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# Central nucleus of the amygdala and the effects of alcohol and alcohol-drinking behavior in rodents

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**Abstract**

This article will review key literature on the effects of alcohol on the amygdala and the involvement of the amygdala in regulating alcohol drinking in mice and rats. Special emphasis will be placed on the central nucleus of the amygdala (CeA) because this nucleus is a major component of the extended amygdala, which has been implicated in regulating alcohol-drinking behavior. Immunocytochemical and in situ hybridization studies indicate that acute high-dose ethanol administration increases c-*fos* expression in GABAergic neurons within the CeA of the rat, suggesting activation of these neurons by ethanol. A similar high-dose (4 g/kg ethanol) effect on c-*fos* expression in the CeA of C57 mice was also observed, whereas the DBA mice showed increased c-*fos* expression in the CeA in the dose range of 1.25–4.0 g/kg. Studies with DBA × C57 F2 intercross mice suggest that there may be a relationship between the neuronal activating effects of ethanol in the CeA and the locomotor stimulating effects of ethanol. Studies with rats examining the effects of acute ethanol or chronic alcohol drinking on local cerebral glucose utilization (LCGU) rates (as a measure of synaptic activity) indicated that (a) acute ethanol (0.25–2.0 g/kg) had little effect on LCGU rates in the CeA; (b) basal LCGU rates were reduced in the CeA as a result of chronic alcohol drinking; and (c) oral self-administration of ethanol increased LCGU values within the CeA. Microdialysis studies demonstrated that acute ethanol (2 g/kg) injection increased dopamine (DA) and serotonin (5-HT) release in the CeA. Microinjection studies indicate that $GABA_A$ receptors within the CeA are involved in oral ethanol self-administration. Overall, the findings from the various studies support a role for the CeA in mediating the stimulating actions of alcohol in mice and regulating alcohol-drinking behavior in mice and rats. © 2002 Elsevier Science Inc. All rights reserved.

*Keywords:* Central nucleus of the amygdala; Alcohol drinking; Extended amygdala; Ethanol; Rodents

## 1. Introduction

The extended amygdala and its interactions with certain limbic structures appear to have important roles in drug addiction and reinstatement of drug self-administration in rodents (Koob, 1999; Koob and LeMoal, 2001; Koob et al., 1998a,b). The major components of the extended amygdala are the central medial nucleus of the amygdala (CeA), the bed nucleus of the stria terminalis (BNST), the nucleus accumbens shell (ACB-sh) and the sublenticular substantia innominata (Alheid and Heimer, 1988; Heimer and Alheid, 1991). These structures have similarities in cellular morphology, immunocytochemistry and connectivity (Alheid and Heimer, 1988). The major components of the extended amygdala receive afferent connections from a number of sources, e.g., the ventral tegmental area (VTA), limbic cortices, hippocampus and basolateral amygdala (BLA), and project to a number of regions, e.g., ventral pallidum (VP), lateral hypothalamus (LH), etc. (Heimer et al., 1991).

A simplified diagram of the extended amygdala and some of its interactions with key limbic structures is shown in Fig. 1. The diagram shows three of the major components of the extended amygdala (i.e., CeA, BNST and ACB-sh). The sublenticular substantia innominata is not included to simplify the diagram. In addition, not all possible connections are illustrated for the regions shown, e.g., the VTA receives reciprocal connections from all the regions that it innervates (Kalivas, 1993; Oades and Halliday, 1987). In addition, within certain regions, there are topographical

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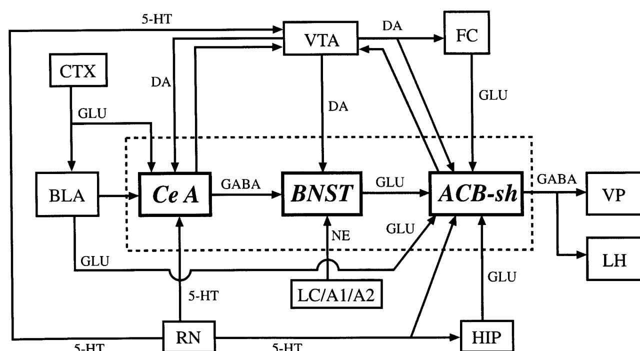


