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Ethanol-Induced c-Fos Expression in Catecholamine- and Neuropeptide Y-Producing Neurons in Rat Brainstem

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Background: Previous studies have used c-Fos-like immunoreactivity (cFLI) to examine the neuroanatomical location of cells that are activated in response to ethanol administration. However, the use of cFLI alone fails to reveal the phenotypical identity of cells. In the present study we used double-labeling procedures to identify the neurochemical phenotype of neurons that showed ethanol-induced cFLI in the rat brainstem.

Methods: Individual groups of rats received intraperitoneal injection of ethanol (1.5 g/kg or 3.5 g/kg) or isotonic saline (23 ml/kg). To assess the specificity of cFLI induced by ethanol, we injected other rats with the drug lithium chloride (LiCl; 76 mg/kg). Two hours after injection, rats were killed and their brains were processed for immunohistochemistry.

Results: Both doses of ethanol promoted cFLI in several brainstem regions, including the nucleus of the solitary tract (NTS), the locus coeruleus (LC), and the ventrolateral medulla (VLM). Although LiCl caused significant cFLI in the NTS, this drug promoted only minimal cFLI in the VLM and no significant activation in the LC. We found that a significant proportion of tyrosine hydroxylase (TH)-positive neurons coexpressed ethanol-induced cFLI in the VLM (~75–85%), the NTS (~65–75%), and the LC (~30–65%). Additionally, a significant proportion of neuropeptide Y (NPY)-producing neurons in the VLM coexpressed ethanol-induced cFLI (~60–75%). On the other hand, LiCl promoted activation of TH-positive neurons in the VLM and the NTS but failed to stimulate cFLI in TH-producing neurons in the LC or in NPY-producing neurons of the VLM.

Conclusions: Neurons in the rat brainstem that show ethanol-induced c-Fos expression produce catecholamines and NPY. This research demonstrates the usefulness of double-labeling immunohistochemistry procedures for identifying the neurochemical identity of neurons that are activated after ethanol administration.

Key Words: Alcohol, Locus Coeruleus, Neuropeptide Y, Norepinephrine, Ventrolateral Medulla.
by itself, fails to reveal the phenotypical identity of activated cell populations. However, by labeling for cFLI and specific neurotransmitters in the same tissue by using double-labeling immunohistochemistry procedures, it is possible to identify the neurochemical phenotype of cells that show cFLI in response to drug administration (Hoffman et al., 1992, 1993; Matta et al., 1993, 1997). This is possible because c-Fos protein is typically confined to the cell nucleus whereas neurotransmitter is located in cytoplasm, thus making it possible to simultaneously visualize both labeled proteins.

In the present study, we used double-labeling procedures to begin characterizing cells that are activated by ethanol administration in the brainstem. Previous research has indicated that the catecholamine norepinephrine (NE) may be involved in regulating voluntary ethanol ingestion and the intoxicating effects that are produced by this drug (Brown et al., 1977; Hodge et al., 1996; Lister et al., 1989; Mao and Abdel-Rahman, 1996). Additionally, ethanol administration has been found to increase synthesis, turnover, and release of NE (Carlsson and Lindqvist, 1973; Corrodi et al., 1966; Hunt and Majchrowicz, 1974; Karoum et al., 1976; Pohorecky and Jaffe, 1975), and ethanol induces cFLI in brainstem regions known to be populated by catecholaminergic cells (i.e., the LC, ventrolateral medulla [VLM], and NTS) (Cunningham and Sawchenko, 1988; Palkovits et al., 1992; Riche et al., 1990; Zardetto-Smith and Gray, 1990, 1995). Therefore, we assessed coexpression of cFLI with tyrosine hydroxylase (TH) (the rate-limiting enzyme in catecholamine biosynthesis) in the brainstem. Furthermore, we examined coexpression of ethanol-induced cFLI with neuropeptide Y (NPY), a neuropeptide that is coexpressed with catecholamines in the brainstem (Everitt et al., 1984; Sawchenko et al., 1985) and that recently has been implicated in modulating sedative effects produced by ethanol and voluntary ethanol consumption (Ehlers et al., 1998; Hwang et al., 1999; Thiele et al., 1998a).

