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Reduction of Spontaneous Alcohol Drinking and Physical Withdrawal by Levemopamil, a Novel Ca^{2+} Channel Antagonist, in Rats

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REZVANI, A. H., O. PUCILOWSKI, D. R. GRADY, D. JANOWSKY AND R. A. O'BRIEN. *Reduction of spontaneous alcohol drinking and physical withdrawal by levemopamil, a novel Ca^{2+} channel antagonist, in rats.* PHARMACOL BIOCHEM BEHAV **46**(2) 365–371, 1993.—Neuronal Ca^{2+} channels have been shown to be involved in both alcohol drinking behavior in rats and nonhuman primates and in the manifestation of alcohol withdrawal symptoms in rodents. Experiments were performed to determine the effect of a single injection of levemopamil, a novel Ca^{2+} channel antagonist with antiserotonergic [5-hydroxytryptamine$_2$ (5-HT$_2$)] properties, on alcohol preference and alcohol withdrawal symptoms in alcohol-preferring (P) and Wistar rats, respectively. P rats were individually housed and provided free access to food, water, and a solution of 10% (v/v) ethanol. Ethanol, food, and water intakes were measured daily. After establishing a stable baseline, P rats were injected with levemopamil (0, 3.3, 10, 15, and 20 mg/kg) and their food, water, and alcohol intakes measured 24 h later. In a separate experiment, the ability of acute and chronic (12 consecutive days) administrations of levemopamil to suppress alcohol withdrawal symptoms in chronically alcohol-treated rats was studied. In addition, the effects of levemopamil on the level of monoamines in different areas of the brain, as well as its action in alcohol metabolism, were examined. Our findings showed that a single administration of levemopamil (10, 15, and 20 mg/kg) significantly and dose-dependently attenuated alcohol intake and increased water intake in P rats. Both acute and chronic treatment with levemopamil reduced the alcohol withdrawal symptoms, overall seizure scores, and proportion of rats seizing. A single injection of levemopamil produced a clear, but not significant, trend to increase the 5-HT turnover rate in certain brain areas. This drug did not influence the pharmacokinetics of alcohol. Our results show that levemopamil exerts an inhibitory action on alcohol preference in alcohol-preferring rats and suppresses alcohol withdrawal symptoms in chronically alcohol-treated rats. Although the mechanism(s) of action is not fully understood, it is likely that levemopamil exerts its action by interfering with either neuronal Ca^{2+} channels and/or serotonergic systems, particularly 5-HT$_2$ receptors.

Ca^{2+} channel antagonist Alcohol withdrawal Alcohol drinking Seizures Monoamines
Serotonin Blood alcohol Ca^{2+} channels

MANY studies suggest an involvement of neuronal Ca^{2+} channels in both alcohol preference (4,5,21,23,25,26) and alcohol withdrawal (1,3,10,11,20). Confirming an earlier report by Engel et al. (4), we recently demonstrated a dose-dependent inhibitory action on ethanol intake of several Ca^{2+} channel inhibitors from different chemical classes including verapamil (23,25), Goe 5438 (21), and nimodipine (24).

Neuronal Ca^{2+} channels also have been proposed to be involved in alcohol withdrawal. The development of physical dependence on alcohol has been associated with Ca^{2+} channels in the brain sensitive to dihydropyridine. These investigators associated the ethanol physical withdrawal syndrome with the upregulation of voltage-sensitive Ca^{2+} channels in the CNS that can be reduced or blocked by Ca^{2+} channel antagonists (3,9–11).

The objective of the present study was to examine the effects of a novel Ca^{2+} inhibitor, levemopamil, on both alcohol preference and alcohol withdrawal syndromes in rats. Levemopamil or (*S*)-emopamil is a novel compound in the phenylalkylamine group of Ca^{2+} channel antagonists. Apart from its calcium influx blocking properties, it has a strong 5-hydroxytryptamine$_2$ (5-HT$_2$) antagonistic effect. Levemopamil's affinity for [^{3}H]ketanserine-labeled 5-HT$_2$ binding sites is higher than that of other phenylalkylamines such as gallopamil and verapamil (7). The latter drug has an anti-alcohol effect in both rats (23) and monkeys (25). Levemopamil

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readily crosses the blood-brain barrier and, compared to another phenylalkylamines such as verapamil and gallopamil, is superior with respect to cerebral availability and blood-brain barrier permeability (25,29).

