Pharmacology Biochemistry & Behavior, Vol. 31, pp. 163–168. © Pergamon Press plc, 1988. Printed in the U.S.A. 0091-3057/88 $3.00 + .00

Ethanol Withdrawal Alters Apomorphine-Induced Motility[1]

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Received 17 August 1987

GONZALEZ, L. P. AND J. F. CZACHURA. *Ethanol withdrawal alters apomorphine-induced motility.* PHARMACOL BIOCHEM BEHAV **31**(1) 163–168, 1988.—Acute administration of ethanol is accompanied by alterations in dopamine turnover and release, and chronic ethanol exposure is associated with changes in biochemical measures of dopamine receptor function. This paper presents data examining the effects of chronic ethanol exposure on behavioral responses to the dopamine receptor agonist apomorphine. Measurements of behavior were obtained through the use of an electronic motility monitor which permitted the quantification of movements in terms of their characteristic frequency components. Results are presented which indicate that apomorphine-induced movements with modal frequencies of 2 Hz and of 8–9 Hz are significantly increased during the 12 to 24 hr following ethanol withdrawal, suggesting an increase in the functional responsiveness of central dopaminergic systems.

Ethanol Withdrawal Apomorphine Stereotypy Locomotion Motility

CHANGES in biochemical, electrophysiological, and behavioral measures of central dopamine function suggest the involvement of this neurotransmitter system in the mediation of certain effects of acute and chronic ethanol exposure. The results of studies examining ethanol effects on the functioning of dopamine systems, however, have been inconsistent and provide conflicting views of the specific role of dopaminergic neurons in the actions of ethanol.

Single doses of ethanol are reported to increase (4, 12, 20, 30), decrease (28,47), or have no effect (8,12) on dopamine synthesis or turnover. These effects on turnover may be dependent upon the specific neuronal sites investigated (3) or on the dose of ethanol. Dopamine turnover is reported to be elevated after low doses of ethanol (7), but reduced by high doses (28). Similarly, dopamine release is increased by low ethanol doses (13,14) and reduced at high doses (13). Inconsistent effects on dopamine turnover are also reported after chronic ethanol exposure (1,28). Measurements of receptor sensitivity after chronic ethanol treatment have sometimes suggested increases in the sensitivity of dopamine receptors (19,34), but decreases in sensitivity (27,45) or no change (41) have also been reported.

Although few studies have examined the electrophysiological effects of ethanol at central dopaminergic sites, these studies are also inconsistent in their conclusions. Ethanol produced dose-related, biphasic effects on electroencephalographic activity in the amygdala (39), but had no effect on multiple-unit activity recorded from this area (31,32). Systemic ethanol reduced single-unit activity in the lateral hypothalamus (48), but microiontophorectically-applied ethanol increased single-unit activity at this site (49). Ethanol increased single-unit activity in substantia nigra at low doses (0.5–2.0 g/kg) and decreased activity with higher doses (37).

Results of studies using measures of dopamine function after chronic ethanol treatment are also confusing. Animals withdrawn from chronic ethanol exposure have shown either increased or decreased locomotor responses to dopamine receptor agonists (19,45) as compared to controls.

The differences observed in these studies might be the result of differences in species, ethanol dose, length of chronic ethanol exposure, or neural site of dopamine receptors whose function is measured. In spite of these inconsistencies, the question of dopamine involvement in the effects of ethanol exposure is an important one. In addition, human abuse of ethanol is often also associated with abuse of dopamine agonists (i.e., amphetamine or cocaine) (16,42), so that knowledge of ethanol effects on the function of dopaminergic pathways may be important for an understanding of these drug interactions.

The studies presented here examine the effects of chronic ethanol exposure and withdrawal on behavioral responses to the direct dopamine receptor agonist apomorphine. Systemic administration of apomorphine is associated with an array of dose-related behaviors in rodents. These range from a decrease in gross locomotor activity at very low doses (6,15) to

[1]This study was supported in part by NIAAA grant AA06254.

increased locomotion and then intense stereotypy at higher doses (2,35). The effects of apomorphine on locomotor activity have been attributed to the stimulation of dopamine receptors at mesolimbic, and to a lesser extent, nigrostriatial dopaminergic sites (10, 11, 29). The low dose decrease in locomotion is suggested to reflect a presynaptic effect of apomorphine, whereas higher doses may increase locomotion through activation of postsynaptic receptors (21, 26, 40, 46). The stereotypies induced by higher doses of apomorphine are dependent to a large extent upon the stimulation of postsynaptic striatal dopamine receptors (10, 11, 29). The following experiment investigated the effects of chronic ethanol exposure and withdrawal on an automated measurement of apomorphine-induced movements.