Fig. 1. Simplified diagram of major components of the extended amygdala and their interactions with other limbic structures. The major components of the extended amygdala are the CeA, BNST, ACB-sh and the sublenticular region (not shown). All possible connections are not shown, e.g., most of the reciprocal connections of the VTA are not shown. In addition, within certain regions, there are topographical organizations of connections, which are not indicated. Also, not all regional interconnections of the extended amygdala are illustrated. Rather, only regions, which have been implicated in alcohol addiction, are shown. The extended amygdala appears to integrate inputs from a number of different regions with a major convergence of information occurring in the ACB-sh. The major output of the extended amygdala appears to be via GABA projections from the ACB-sh to the VP and LH. Other abbreviations used: CTX, cerebral cortex; FC, frontal cortex; HIP, hippocampus; LC/A1/A2, locus coeruleus and A1 and A2 norepinephrine (NE) projection regions; RN, raphe nucleus.

organizations (Kalivas et al., 1993; Oades and Halliday, 1987) that are not indicated to maintain the diagram simplicity. The VTA dopamine (DA) system plays a major role in mediating the reinforcing effects of alcohol and alcohol-drinking behavior (Koob et al., 1998a,b; McBride and Li, 1998). The VTA DA system sends major projections to a number of CNS sites, including the CeA (Asan, 1998) and the ACB-sh (Kalivas et al., 1993; Oades and Halliday, 1987). These two components of the extended amygdala may be involved in alcohol drinking (Koob and LeMoal, 2001; Koob et al., 1998a,b). In addition, there is evidence for the involvement of the serotonin (5-HT) system in regulating alcohol drinking (McBride and Li, 1998). Moreover, findings from microdialysis and microinjections studies suggest the involvement of the amygdala 5-HT system in mediating the acute effects of moderate to high doses of alcohol (Yoshimoto et al., 2000) and alcohol-drinking behavior (Dyr and Kostowski, 1995). The norepinephrine (NE) systems projecting primarily from the A1 and A2 areas appear to be involved in opiate withdrawal and relapse in rats (Aston-Jones et al., 1999) and these two regions, along with the locus coeruleus (LC), may have a role in reinstatement of alcohol self-administration following a prolonged period of abstinence. The major output of the extended amygdala occurs through the ACB-sh where DA, 5-HT and glutamate (GLU) inputs from several CNS regions converge (Fig. 1). The major feed forward system appears to be from the medium GABA spiny neuronal projections in the ACB-sh to the VP and LH.

This review will focus on the CeA part of the extended amygdala with regard to the involvement of this nucleus in alcohol drinking and the acute effects of alcohol in rodents. This review will attempt to integrate findings from several disciplines and target the effects of acute and chronic alcohol on CeA neuronal systems.

## 2. Effects of alcohol on CeA neurons

The protooncogene c-*fos* has received much attention as a marker for cellular activity and as a tool for mapping functional neuronal pathways (Chiasson et al., 1997; Curran and Morgan, 1985; Dragunow and Faull, 1989; Greenberg et al., 1986; Herrera and Robertson, 1996; Kovacs, 1998; Morgan and Curran, 1989), with maximal expression of Fos protein occurring between 1 and 3 h after stimulation (Cullinan et al., 1995; Ding et al., 1994; Sonnenberg et al., 1989). Under basal conditions, the detectable levels of c-*fos* mRNA and its protein Fos are very low (Hughes et al., 1992), indicating that normal neuronal activity is usually not sufficient to induce c-*fos*. In addition, neurons may differ in their stimulus threshold for c-*fos* induction and in the time course of c-*fos* elevation and decay (Dragunow and Faull, 1989). Although positive c-*fos* induction could provide valuable information regarding activated pathways, negative results with c-*fos* do not necessarily indicate that neuronal activity did not increase as a result of experimental manipulation.