Finally, as a control to assess specificity of ethanol-induced cFLI, we also examined double labeling in animals that were administered lithium chloride (LiCl). We used a dose of LiCl that has been found to yield comparable conditioned taste aversions and that has been shown to cause cFLI induction in some of the same brainstem regions as the largest dose of ethanol used in the present study (Thiele et al., 1996).

**METHODS**

**Animals**

Subjects were male Long-Evans rats that weighed between 300 and 400 g and were individually housed in stainless steel cages on a 12 hr light-dark cycle. Laboratory rat chow and water were provided ad libitum. In an attempt to reduce stress-induced c-Fos induction, rats were acclimated to handling for approximately 2 weeks before the start of the experiment. All procedures used in the present research were in compliance with National Institutes of Health guidelines, and the protocols were approved by the University of Washington Animal Care Committee.

**Drug Administration**

Different groups of rats were used for NPY and TH double-labeling studies, and the studies were run at different times; however, the procedures were identical and were as follows. On the test day, rats were distributed to four groups equated for body weight (n = 5 per group). Each rat was removed from its cage, given an intraperitoneal injection of drug, and then immediately returned to its cage. To assess potential dose-dependent effects of ethanol on cFLI, we administered two doses of ethanol: 1.5 g/kg or 3.5 g/kg, 15% (w/v) mixed in isotonic saline. As a control, rats in a third group were given an injection of isotonic saline in a volume equal to the largest dose of ethanol (23 ml/kg). Finally, a fourth group of rats were given an injection of LiCl (76 mg/kg; 0.15 M). This dose of LiCl and the largest dose of ethanol yield comparable saccharin aversions after one-trial taste aversion conditioning and produce similar patterns of cFLI in the brainstem (Thiele et al., 1996). Two hours after injection, rats were anesthetized with Equithesin (3.3 ml/kg ip) and trancardially perfused with isotonic phosphate-buffered saline (PBS) followed by 4% paraformaldehyde in 0.1 M phosphate buffer. Brains were removed and postfixed for approximately 48 hr and then were processed for immunohistochemistry.

**Immunohistochemistry Procedures**

We cut 50 μm slices from the brainstem with a vibrotome in the coronal plane. Tissue was collected just caudal to the AP (approximately −14.30 mm relative to bregma) and rostral through the LC (approximately −10.60 mm relative to bregma). Tissues were rinsed in PBS, incubated 20 min in 0.3% H2O2 in absolute menthol to quench endogenous peroxidase, rinsed, and incubated 1 hr in 1% gelatin and 5% normal goat serum in PBS. Slices were then transferred without rinsing to the primary antibody solution (mixed in PBS) that consisted of 0.005 g/ml polyclonal rabbit antisemur (Santa Cruz Biotechnology, Santa Cruz, CA; 1:20,000), which recognizes residues 3 through 16 of the c-Fos protein. After approximately 48 hr of incubation at 4°C, slices were rinsed and processed by using the ABC method (Vector Laboratories, Burlingame, CA). Slices were transferred to biotinylated goat antirabbit antibody for 1 hr, rinsed, transferred to avidin-biotinylated peroxidase for 1 hr, rinsed again, and developed with diaminobenzidine substrate intensified with nickel sulfate (6 min), which produced dark blue-black cFLI nuclei. After an overnight rinse in PBS, sections were run through a second assay. Sections from the NPY study were incubated for 1 hr in 1% gelatin and 5% normal goat serum in PBS, whereas sections from the TH study were incubated for 1 hr in 1% gelatin and 5% normal horse serum in PBS. Sections were then transferred without rinsing to either rabbit anti-NPY (Sigma Chemical, St. Louis, MO; 1:50,000) or mouse anti-TH (Sigma Chemical; 1:80,000). After approximately 48 hr of incubation on ice (4°C), slices were rinsed and transferred to avidin-biotinylated goat antirabbit antibody (NPY study) or biotinylated horse antimouse antibody (TH study) for 1 hr. Sections were then rinsed and transferred to avidin-biotinylated peroxidase for 1 hr, rinsed again, and developed in diaminobenzidine substrate without the nickel sulfate (which produced light-brown cell bodies). Thus, double-labeled cells were seen as dark blue-black nuclei surrounded by light-brown cell bodies. Finally, slices were rinsed, mounted on slides, and cover-slipped with Permoun. As a control to assess potential nonspecific staining in each assay, some sections were run through the assay either without primary antibody (anti-NPY or anti-TH) or without secondary antibody. Cell staining was absent when primary or secondary antibody was omitted.