METHOD

Subjects

The subjects for these experiments were 96 male, Sprague-Dawley rats, 60 to 90 days old, and weighing 200 to 250 g. Rats were housed in individual cages with free access to food and water, and were maintained for at least seven days under the same conditions of environment, diet, and daily handling before any experimental treatment.

Apparatus

Quantitative assessment of motor behavior was performed in a Stoelting activity monitor, modified to permit the quantification of repetitive behaviors (17,22). The motility monitor consists of a pair of parallel copper plates (20.0×30.0 cm) connected to a Stoelting movement sensoring module. The plates are housed in a 40.0×40.0×40.0 cm Faraday cage to eliminate the influence of external electrical fields. An animal was placed in the center of a radio frequency capacitance field generated between the plates such that the movement of the animal disrupted the field. Based upon this disruption, the motility monitor produced an analog signal with a frequency of oscillation equal to the frequency of occurrence of movements within the field of the monitor. This signal was then amplified with a Grass 7P511 amplifier and recorded on an FM tape recorder for subsequent playback and analysis.

Quantification of movement was accomplished by spectral analysis of the frequency components of the amplified analog output of the motility monitor. The resulting amplitude-frequency distribution has been shown (17, 18, 23) to accurately depict the occurrence of specific repetitive movements (sniffing, licking, head bobbing, etc.).

For the measurement of motility, rats were placed in Plexiglas chambers, 19×13.0×8.0 cm, which were then positioned within the movement sensor of the motility monitor. Analog-to-digital conversion and spectral analysis of the transduced signal were performed with an Apple II microcomputer.

Procedures

Sixty-four rats received chronic exposure to ethanol in ethanol-vapor inhalation chambers. The chambers are 24-in. Plexiglas cubes subdivided vertically at 12 in. to provide two cages (24″×24″×12″). The air flow to each cage is regulated independently and provides individual housing for four animals. The rats had unlimited access to food and water. Fresh air was flushed through the chamber continuously at the rate of two liters per min to provide for the respiratory needs of the animals. To this fresh air flow was added ethanol vapor (0 to 30 mg/ml) obtained by pumping air through a one-liter aspirator bottle containing 1000 ml of 95% ethanol, at flow rates of 0–700 ml/min. The ethanol flow rate was adjusted to maintain behavioral levels of intoxication between Ataxia-2 and Ataxia-3 as described by Majchrowicz (36). Using this procedure, blood ethanol levels were increased gradually, approaching 200 mg/dl after 14 days of exposure, at which time the animals were removed from the chambers. Thirty-two control animals (ETOH-naive) received similar handling for the same length of time, but received no exposure to ethanol.

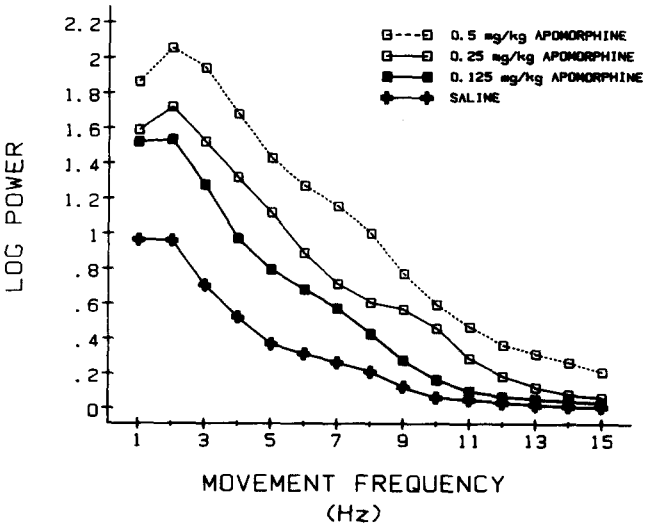

FIG. 1. Apomorphine-induced motility in ethanol-naive subjects, 20 min after saline (1 cc/kg, SC) or apomorphine (0.125, 0.25, or 0.5 mg/kg, SC). Data is presented as arbitrary units of log power at each movement frequency. The SEM's for the data presented in this figure ranged from ±0.03 to ±0.27.