With the above caveats in mind, intraperitoneal (ip) injection of 1.5 or 3.0 g/kg ethanol into Sprague–Dawley rats increases c-*fos* immunoreactivity 2–4 h later in the BNST, CeA and LC, as well as in the hypothalamic paraventricular nucleus, Edinger-Wesphal nucleus and the parabrachial nucleus (Chang et al., 1995). Although somewhat diminished, Fos immunoreactivity was still evident in the CeA 16 h after the ethanol injection. The intraperitoneal administration of a low dose of ethanol (0.75 g/kg) produced only a small increase in Fos immunoreactivity. Furthermore, chronic intraperitoneal injection of a sedative dose (3 g/kg ethanol) for 17 or 24 days resulted in a desensitization of Fos immunoreactivity (Chang et al., 1995). The results with acute administration suggest that moderate to high doses of ethanol can activate neurons within the CeA of the rat and that this effect is lost with repeated high-dose ethanol injections.

Using c-*fos* immunoreactivity and in situ hybridization, it was determined that acute intraperitoneal injection of high-dose (2 g/kg) ethanol increased c-*fos* immunoreactivity in the CeA of rats and that over 70% of the cells expressing increased c-*fos* immunoreactivity were GABAergic neurons (Morales et al., 1998). Within the CeA, GABAergic neurons usually contain either corticotropin-releasing factor (CRF) or pro-enkephalin (ENK; Veinante et al., 1997). The ethanol-induced c-Fos immunoreactivity was confined mainly to neurons expressing

ENK with only a small number expressing CRF (Criado and Morales, 2000). These results suggest that a subpopulation of GABAergic cells, i.e., those expressing ENK, is activated by ethanol at doses, which produce motor impairment and sedation in rats. However, it is not possible to determine if the acute effects of high-dose ethanol are occurring within the CeA directly or indirectly on GABAergic neurons and/or if the effects are occurring at sites projecting to the CeA resulting in the activation of GABAergic cells. For example, acute systemic administration of similar doses of ethanol increase VTA DA neuronal activity (Campbell et al., 1996; Gessa et al., 1985) and pharmacological stimulation of the VTA with a substance P analogue increased c-*fos* expression in the CeA (Cornish and van den Buuse, 1996). Therefore, the effects of ethanol observed in the CeA could be produced by its actions outside this nucleus.

Ethanol-induced c-Fos expression was studied in rat lines selected for low and high alcohol consumption, i.e., the alcohol-preferring (P) and -nonpreferring (NP) lines and the Alko-alcohol (AA) and Alko-nonalcohol (ANA) lines (Thiele et al., 1997). These rat lines were obtained by selectively mating the highest alcohol-drinking male and female rats with each other and the lowest alcohol-drinking male and female rats with each other (see McBride and Li 1998). Expression of c-Fos was examined 2 h after the intraperitoneal injection of 1 (moderate)- or 3 (sedative)-g/kg ethanol. Both doses produced marked increases in c-Fos production in the CeA of these rat lines but there were no significant differences between the high alcohol- and low alcohol-consuming lines. These data suggest that there may not be a relationship in rats between alcohol preference and sensitivity of CeA neurons to acute ethanol. However, a more comprehensive study with lower ethanol doses (and perhaps multiple injections) would need to be tested before any conclusion could be drawn regarding this relationship. However, lower tissue levels of neuropeptide-Y have been reported in the CeA of alcohol-naive P versus NP rats and in alcohol-naive high alcohol-drinking (HAD) versus low alcohol-drinking (LAD) rats (Hwang et al., 1999), suggesting that there may be innate differences in this amygdaloid nucleus, which could contribute to the disparate alcohol-drinking behaviors of these selectively bred lines of rats.