**Scoring Immunohistochemistry and Data Analyses**

Group treatments were masked on all slides during data quantification. For each brain region examined, one section was scored per brain, and care was taken so that structures were scored in approximately the same
plane between brains. Camera lucida drawings were prepared in an area of approximately 0.38 mm² from c-Fos immunoreactive sections, in which the number and location of c-Fos positive nuclei were recorded. Counts were also made of neurotransmitter-positive cells (NPY or TH) and of cells that coexpressed the c-Fos and neurotransmitter proteins. We used analyses of variance (ANOVA) to analyze the cell count data and conducted post hoc analyses by using Bonferroni tests. One-way ANOVAs assessed differences between drug-treated groups (data collected from the LC), whereas two-way ANOVAs assessed differences between drug treatment at different brain regions through the caudal-rostral extent of the brainstem (data collected from the NTS and VLM). For both cFLI data and double-labeling data, the group injected with saline served as the control comparison. In all cases, significance was accepted at $p < 0.05$ (two-tailed).

RESULTS

As reported previously (Thiele et al., 1996), ethanol-induced cFLI was observed in the AP and the PBN; however, because significant double labeling was not observed in these regions, these data are not presented. The pattern of ethanol-induced cFLI did not differ between the NPY and the TH studies, so only cFLI data from the TH study are reported. Although NPY staining in the LC and the NTS has been reported with immunohistochemistry procedures (Everitt et al., 1984), the antibody we used in the present study revealed NPY staining only in the VLM.

Ethanol-Induced cFLI and Double Labeling With TH and NPY in the VLM

Drug-induced cFLI in the VLM is presented in Fig. 1A. Both the 1.5 g/kg and 3.5 g/kg doses of ethanol induced significant cFLI relative to the saline injection throughout the caudal-rostral extent of the VLM, in both the noradrenergic A1 (caudal) and adrenergic C1 (rostral) subregions. Furthermore, the 3.5 g/kg dose of ethanol induced significantly greater c-Fos expression than the 1.5 g/kg dose, which indicated a dose-response effect. However, when compared with the saline injection, LiCl promoted significant cFLI only at −13.80 mm relative to bregma. ANOVA on the data revealed a significant drug treatment effect [$F(3,16) = 51.81$], a significant brain regions effect [$F(3,48) = 27.61$], and a significant interaction between these variables [$F(9,48) = 2.46$]. A Bonferroni test confirmed the individual group differences.

Double-labeling data of cFLI with TH in the VLM are presented in Fig. 1B, and photomicrographs representative of these data are in Fig. 2A through 2C. When compared with the saline injection, both doses of ethanol caused cFLI in a significant percentage of TH-producing cells throughout the entire extent of the VLM, and there were no significant differences between the two ethanol-treated groups. LiCl induced significant levels of cFLI in TH-producing cells near the caudal end of this brainstem region. At −14.30 mm and −13.80 mm relative to bregma, ~75% to 85% of the TH-positive cells coexpressed ethanol-induced cFLI. In this same region, double labeling was seen in ~35% to 55% of the TH-positive cells after LiCl injection. ANOVA revealed a significant drug treatment effect [$F(3,16) = 110.55$] and a significant brain regions effect [$F(3,48) = 18.17$]. A Bonferroni test confirmed the group differences. A slightly different pattern of coexpression emerged with the NPY data (Fig. 1C and Fig. 2D through 2F). Both doses of ethanol induced cFLI in a significant number of NPY-positive cells throughout the entire VLM (~60–75% coexpression in the caudal region) relative to the saline treatment, and there were no significant differences between the ethanol-treated groups. However, LiCl completely failed to promote any significant level of coexpression. ANOVA was significant and showed a significant drug treatment effect [$F(3,16) = 26.04$] and a significant brain regions effect [$F(3,48) = 4.28$]. A Bonferroni test run on the data confirmed the conclusions.
Drug-induced cFLI in the NTS is presented in Fig. 3A. Relative to saline injection, both doses of ethanol and LiCl induced significant cFLI in this A2 (noradrenergic) region of the NTS, and these three groups did not differ significantly. ANOVA revealed a significant drug treatment effect \([F(3,16) = 5.25]\) and a significant brain regions effect \([F(1,16) = 6.98]\). Data that show double labeling of cFLI with TH in the NTS are presented in Fig. 3B, and representative photomicrographs through the NTS are presented in Fig. 4A through 4C. When compared with the saline treated group, in the most caudal aspect of the A2 region (\(-14.30\) mm relative to bregma) ethanol promoted a significant level of cFLI in TH-producing cells (\(\approx 20\%\) coexpression), whereas significant coexpression was caused by both ethanol (\(\approx 65-75\%\) of TH-positive cells) and LiCl (\(\approx 50\%\) of TH-positive cells) at \(-13.80\) mm relative to bregma. There were no significant differences between the LiCl- and ethanol-treated groups. ANOVA on the double-labeling data revealed a significant drug treatment effect \([F(3,16) = 13.08]\), a significant brain regions effect \([F(1,16) = 35.15]\), and a significant interaction between the variables \([F(3,16) = 3.85]\). Post hoc tests confirmed the conclusions.