In the present study, to examine the effect of levemopamil on alcohol consumption and preference we used alcohol-preferring (P) rats provided by the Indiana University, Indianapolis. These rats have been selectively bred for their preference for alcohol and have been extensively used in the field of alcohol research for their high alcohol consumption (13,22,23,27).

METHOD

Animals

Three groups of adult, male rats were used for these experiments: selectively bred alcohol-preferring (P) rats weighing 0.6 ± 0.23 (SEM) kg for alcohol intake studies, normal Wistar rats weighing 0.47 ± 0.01 (SEM) kg for alcohol withdrawal experiments, Wistar rats weighing 0.31 ± 0.01 (SEM) kg for monoamine determinations, and Sprague-Dawley rats weighing 0.38 ± 0.01 (SEM) kg for blood ethanol determinations. P rats were housed individually in wire mesh cages (26 × 34 × 20 cm) under a constant temperature of 21 ± 1°C and a 12 L : 12 D cycle (dark 10:00 a.m.-10:00 p.m.). Wistar and Sprague-Dawley rats were housed three per cage under the same conditions. Rats were fed Agway/Prolab Rat/Mouse/Hamster 3000 Formula (Agway, Syracuse, NY) and water ad lib. Using the standard method of Waller et al. (31), P rats were screened and tested for ethanol preference as follows. They were first given free access to water in a Richter tube and food for 2 days. Next, they were given free access to food and a solution of 10% (v/v) ethanol as a sole source of fluid for 3 days. During this period, rats became accustomed to drinking from Richter tubes and to the taste of ethanol (25). Thereafter, they were given free access to both water and a 10% solution of ethanol for at least 3 weeks. To prevent position preference, the position of the tubes was randomly changed. Food was available throughout the experiment. Food, water, ethanol intake, and body weight were recorded every day between 9:00 and 9:30 a.m.

Preparation of Drugs

Solutions of levemopamil (Knoll Pharmaceuticals, Whippany, NJ) were prepared in pyrogen-free glassware and sterilized isotonic saline (vehicle) and passed through a 0.22-μM filter (Millipore Corp., Bedford, MA) into a pyrogen-free glass bottle and stoppered. Four different doses of levemopamil were used (3.3, 10, 15, and 20 mg/kg). The volume of vehicle or drug injected was 1 ml/kg body weight. A 10% solution of ethanol was prepared from 95% grade ethanol and distilled water (22).

Experimental Protocol

Effects of levemopamil on ethanol intake. Following the method of Waller et al. (30), after establishing a stable baseline for ethanol and water intake during testing for alcohol preference at approximately 9:30 a.m. P rats (n = 9) were given a single IP injection of the control vehicle or one of the four doses of levemopamil in a randomly designed order. The interval between each injection was at least 1 week. Throughout the study, water, food, and ethanol intake were measured every day between 9:00 and 9:30 a.m. for the proceeding 24 h.

Effects of levemopamil on blood ethanol. To determine the effect of levemopamil administration on alcohol metabolism, the following experiments were carried out. Nine adult, male Sprague-Dawley rats naive to alcohol and levemopamil were injected with 20 mg/kg levemopamil or an equal volume of vehicle and 15 min later with 2.5 g/kg alcohol (16% v/v) following a crossover design with a 1-week interval. Twenty-microliter blood samples were obtained from the tip of the tail of each rat 1, 3, and 5 h after alcohol administration. Blood samples were transferred immediately to a microcentrifuge tube containing 180 μl tertbutanol (0.3 mg/ml as an internal standard). After shaking, the tubes were stored at −70°C until the gas chromatography (GC) analysis. Then, each vial was centrifuged and 5.0 μl of this supernatant was injected into a GC (Varian Aerograph Model 2400, Palo Alto, CA), equipped with a flame ionization detector and a 60/80 Carbopack B/5% Carbowax 20 M, 6 × 2-mm I.D. glass column (Supelco, Madison, WI). The chromatographic conditions were: carrier gas (N_2), flow rate 20 ml/min; 60–110°C at 10°C/min temperature program; injector temperature 120°C; detector temperature 140°C. Blood ethanol concentrations are expressed as mg/dl.