Blood ethanol levels were determined periodically during chronic ethanol exposure and following withdrawal by a head-space gas chromatographic method. In this procedure, 20 μl samples of blood obtained from the dorsal tail vein were added to 1.0 ml of deionized water in a 25 ml flask, with 0.025 mg of propanol added as an internal standard. The flask was immediately sealed and then warmed in a water bath, 50°C, for 15 min. A 1.0 ml sample of the gas volume from the flask was injected into the port of a Hewlett-Packard 5790A gas chromatograph equipped with a flame ionization detector. Ethanol levels were quantified by comparison to standards prepared by adding known amounts of ethanol to the propanol solution.

After 14 days of ethanol exposure, the animals were removed from the chambers. Blood samples were taken periodically to permit a determination of the rate of ethanol elimination. Half of the subjects (ETOH-12) were then selected for testing 12 hr after ethanol withdrawal, with the remaining subjects (ETOH-24) tested 24 hr after withdrawal. Each of these two groups of animals was then further subdivided into one of four treatment groups (eight subjects per group). At the time of testing (12 or 24 hr after ethanol withdrawal) the animals were placed within the sensor of the motility monitor and, after a 30-min adaptation period, a 40-sec sample of motility was obtained. Animals then received subcutaneous injections of either saline or apomor-

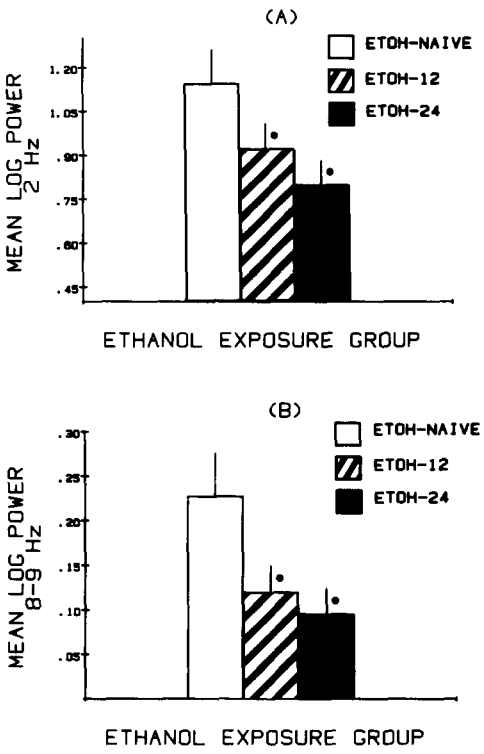

FIG. 2. Motility prior to acute drug treatment in ethanol-naive (ETOH-naive) animals or in animals withdrawn 12 hr (ETOH-12) or 24 hr (ETOH-24) from chronic ethanol exposure. Motility measurements are presented in arbitrary units of log power (±SEM) for (A) 2 Hz movements and (B) 8–9 Hz movements. ●=$p<0.05$, compared to group ETOH-naive.

phine HCl (0.125, 0.25, or 0.5 mg/kg), as appropriate to the group designation of a subject. Motility was again monitored for 40-sec periods, five, ten, 15, 20, and 25 min after injection. Motility was also observed in four groups of ethanol-naive rats (eight subjects per group) which received handling and treatments similar to that of the other groups, with the exception of their having received no ethanol exposure.

A Fast Fourier Transform (FFT) was used to obtain power spectra for each one-sec segment of motility data, and the spectra were averaged across the 40 sec of each sampling period. Following a log transformation of the mean power spectra, an analysis of variance with repeated measures was used to determine the significance of group differences at the various sampling periods and at various movement frequencies, with Duncan's multiple range test used for individual post-hoc group comparisons.

RESULTS

Mean blood ethanol levels for all of the animals during the period of chronic exposure exceeded 140 mg/dl after five days of ethanol exposure, and averaged 180.4±14.0 mg/dl at the time of ethanol withdrawal. Blood samples were also taken during the withdrawal period; ethanol was not detected in blood four hr or later after removal from the ethanol inhalation chambers, nor was ethanol detectable at the time of behavioral testing at 12 or 24 hr after withdrawal.