In mice, the acute intraperitoneal administration of 1.25–4.0-g/kg ethanol increased c-*fos* immunoreactivity after 1 h in the CeA of DBA/2J inbred mice but only the highest dose produced an increase in c-*fos* expression in the CeA of C57BL/6J (Hitzemann and Hitzemann, 1997). Although strain differences were also observed in other regions, higher c-*fos* expression in the DBA compared to C57 mice was usually observed only at the highest dose in these other regions. However, after repeated injections of high doses of ethanol (4 g/kg for 4 days), the increased c-*fos* expression was no longer observed in the CeA of DBA mice (Ryabinin and Wang, 1998), suggesting that desensitization to the activating effects of this high dose of ethanol may have developed. These results indicate a strain difference to the neuronal activating effects of acute ethanol in the amygdala between C57 and DBA mice (Hitzemann and Hitzemann, 1997). The differences in the CeA are in agreement with data obtained from behavioral experiments in which the effects of moderate doses of ethanol on locomotor activity were examined. These studies indicated that moderate doses of ethanol (1–2 g/kg) stimulated locomotor activity in DBA mice but had little effect in C57 mice (Crabbe, 1986; Crabbe et al., 1982; Dudek and Phillips, 1990; Dudek and Tritto, 1994; Dudek et al., 1991). In a follow-up study, B6D2 $F_2$ intercross mice were first phenotyped with regard to their locomotor activity response to ethanol, and the highest and lowest responders were then tested for c-*fos* expression following ethanol administration (Demarest et al., 1998). The mice with the highest locomotor response also exhibited the highest increase in c-*fos* expression in the CeA following ethanol administration, suggesting a relationship between the activating effects of alcohol on CeA neurons and the locomotor stimulating effects of ethanol (Demarest et al., 1998).

On the other hand, an inverse relationship between sensitivity to the stimulating effects of ethanol on neuronal activity within the CeA and alcohol preference in these mouse strains is indicated because C57 mice are high alcohol consumers, whereas DBA mice are low alcohol drinkers (Roger and McClearn, 1962). However, it is difficult to relate CNS effects of ethanol with preference in these two mouse strains because taste and caloric factors play major roles in influencing ethanol intake of the C57 strain (McMillen and Williams, 1998). Moreover, additional inbred strains with diverse alcohol preference characteristics would need to be studied to possibly validate an inverse relationship between alcohol preference and sensitivity to the stimulating effects of ethanol on neuronal activity with the CeA.

Alcohol drinking did produce regional changes in c-Fos expression in C57BL/6H mice (Bachtell et al., 1999). C57 mice trained to consume a 10% ethanol/10% sucrose solution during a 30-min limited access period had an increased number of c-Fos positive cells in the CeA, ACB-core and Edinger-Wesphal nucleus. These results indicate that the CeA of the C57 mice is sensitive to the chronic effects of alcohol under these drinking conditions. Desensitization may not have developed under these conditions because intermittent exposure to only relatively low levels of ethanol occurred. In fact, sensitization to the effects of ethanol may have developed with this limited access paradigm because the blood levels of ethanol attained with chronic drinking would be well below the levels reached following an injection of 4 g/kg, the only dose that increased c-*fos* expression in the CeA of C57 mice. Furthermore, these results suggest

that the CeA may have a role in regulating alcohol drinking in mice.