Effects of levemopamil on brain monoamines. Twelve adult, male Wistar rats were used for this experiment. Rats were divided into two equal groups. One group was injected with saline and the other with 15.0 mg/kg levemopamil. Sixty minutes later, rats were decapitated. Their brains were quickly removed and hippocampi, hypothalami, striatas, and frontal cortices dissected on dry ice. Tissue samples were kept at −70°C for 2 weeks when the biochemical assays were carried out. Dopamine (DA), dihydroxyphenylacetic acid (DOPAC), 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) levels were determined by high-performance liquid chromatography with electrochemical detection (HPLC-EC). The tissue samples were homogenized in the mobile phase (1.3 volume) with Polytron PCS-10, setting 9, for 5 s. The mobile phase composition used was: 0.05 M sodium phosphate, 0.03 M citric acid, 0.1 mM disodium EDTA, 0.04% sodium octyl sulfate, and 22% methanol, pH 3.4. After spinning for 15 min (1,000 × g), 0.1 ml supernatant was injected directly into the HPLC system. D,L-Isoproterenol was used as an internal standard. A C 18 reversed-phase analytic column (Phenomenex ID-SIL 3 M. 150 × 4.6 mm) was used, the flow rate was 0.7 ml/min, and the detector (EC and G Princeton Model 400) glassy carbon electrode was set at a potential +0.75 V relative to an Ag/AgCl reference electrode. Protein content of samples was determined with the BioRad protein assay kit.

Effects of levemopamil on alcohol physical withdrawal. Twenty-three adult, male Wistar rats were used for this study. Rats were placed on a nutritionally complete alcohol diet (dextrose diet containing 10% ethanol; ICN Biochemicals, Cleveland, OH) for 12 consecutive days and then were withdrawn from diet and 6 h later tested for alcohol withdrawal syndromes. Rats were divided into three groups. The control group (n = 7) received chronic injections of saline once daily for 12 days. The second group (n = 8) received chronic injection of levemopamil (15 mg/kg, IP, once a day) throughout the experiment (12 days). The third group (n = 8) received only one dose of levemopamil (15 mg/kg) 30 min before the withdrawal test. Using the method of Majchrowicz (12), animals were individually evaluated for withdrawal behaviors

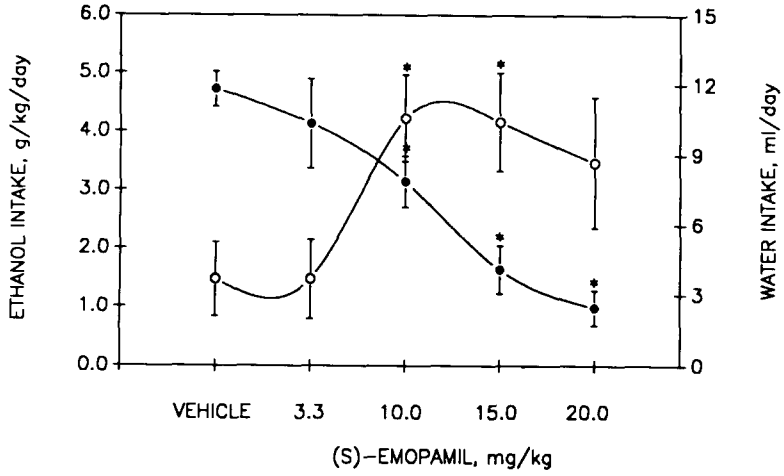

FIG. 1. Effects of different doses of levemopamil on ethanol (●—●) and water (○—○) intake in alcohol-preferring rats. Data are means ± SEM, $p < 0.02$ comparing levemopamil with control vehicle. $n = 9$.

and audiogenic seizure by two independent investigators unaware of the treatment. This method has been previously employed in this laboratory successfully (17). Six hours after withdrawal from alcohol diet, animals were placed at the center of a wooden open-field box (75 × 75 × 10 cm). Spontaneous and induced activities such as fright behavior, hyperactivity, vocalization, general spasticity, tremors, and piloerection were recorded over 2 min and only at one time. The presence of audiogenic seizures was tested by exposing the animal to a loud tone (90–100 dB) for 1 min. The presence of clonic-tonic convulsions and wild running behavior was recorded. The behaviors and seizures were rated on a three-point scale with zero indicating no behavioral changes and three indicating a maximum behavioral change or seizures (17).