**Ethanol-Induced cFLI and Double Labeling With TH in the NTS**

Drug-induced cFLI in the NTS is presented in Fig. 3A. Relative to saline injection, both doses of ethanol and LiCl induced significant cFLI in this A2 (noradrenergic) region of the NTS, and these three groups did not differ significantly. ANOVA revealed a significant drug treatment effect \([F(3,16) = 5.25]\) and a significant brain regions effect \([F(1,16) = 6.98]\). Data that show double labeling of cFLI with TH in the NTS are presented in Fig. 3B, and representative photomicrographs through the NTS are presented in Fig. 4A through 4C. When compared with the saline treated group, in the most caudal aspect of the A2 region (\(-14.30\) mm relative to bregma) ethanol promoted a significant level of cFLI in TH-producing cells (\(\approx 20\%\) coexpression), whereas significant coexpression was caused by both ethanol (\(\approx 65-75\%\) of TH-positive cells) and LiCl (\(\approx 50\%\) of TH-positive cells) at \(-13.80\) mm relative to bregma. There were no significant differences between the LiCl- and ethanol-treated groups. ANOVA on the double-labeling data revealed a significant drug treatment effect \([F(3,16) = 13.08]\), a significant brain regions effect \([F(1,16) = 35.15]\), and a significant interaction between the variables \([F(3,16) = 3.85]\). Post hoc tests confirmed the conclusions.

**Ethanol-Induced cFLI and Double Labeling With TH in the LC**

Data showing drug-induced cFLI in the LC are presented in Fig. 5A. As with the VLM and NTS, when compared with the saline treatment, both doses of ethanol caused significant induction of cFLI in the LC, at approximately \(-10.60\) mm relative to bregma. Furthermore, the 3.5 g/kg dose of ethanol promoted significantly greater
cFLI than the 1.5 g/kg dose in this region. On the other hand, LiCl injection failed to promote cFLI in the LC. ANOVA run on LC data attained statistical significance \[ F(3,16) = 5.69 \], and a Bonferroni test confirmed the individual group differences.

**DISCUSSION**

Consistent with previous research (Ryabinin et al., 1997; Thiele et al., 1996, 1997, 1998b), ethanol caused dose-dependent cFLI in several brainstem regions, including the NTS (Fig. 3A) and the LC (Fig. 5A), as well as the AP and PBN (data not shown). Additionally, we found that ethanol caused robust cFLI through the caudal-rostral extent of the VLM (Fig. 1A). Interestingly, c-Fos induction in the LC was limited to ethanol injection, with no significant cFLI observed in this region following LiCl injection.