## 3. Effects of alcohol and alcohol drinking on general synaptic activity within the CeA

The 2-[$^{14}$C]-deoxyglucose (2-DG) technique has been used in alcohol research mainly to determine local cerebral glucose utilization (LCGU) rates immediately following alcohol administration or consumption. Studies thus far indicate that the acute administration of alcohol produces anatomically distinct changes in LCGU that are dependent upon time, dose and route of administration (Lyons et al., 1998; Porrino et al., 1998; Williams-Hemby and Porrino, 1994, 1997; Williams-Hemby et al., 1996). The highest demand for glucose utilization involves synaptic activity (Kadekaro et al., 1983; Kurumaji et al., 1993; Schwartz et al., 1979). Therefore, changes in LCGU rates following ethanol administration may indicate mainly changes in synaptic activity. Unfortunately, the 2-DG method cannot discriminate between changes in excitatory or inhibitory synaptic activity. Therefore, increases in LCGU values following ethanol administration do not necessarily indicate increased excitation, and conversely, decreases in LCGU rates do not necessarily indicate decreased excitation. Despite this shortcoming, the 2-DG procedure can provide valuable information on the global regional effects of acute and chronic alcohol administration, which can identify CNS sites where ethanol in having an action.

The acute administration of 0.25-g/kg ethanol (either intraperitoneal or intragastric) to Sprague–Dawley rats tended to increase LCGU rates in many CNS regions but did not alter LCGU values in the CeA (Williams-Hemby and Porrino, 1994, 1997). Higher intraperitoneal doses of 0.5 and 1.0 g/kg ethanol had little effect on LCGU rates in the CeA, but the 1.0 g/kg dose did have a tendency to reduce LCGU in many other CNS regions (Williams-Hemby and Porrino, 1994). Moderate to high intragastric doses of ethanol (1 and 2 g/kg) also did not alter LCGU values in the CeA of rats. These ethanol doses, however, did produce elevated LCGU rates in many other CNS regions (Williams-Hemby and Porrino, 1997). On the other hand, male Wistar rats trained to consume a 10% ethanol/5% sucrose solution during a 15-min session had higher LCGU rates in the CeA, as well as in several other CNS regions (e.g., ACB-sh and VTA), relative to values for the water control group (Porrino et al., 1998), when measured shortly after ending the drinking session. The results of these studies suggest that, compared to other CNS regions, synaptic activity in the CeA of the rat is relatively insensitive to acute low to moderate doses of ethanol. On the other hand, chronic alcohol drinking under limited access conditions did increase synaptic activity in the CeA when measured following the access session. Because the blood alcohol levels attained under this limited access condition would likely fall within the range of values produced by acute ethanol administration, the results suggest that repeated low-dose ethanol exposure may produce sensitization to the effects of ethanol on synaptic activity within the CeA.

In another study, the effects of chronic alcohol drinking under limited access conditions were examined using the selectively bred alcohol-preferring P line of rats (Smith et al., 2001). In addition to the rat line used, this study differed in a number of ways from the study with Wistar rats (Porrino et al., 1998). For example, a sweetened alcohol solution was not needed to induce drinking with P rats. Also, the intakes of the P rats were threefold higher, and with Wistar rats, LCGU measurements were taken shortly after ending the limited access session, whereas, with the P rats, LCGU measurements were obtained 1 h prior to the normally scheduled access period. Consequently, the study with Wistar rats measured the response to ethanol in rats with a chronic history of intermittent exposure to low levels of ethanol, whereas the study with P rats examined the effects of chronic intermittent exposure to moderate levels of ethanol on subsequent basal synaptic activity (Smith et al., 2001). Significantly lower LCGU values (20–25%) were observed in the CeA and ACB-sh, as well as in other key structures (e.g., VTA, BLA, VP and LH), of the alcohol-drinking group of P rats compared to the water control group. These results suggest that there is a pronounced reduction in basal synaptic activity associated with chronic drinking on a limited access schedule. This reduction may be a reflection of an adaptive response of neuronal systems to compensate for the chronic intermittent activating effects of ethanol following the daily scheduled access sessions. Daily episodes of alcohol drinking may, over time, produce in the P rats a heightened synaptic response to ethanol that is overcompensated for when ethanol is not available during the interval between access sessions, resulting in reduced basal LCGU rates.