RESULTS

Intake

In a two-bottle choice situation, when P rats had free access to water, ethanol (10% v/v), and food they consumed an average of 5.38 ± 0.54 g/kg b.w./day ethanol, 3.37 ± 0.84 ml/kg b.w./day water, and 29.67 ± 1.14 g/kg b.w./day food. The total fluid intake was 43.44 ± 2.73 ml/kg b.w./day. As Fig. 1 illustrates, a single injection of 10, 15, and 20 mg/kg levemopamil significantly ($p < 0.02$, $p < 0.001$, and $p < 0.0001$, respectively) reduced the amount of ethanol intake compared with injection of control vehicle. Administration of 10, 15, and 20 mg/kg levemopamil, but not the low dose (3.3 mg/kg) or control vehicle, increased water intake but only that of 10 and 15 mg/kg were significantly ($p < 0.05$) higher than control vehicle (Fig. 1). The proportion of ethanol intake that is being used as a reliable index of alcohol preference (22,31) was significantly ($p < 0.01$) reduced by acute administration of 10-, 15-, and 20-mg/kg doses of levemopamil compared with injection of control vehicle (Fig. 2). Acute administration of 3.3, 10, and 15 mg/kg levemopamil did not exert a significant effect on food intake. However, administration of 15 and 20 mg/kg levemopamil significantly ($p < 0.01$) reduced the total fluid intake (Table 1).

Monoamine Assay

Additional experiments were conducted to examine the effect of an acute injection of levemopamil on certain monoamines in different areas of the brain. The mean values of amine/metabolite determinations are given in Table 2. Compared with the corresponding control, levemopamil injection produced a clear trend to increase the concentration of 5-HIAA, the major metabolite of 5-HT, in the frontal cortex, striatum, and hippocampus up to 85, 30, and 76%, respectively. These differences, however, did not reach the required statistical significance level. Administration of levemopamil either did not change or reduced the activity of the dopaminergic system (Table 2). However, these trends did not reach the required statistical significance level.

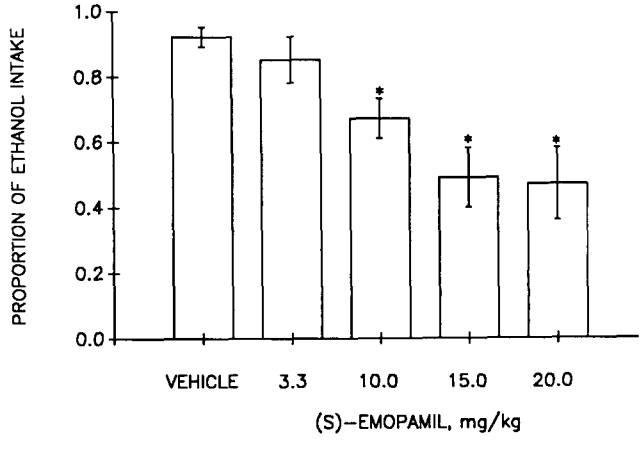

FIG. 2. Effects of different doses of levemopamil on proportion of ethanol intake (% of total fluid) in alcohol-preferring rats. Data are means ± SEM, $p < 0.01$ comparing levemopamil with control vehicle. $n = 9$.

TABLE 1

EFFECT OF DIFFERENT DOSES OF LEVEMOPAMIL ON ETHANOL, WATER, PROPORTION OF ETHANOL, FOOD, AND TOTAL FLUID INTAKE IN ALCOHOL-PREFERRING RATS (n = 9)

		Levemopamil, (mg/kg)			
	Saline	3.3	10	15	20
Ethanol (g/kg b.w./day)	4.72 ± 0.3	4.13 ± 0.76	3.14* ± 0.44	1.63* ± 0.41	0.98* ± .3
Water (g/kg b.w./day)	3.67 ± 1.59	3.67 ± 1.69	10.56* ± 1.85	10.4* ± 2.1	8.67 ± 2.8
Proportion (% ethanol)	0.92 ± 0.03	0.85 ± 0.07	0.67* ± 0.06	0.49* ± 0.09	0.47* ± 0.11
Food (g/kg b.w./day)	24.76 ± 2.87	21.0 ± 1.36	24 ± 1.62	23.41 ± 3.9	9.74* ± 1.6
Total fluid (ml/kg b.w./day)	38.89 ± 2.14	33.33 ± 4.37	33.67 ± 2.43	22* ± 3.0	15.67* ± 2.96

*Significantly different from the corresponding saline value. Data are means ± SEM.