The main goal of this research was to characterize the neurochemical phenotype of cells in the brainstem that are activated by ethanol administration. Two distinct cell populations have been identified in the VLM: a noradrenergic cell group at the caudal end (A1 group) and an adrenergic cell group that begins rostral to the obex (C1 group) (Kalia et al., 1985a, 1985b; Tucker et al., 1987). NPY is colocalized with catecholaminergic neurons of both groups. Additionally, the catecholamine NE and NPY are produced in the LC (A6 group) and in the NTS (A2 group) (Everitt et al., 1984). Thus, we assessed coexpression of drug-induced
cFLI with TH- or NPY-immunoreactivity in these brainstem regions. A significant percentage of TH-immunoreactive cells in the VLM coexpressed cFLI after ethanol injection, with highest levels of coexpression at ~75% to 85% in the caudal VLM (Fig. 1B). Similarly, ethanol injection promoted cFLI in a significant proportion of TH-positive neurons in the caudal NTS (Fig. 3B; ~65–75% coexpression) and in the LC (Fig. 5B; ~30–65% coexpression). On the other hand, although LiCl-injection was associated with a high proportion of TH-producing neurons that were c-Fos positive in the VLM (~35–55%) and the NTS (~50%), LiCl completely failed to stimulate significant cFLI in TH-positive cells in the LC.

We found that a large proportion of NPY-producing cells in the VLM coexpressed ethanol-induced cFLI (Fig. 1C; ~60–75% coexpression in the caudal VLM). In contrast, LiCl injection failed to stimulate any significant cFLI in NPY-producing neurons in the VLM. Together, these data suggest that catecholamine- and NPY-producing neurons in the brainstem are activated in response to ethanol administration. Importantly, these data provide the first evidence that ethanol administration activates neurons that produce NPY. Activation of catecholaminergic neurons in the LC and NPY neurons in the VLM was specific to ethanol administration, because LiCl failed to stimulate cFLI in these cell groups. On the other hand, LiCl and ethanol administration produced similar patterns of cFLI in catecholaminergic cells in the NTS and in the caudal aspect of the VLM. We have shown previously that LiCl, ethanol, and tastes that have become aversive by virtue of their association with these drugs activate neurons in the NTS, a region hypothesized to play a role in conditioned taste aversion learning (Thiele et al., 1996). Given the importance of the NTS in taste aversion learning, the present data suggest that activation of catecholaminergic cells in the NTS may be a cellular response to the aversive effects of ethanol and the toxin LiCl. The similar activation of catecholaminergic cells in the caudal VLM by LiCl and by ethanol suggests that these cells may also respond to the aversive effects caused by these drugs.

The present report and previous studies have found robust cFLI in the LC after ethanol administration (Ryabinin et al., 1997; Thiele et al., 1997, 1998b), which suggests that ethanol stimulates neuronal activity in this brain region. However, although evidence for ethanol-induced stimulation of LC neurons also has been found by using local glucose utilization as a measure of neuronal activity (Williams-Hemby et al., 1996), others have found that ethanol administration is associated with inhibition of neuronal activity in the LC (Aston-Jones et al., 1982; Pohorecky and Brick, 1977; Strahlendorf and Strahlendorf, 1983). A possible explanation for this apparent discrepancy is that ethanol-induced cFLI is located in inhibitory γ-aminobutyric acid (GABA) intraneurons located within the LC (Iijima et al., 1988; Van Bockstaele, 1998). Thus, ethanol may activate GABA cells in the LC, which in turn contributes to a general inhibition of neuronal activity in this region. At odds with this explanation, however, is our observation that ethanol-induced cFLI is found in TH-positive neurons. Previous reports indicate that tyrosine hydroxylase and GABA are not expressed in the same neurons within the LC (Van Bockstaele, 1998). A second explanation is based on evidence of cellular inhibition in the LC via recurrent axonal collaterals (Aghajanian et al., 1977; Egan et al., 1983). It is possible that catecholaminergic cells in the LC are initially activated by ethanol administration, which induces c-Fos expression. Initial activation of catecholaminergic cells may be followed by inhibition caused by inhibitory recurrent axonal collaterals from the same cells (Aghajanian et al., 1977; Egan et al., 1983). This could explain evidence of ethanol-induced c-Fos expression, and inhibition of neuronal activity by ethanol, in the LC.