Apomorphine administered to ethanol-naive control

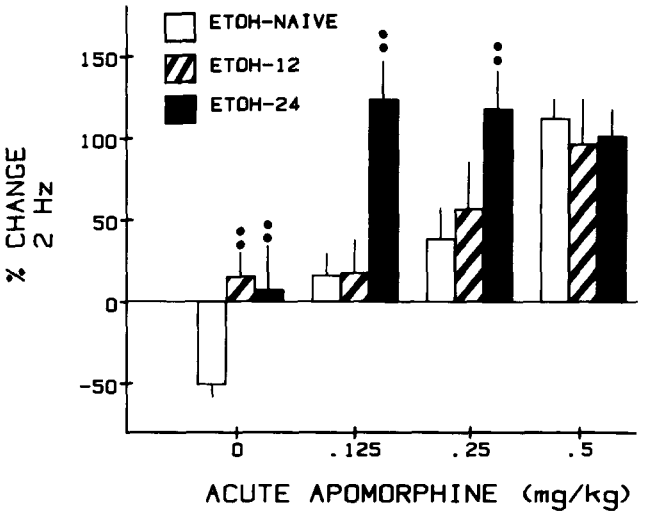

FIG. 3. Mean percent change (±SEM) in 2 Hz motility following acute saline or apomorphine administration, relative to predrug motility. ●●=$p<0.001$, compared to group ETOH-naive.

animals (Fig. 1) resulted in dose-related changes in motility consistent with our previous reports of the effects of dopaminergic agonists on motility (22,25). This included a general increase in power at all observed frequencies (1 to 15 Hz). The largest effect of low dose (0.125 mg/kg) apomorphine was an increase in low frequency (2 Hz) movements, with higher doses also producing increases particularly in a band of movement frequencies centered at 8–9 Hz. Previous research (17) has indicated that 2 Hz motility reflects the occurrence of gross, whole body movements, slow head swings, and respiration; 8–9 Hz motility has been shown to reflect the occurrence of stereotyped sniffing. Since the observed effects of apomorphine were most evident in these two frequency ranges, subsequent analyses were performed separately on 2 Hz motility and on 8–9 Hz motility.

Ethanol-withdrawn animals (ETOH-12 and ETOH-24) exhibited significantly less ($p<0.05$) motility than ethanol-naive animals prior to drug injection (Fig. 2). In order to determine the significance of group differences in the change in motility after apomorphine, a repeated measures ANOVA was performed comparing the effect of ethanol treatment (three groups), apomorphine dose (four doses), and time postapomorphine (five times) on measurements of either 2 Hz or 8–9 Hz movements.

Analysis of 2 Hz motility (Fig. 3) indicated a significant effect of ethanol treatment ($p<0.002$), of apomorphine dose ($p<0.0001$), and of time postapomorphine ($p<0.0001$). In addition, the interactions of apomorphine dose with ethanol group ($p<0.01$) and with time ($p<0.0001$) were also significant. Post-hoc analysis indicated that of the groups receiving apomorphine, only the animals withdrawn 24 hr from chronic ethanol (ETOH-24), and receiving 0.125 or 0.25 mg/kg apomorphine, were significantly different from the others ($p<0.001$). These animals exhibited significantly more apomorphine-induced 2 Hz motility.

Similarly, analysis of 8–9 Hz motility (Fig. 4) also showed significant effects of ethanol group ($p<0.02$), dose ($p<0.0001$), time ($p<0.0001$), and time by dose ($p<0.0001$). Post-hoc analysis indicated that both the ETOH-12 and the ETOH-24 animals showed significantly more 8–9 Hz motility

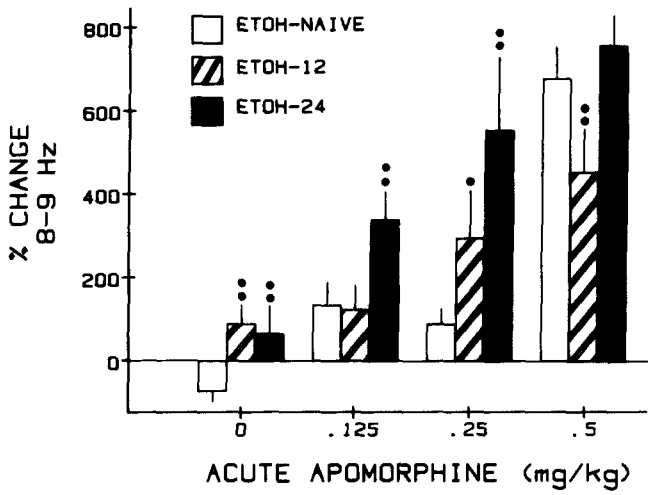

FIG. 4. Mean percent change (±SEM) in 8–9 Hz motility following acute saline or apomorphine administration, relative to predrug motility. ●=$p<0.05$, ●●=$p<0.005$ compared to group ETOH-naive.