Blood Ethanol

As presented in Fig. 3, compared with control vehicle administration of the most effective dose of levemopamil (20 mg/kg) did not significantly affect the pharmacokinetics of ethanol in rats.

Alcohol Withdrawal

Although all three groups consumed about the same amount of alcohol diet (12 g/kg b.w./day), they showed a significantly different hyperactivity and sensitivity to seizure inducing stimulus (Fig. 4). Compared with the control group that received chronic saline (12 days), rats on alcohol diet that received chronic (12 days) levemopamil showed a significantly less incidence of seizures upon removal from the alcohol diet. For example, 12.5% of all rats chronically treated with levemopamil showed seizures, while 43% of rats chronically treated with saline (control group) showed seizure incidences. Rats treated with one injection of levemopamil 30 min before the withdrawal test also showed less incidence of seizures (25 vs. 43% in saline-treated group). Compared with controls, administration of levemopamil also suppressed both spontaneous and induced withdrawal symptoms. This effect was significant ($p < 0.02$) with chronic administration of levemopamil.

DISCUSSION

The present study supports previous findings with respect to the involvement of the neuronal Ca^{2+} channels in alcohol drinking behavior (4,5,21,25) and alcohol actions (1,2,26). In this study, we showed that a single injection of levemopamil significantly attenuated alcohol intake in alcohol-preferring rats in a dose-dependent fashion. Attenuation of alcohol intake was accompanied by an elevation in water intake, thus leading to a reduction in alcohol preference. Food intake was not influenced by administration of levemopamil except for the highest dose of 20 mg/kg. This indicates that reduction in ethanol intake is unlikely to be related to overall suppression of consummatory behaviors; rather, levemopamil has a specific action on alcohol intake.

There is some evidence to suggest that several Ca^{2+} channel inhibitors can decrease the reinforcing properties of alcohol (4,25,26), cocaine (8,18), and morphine (8). Although the mechanism(s) of the anticraving effect of levemopamil on alcohol consumption is not clear at this point, several speculations can be made. One possible mechanism is that levemopamil exerts its action through its 5-HT_2 antagonistic property. Recently, a role for 5-HT_2 receptor subtypes in drug abuse has been postulated. For example, ritanserin, a potent

TABLE 2

EFFECT OF 15 mg/kg B.W. ADMINISTRATION OF LEVEMOPAMIL ON AMINE/METABOLITE CONCENTRATIONS IN DIFFERENT AREAS OF THE RAT BRAIN

Group	DA	DOPAC	5-HT	5-HIAA
Hypothalamus				
Controls	–	76 ± 9	–	349 ± 33
Levemopamil	–	53 ± 15	–	352 ± 36
Frontal cortex				
Controls	22 ± 3	35 ± 17	36 ± 4	91 ± 9
Levemopamil	19 ± 5	28 ± 14	43 ± 10	169 ± 39
Striatum				
Controls	388 ± 21	1159 ± 115	–	120 ± 24
Levemopamil	376 ± 29	1120 ± 133	–	157 ± 25
Hippocampus				
Controls	–	–	12 ± 2	115 ± 11
Levemopamil	–	–	31 ± 11	203 ± 49

Values are expressed as mean ± SEM ng/mg protein. n = 6 for both control and levemopamil groups.