The study with the P rats also examined whether the effects of chronic alcohol drinking on LCGU rates persisted following a prolonged alcohol-free period (Smith et al., 2001). LCGU rates were determined in P rats that had been abstinent from alcohol for 2 weeks following chronic alcohol drinking under limited access conditions. LCGU values in the group of P rats deprived of alcohol for 2 weeks tended to return toward control (alcohol-naive) levels in many CNS regions, although in a number of CNS regions, there was only a partial (e.g., ACB-sh and LH) or very little (e.g., VP and VTA) return to control values. LCGU values in the BLA and, to a lesser degree, the CeA returned to control levels (Smith et al., 2001). These results suggest that alterations in basal synaptic activity are produced in the extended amygdala and associated structures with chronic alcohol drinking and that some of these changes persist in the absence of alcohol such that the regional CNS pattern of LCGU rates does not resemble either the naive or the alcoholic state.

Overall, the results suggest that the acute administration of low to moderate doses of ethanol has little effect on synaptic activity within the CeA of the rat. However, chronic intermittent exposure to ethanol may produce sensitization to the effects of ethanol on synaptic activity and may also reduce basal synaptic activity within the CeA. Furthermore, chronic alcohol drinking can produce long-lasting alterations in regions within the extended amygdala in the absence of alcohol, which may contribute to the reinstatement of alcohol self-administration following a prolonged period of abstinence.

## 4. Microdialysis studies to examine neurotransmitter systems and the effects of ethanol in the CeA

In one study, the effects of acute intraperitoneal ethanol on the extracellular levels of DA and 5-HT in the CeA of Wistar rats were examined (Yoshimoto et al., 2000). Within 20 min of intraperitoneal injection of 2-g/kg ethanol, the extracellular levels of DA and 5-HT in the CeA significantly increased by 270% and 160% over baseline, respectively. The administration of 1-g/kg ethanol produced a slightly smaller response, whereas the 0.5-g/kg dose had no measurable effect on the extracellular levels of DA or 5-HT. A similar dose response effect for ethanol has been previously reported in the ACB of Wistar rats (Yoshimoto et al., 1991). With systemic injections, it is not possible to determine the site or sites of action of ethanol. As discussed above, this could occur at the level of the DA cell bodies in the VTA, where there is evidence ethanol can activate DA neurons both in vivo (Campbell et al., 1996; Gessa et al., 1985) and in vitro (Brodie et al., 1990). For the 5-HT system, activation of raphe nuclei 5-HT cell bodies does not appear to underlie the elevated extracellular levels of 5-HT following ethanol administration (Thielen et al., 2001). Local ethanol administration through the dialysis probe did not clearly elevate the extracellular levels of 5-HT in the CeA (Yoshimoto et al., 2000). Therefore, the effects of ethanol on increasing the extracellular levels of 5-HT in the CeA may be occurring at other sites projecting to the CeA that regulate terminal 5-HT release.

Dysregulation of the stress-regulatory CRF system in the CeA has been hypothesized to be a factor in genetically determined alcohol preference (Richter et al., 2000). To test this hypothesis, basal and restraint stress-induced CRF efflux was examined using microdialysis procedures in the Sardinian alcohol-preferring (sP) and -nonpreferring (sNP) rats. Basal extracellular levels of CRF in the CeA were higher in the sP than sNP rats (Richter et al., 2000) and stress significantly elevated the extracellular levels of CRF in the CeA of both lines. These results suggest that the sP rats have a higher basal efflux of CRF in the CeA, which may contribute to the initiation and maintenance of their high alcohol-drinking behavior.

Another microdialysis study examined the possible involvement of the excitatory amino acid (EAA) system within the amygdala on cues associated with ethanol, i.e., conditioned ethanol effects (Quertemont et al., 1998). In this study, changes in the extracellular levels of GLU within the BLA to an odor cue repeatedly associated with acute ethanol injections were determined. Whereas ethanol administration without the cue did not alter the extracellular levels of GLU, the presentation of both the odor cue and ethanol injection significantly increased the extracellular levels of GLU in the BLA (Quertemont et al., 1998). The odor cue paired with saline injections was without effect. These results suggest that the EAA system within the BLA may be involved in learning associations between external stimuli (odor) and the intrinsic effects of ethanol, i.e., a conditioned drug response. The BLA projects to the CeA (Fig. 1) and the GLU response in the BLA may alter the functioning of the CeA, especially with regard to the effects of repeated ethanol administration.

