimulation and sensitization exist.

Because of the growing literature supporting HPA axis involvement in cocaine, amphetamine, and morphine sensitization, we initiated studies designed to examine HPA axis involvement in ethanol sensitization. Our first study determined whether repeated intermittent restraint would produce sensitization to the stimulant effects of ethanol. Subsequent experiments focused on the role of glucocorticoid receptors in mediating the effect of repeated stressor exposures and of repeated ethanol treatment (91). DBA/2J mice, a strain particularly susceptible to the acute stimulant effects of ethanol and to ethanol sensitization, as reviewed above, were used in all studies. We found that untreated mice were significantly less responsive to ethanol than were mice subjected to repeated episodes of restraint stress, mice receiving 10 injections of 1.5 g/kg ethanol, or mice receiving 10 injections of saline. Repeatedly ethanol-treated mice showed the greatest amount of sensitization relative to saline and untreated groups. Restraint-stressed animals also showed sensitization

relative to their untreated controls. These data demonstrate cross-sensitization between stress and ethanol, and suggest a potential role for HPA axis associated changes in ethanol sensitization. This is consistent with mechanisms likely contributing to sensitization to other abused drugs.

In two subsequent studies, the importance of glucocorticoid receptors (GR) in stress-induced and ethanol-induced sensitization of ethanol's locomotor stimulant effects was examined (91). As an oversimplification of our reasoning, because GR are thought to be involved in information storage, and the alternate type of corticosteroid receptors (mineralocorticoid; MR) are thought to be involved in the regulation of the threshold of the stress response [see (18)], it was speculated that GR were more likely to be involved in the long-term changes associated with sensitization. In adrenalectomized rats in which amphetamine sensitization was prevented, treatment with the GR agonist dexamethasone completely restored the sensitized response to amphetamine (89), providing some support for our hypothesis. Also, the sensitization produced by repeated exposure to MK-801, the glutamate antagonist at the NMDA receptor, was blocked by the GR antagonist RU 38486 (113).

In our first study, DBA/2J mice subjected to repeated bouts of restraint stress were more stimulated by ethanol than were mice pretreated with the GR antagonist RU 38486 (20 mg/kg), alone or prior to restraint. Antagonist-treated mice, whether subjected to restraint or not, were no different from untreated controls. In our second study, DBA/2J mice exhibited ethanol sensitization after repeated ethanol treatments that was blocked by pretreatment with RU 38486.

The principal findings of this collection of studies were that repeated exposure to restraint stress sensitized mice to the locomotor stimulant effects of ethanol, stress-induced sensitization of ethanol's locomotor stimulant effects was attenuated by the GR antagonist RU 38486, and RU 38486 was also capable of preventing sensitization to ethanol produced by repeated ethanol injections. These results suggest, first, a similarity between ethanol and other drugs of abuse with respect to involvement of the HPA axis in sensitization and, second, specific involvement of corticosterone and, in particular, GR, in the processes of stress- and ethanol-induced sensitization to the locomotor stimulant effects of ethanol.

Results have appeared since the inception of our studies that have also addressed the involvement of different corticosterone receptor subtypes in drug sensitization or drug self-administration. In one study, the development of nicotine sensitization was prevented by adrenalectomy. The ability to develop a sensitized response to nicotine was restored by replacement treatment with corticosterone or the GR agonist dexamethasone, but not the MR agonist aldosterone (43). These results are in agreement with ours. In another study, although ethanol consumption could be enhanced by exogenous corticosterone administration in adrenalectomized rats, ethanol consumption was not affected by either a GR or MR antagonist administered separately or in combination (32). The authors reporting this finding suggested that enhancing effects of corticosterone on alcohol intake may be mediated by nongenomic cellular mechanisms. Thus, it may be that the specific involvement of the HPA axis in ethanol sensitization and ethanol self-administration differs, or that different experimental conditions need to be explored.

SUMMARY

The molecular determinants of ethanol's effects have been difficult to define compared with those of other drugs with psychomotor stimulant actions. This is partly because ethanol does not act by binding to a defined receptor or transporter, as do many of the other drugs of abuse. However, the complex circuits that define the central nervous system provide many avenues through which similar drug effects may be ultimately produced. The initial effects of two different drugs may occur, for example, via interactions with glutamate receptors in one case and dopamine receptors in the other, but result in similar long-term alterations of a common pathway, such as the mesolimbic dopamine pathway. Because the HPA axis is activated by most, if not all, stimuli that produce sensitization, it is possible that GR activation, as found here, will be found to be critical for the development of behavioral sensitization in general. Given the possibility of a biological link between drug reward and drug sensitization involving HPA axis hormones, study of the sensitization process may elucidate mechanisms relevant to drug abuse. However, much work remains to be done to pinpoint the genetic determinants of drug sensitization, to identify the specific role of HPA axis hormones, and to establish the involvement of changes associated with drug sensitization in the addiction process.

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