It is of interest to speculate on the possible role that catecholamines and NPY play in mediating neurobiological responses to ethanol. We have found that mutant mice that lack NPY show high levels of ethanol consumption and are resistant to ethanol-induced sedation. On the other hand, transgenic mice that overexpress NPY were found to drink little ethanol and had increased sensitivity to the sedative effects of this drug (Thiele et al., 1998a). These data suggest that ethanol consumption and resistance to the acute effects of ethanol are inversely related to central NPY levels. Other evidence that suggests a role for NPY in mediating ethanol consumption comes from rats that have been selectively bred for high and low ethanol intake, that is, the Indiana alcohol-preferring (AP) and alcohol-nonpreferring (NP) lines, respectively (Li et al., 1993). Quantitative trait locus analyses run on these rats suggested that line differences in ethanol intake may be modulated by the NPY gene (Carr et al., 1998). Furthermore, NPY levels were found to be low in several brain regions of the AP rats, including the central nucleus of the amygdala (CeA) (Ehlers et al., 1998; Hwang et al., 1999). More recently, the selectively bred high alcohol-drinking (HAD) rats also were found to have abnormally low levels of NPY in the CeA (Hwang et al., 1999). Thus, there is increasing evidence that NPY may be involved with regulating ethanol-seeking behavior and the acute effects that are produced by this drug.

The present data suggest an additional role for NPY by showing that ethanol treatment stimulates activity of cells that contain NPY, which indicates that ethanol may stimulate central NPY activity. It will be important to determine if ethanol administration promotes synthesis and/or synaptic release of NPY in the central nervous system. Interestingly, NPY-producing neurons in the VLM have been shown to project to the CeA (Zardetto-Smith and Gray, 1995). It is tempting to speculate that ethanol-induced activation of NPY neurons in the VLM causes synaptic release of this neuropeptide in the CeA, perhaps serving as a mechanism to prevent overconsumption of...
ethanol. High alcohol-consuming rats (AP and HAD), which show low levels of NPY in the CeA, may have abnormally low ethanol-stimulated NPY activity, which promotes increased consumption of this drug.

Consistent with the present results, acute administration of ethanol has been found to increase synthesis, turnover, and release of NE, which suggests an important role for this catecholamine in regulating the neurobiological effects of ethanol (Carlsson and Lindqvist, 1973; Corrodi et al., 1966; Hunt and Majchrowicz, 1974; Karoum et al., 1976; Pohorecky and Jaffe, 1975). Although chemical-induced lesions of NE-producing cells have produced conflicting results (Kianamra, 1980; Melchior and Myers, 1976; Myers and Melchior, 1975; Richardson and Novakovski, 1978), blocking conversion of dopamine to NE with dopamine β-hydroxylase inhibitors has been found to reduce ethanol consumption in rats (Brown et al., 1977), and infusion of NE into the paraventricular nucleus of the hypothalamus (PVN) has been found to increase ethanol consumption in rats (Hodge et al., 1996). NE-producing neurons from the VLM, the NTS, and the LC all provide projections to the PVN (Cunningham and Sawchenko, 1988; Palkovits et al., 1992; Riche et al., 1990). Thus, in light of the present results, it is possible that activation of brainstem neurons after consumption of alcohol causes synaptic release of NE into the PVN, which may promote continued ingestion of this drug.

In addition to its involvement in ethanol-seeking behavior, there is evidence that NE may be involved with acute effects that are produced by ethanol. For example, antagonists of the α2 adrenoreceptors attenuate the sedative effects associated with ethanol administration, whereas α2 agonists potentiate ethanol-induced sedation (Lister et al., 1989; Mao and Abdel-Rahman, 1996). Thus, NE activity in response to ethanol may contribute to the intoxicating effects of this drug. Additionally, ethanol administration causes vasodilation and dramatically reduces blood pressure (El-Mas and Abdel-Rahman, 1999; Gillespie, 1967). NE promotes vasoconstriction (Taylor et al., 1999), and catecholaminergic projections from the VLM to the forebrain have been implicated in blood pressure regulation (Saper et al., 1983). Thus, it is possible that activation of catecholaminergic neurons in the VLM may represent sympathetic activity that serves as a compensatory mechanism against vasodilation and altered blood pressure produced by ethanol administration.

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