## 5. Manipulation of the CeA transmitter systems and alcohol drinking

The involvement of the $GABA_A$ receptor within the CeA was examined in Wistar rats trained to respond for 10% ethanol and water in a two-lever, free-choice operant task (Hyytia and Koob, 1995). Bilateral microinjection of the competitive $GABA_A$ receptor antagonist SR 95531 into the CeA significantly reduced responses on the ethanol lever without altering responses on the water lever, suggesting that activation of $GABA_A$ receptors within the CeA is involved in mediating ethanol self-administration (Hyytia and Koob, 1995). In addition, ibotenic acid lesions of the CeA reduced the voluntary alcohol consumption of Sprague–Dawley rats from approximately 2.5 to 1 g/kg/day without affecting total fluid intake (Moller et al., 1997), lending support for a role of the CeA in mediating alcohol drinking in the rat. Furthermore, microinjection of the $GABA_A$ receptor agonist muscimol into the CeA decreased operant responding for ethanol in dependent rats but had little effect in nondependent Wistar rats (Roberts et al., 1996). In this study, rats were made alcohol dependent using a vapor chamber method. The control group was handled in a similar manner but was exposed to air only. The authors suggest that muscimol is effective in the dependent rats but not in the nondependent rats because the reinforcing effects of ethanol and the neurotransmitter pathways mediating reward are altered after the development of dependence. One of the problems with this interpretation is that the number of reinforcers given by the nondependent group at the time of the muscimol microinjection is so low that any further reduction could not be detected. To circumvent this problem, the authors did a separate experiment to test the effects of muscimol

injection in the CeA on responding for ethanol and water (Roberts et al., 1996). Although no effect was observed on ethanol or water responding following injection of muscimol in the nondependent rats, a group of dependent rats was not tested under similar conditions. Therefore, it is difficult to reconcile the lack of effect of muscimol in the nondependent group (Roberts et al., 1996) with the data indicating a clear effect of a $GABA_A$ antagonist on ethanol responding (Hyytia and Koob, 1995). One possibility is that, in the nondependent rats, $GABA_A$ receptors in the CeA are nearly maximally activated. Therefore, muscimol has little effect on alcohol drinking.

Another microinjection study indicated that local administration of 5-$HT_3$ antagonists into the amygdala reduced ethanol intake of Wistar rats during a 2-h scheduled access period (Dyr and Kostowski, 1995). These results suggest that activating 5-$HT_3$ receptors within the amygdala may be involved in regulating alcohol drinking. The shortcomings of this study were that ethanol intakes were modest and placements were not consistently within a defined amygdaloid nuclei. Despite the shortcomings, the study did present encouraging evidence for the involvement of the 5-HT system and 5-$HT_3$ receptors within the amygdala in alcohol-drinking behavior.

## 6. Conclusions

The results thus far provide support for the involvement of the CeA in mediating the locomotor stimulating effects of alcohol in mice and alcohol-drinking behavior of mice and rats. Within the CeA of rats, GABAergic neurons and DA and 5-HT projections appear to be activated by acute high-dose ethanol. In addition, alcohol drinking under daily limited access conditions appears to enhance the effects of ethanol in the CeA, as indicated by increased c-*fos* expression and higher LCGU values. Chronic alcohol drinking may also produce long-term alterations in basal synaptic activity within the extended amygdala and associated limbic structures, which may contribute to reinstatement of alcohol self-administration. Furthermore, activation of $GABA_A$ and 5-$HT_3$ receptors within the amygdala may be involved in regulating alcohol drinking. Additional studies need to be undertaken to better define the role of the CeA and its transmitter systems in alcohol drinking and reinstatement of alcohol self-administration.

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