after 0.25 mg/kg apomorphine than did the ETOH-naive animals; the ETOH-24 animals also showed significantly more 8–9 Hz motility following 0.125 mg/kg apomorphine than either of the other groups, but did not differ ($p>0.05$) from the ethanol-naive animals after 0.5 mg/kg apomorphine. In addition, although ethanol-naive subjects showed a decrease in both 2 Hz and 8–9 Hz movements after an acute saline injection, both ethanol withdrawn groups (ETOH-12 and ETOH-24) showed slight increases in both types of movements (Figs. 3 and 4).

DISCUSSION

The observed increases in apomorphine-induced motility following ethanol withdrawal indicate an enhanced responsiveness to apomorphine stimulation of behavior with low (0.125 mg/kg) and intermediate (0.25 mg/kg) doses of apomorphine. Although the ethanol withdrawn animals did not show greater stimulant-induced motility than did ethanol-naive subjects when tested at the highest dose of apomorphine (0.5 mg/kg), this lack of effect may be due to a "ceiling effect," with those doses of apomorphine inducing intense stereotypy in all of the groups. Most interesting is the finding that the lowest dose of apomorphine (0.125 mg/kg), which produced only slight increases in 2 Hz motility in controls and in 12-hr withdrawn ethanol animals (17% and 18%, respectively), induced large increases in 24-hr withdrawn ethanol animals (125%). The effect of this same dose on 8–9 Hz motility was also significantly larger in 24-hr withdrawn ethanol animals.

These data are consistent with an hypothesis of increased dopamine receptor sensitivity after chronic ethanol treatment. Similar results showing increased responsiveness to dopamine agonists after chronic ethanol exposure have also been reported by other investigators. Studies by Liljequist (34) and Engel and Liljequest (19) have reported increased locomotor activity in response to dopamine or to apomorphine administered directly into the nucleus accumbens, and increased stereotypy with systemic administration of apomorphine. In these studies, chronic ethanol administered in the animals' drinking water resulted in significantly greater responses to dopaminergic stimulation in animals treated with ethanol for five, seven, or nine months. Ethanol treatment for 3.5 months, however, did not alter dopaminergically-stimulated behavior. Lai *et al.* (33) reported enhanced responses to intrastriatal dopamine and increased motor responses to apomorphine after chronic ethanol exposure in rats with unilateral lesions of dopaminergic neurons. These effects were observed after only 14 days of chronic ethanol exposure. Recent investigations in our laboratory have indicated increased apomorphine-induced hypothermia following ethanol withdrawal (24). Human alcoholics, during the early abstinence syndrome, have also been suggested to have increased dopamine sensitivity, measured as an increase in apomorphine-stimulated growth hormone secretion (5) and as a reduced prolactin response (38).

These results are in contrast to several studies of dopamine function in mice after short-term ethanol exposure (seven days of ethanol in liquid diet), which have suggested a subsensitivity of central dopaminergic systems after chronic ethanol exposure. Hypothermia following injection of the dopamine agonist piribedil was reduced 24 hr after ethanol withdrawal (45). Similarly, locomotor responses to a very high dose of apomorphine (4 mg/kg) were also reduced (27). Biochemical parameters of dopamine function, including neuroleptic stimulation of tyrosine hydroxylase activity (44,45) and dopamine stimulation of dopamine-sensitive adenylate cyclase activity (43), were also reduced in similarly treated animals.

The results of the present study and of those discussed above, suggest important alterations in dopaminergic systems following chronic ethanol treatment. The direction of change in dopamine function or receptor sensitivity, however, may be dependent upon the duration of ethanol treatment or the species of animal tested. Further, since apomorphine may act at both presynaptic and postsynaptic dopamine receptors, the effects observed following apomorphine administration may reflect the relative balance in the activation of these receptor types (9,46). The changes in responsiveness to apomorphine observed in the present study may thus reflect a change in the sensitivity of presynaptic dopamine receptors as compared to that of postsynaptic receptors. Nevertheless, significant alterations are observed in the response of dopaminergic systems after withdrawal from chronic ethanol exposure, and these changes may reflect an important involvement of this neurotransmitter system in the expression of the ethanol withdrawal syndrome.

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