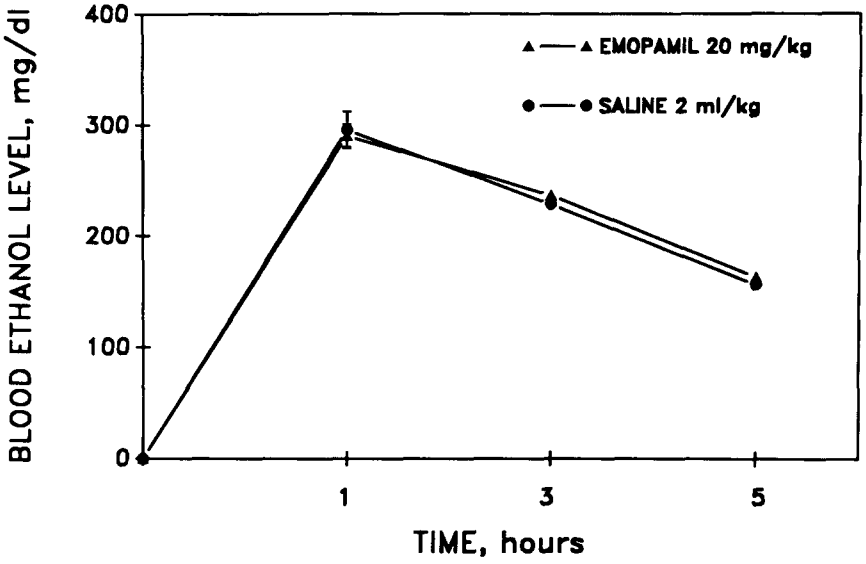

FIG. 3. Effects of 20 mg/kg levemopamil and an equal volume of control saline on blood ethanol level in rats. Data are means ± SEM, $n = 9$.

5-HT_2 antagonist, has been found active against three different agents of abuse—alcohol, cocaine, and phentanyl—without creating aversion for these substances (14). Further, it has been demonstrated that ritanserin has a long-lasting suppression effect on alcohol preference in rats (19). Similar findings have been reported in chronic alcoholics (16). These data support the possible involvement of 5-HT_2 receptor sites in reinforcing properties of alcohol. Thus, the fact that levemopamil has high affinity for 5-HT_2 receptor sites may explain its inhibitory action on alcohol consumption. Interestingly, verapamil, another phenylalkylamine Ca^{2+} channel inhibitor that shows an anticraving effect for alcohol in rats (25) and monkeys (23), also possesses an antiserotonergic property (6). The results of the monoamine assay support this speculation, that is, the observed more than 30% increase in 5-HIAA level in all brain regions tested except in the hypothalamus (Table 1) following acute levemopamil indicates an elevation in 5-HT turnover, a result similar to what is expected from a 5-HT antagonist. However, speculation about a possible role of 5-HT_2 receptors in the action of levemopamil on alcohol intake needs further investigation.

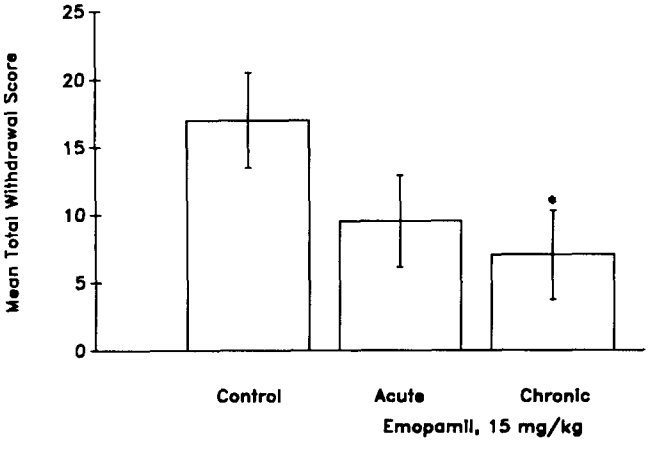

FIG. 4. Effects of acute and chronic administration of levemopamil on total withdrawal scores in rats. Data are means ± SEM, $p < 0.05$ comparing levemopamil with control vehicle. $n = 7$ for the control group and 8 for acute and chronic emopamil groups.

It is possible that levemopamil exerts its inhibitory action on alcohol intake and preference by antagonizing the reinforcing effect of ethanol. Indeed, we have recently shown that verapamil, another Ca^{2+} channel inhibitor of the same category, effectively suppressed the reinforcing properties of the stimulant *d*-amphetamine in the conditioned place preference paradigm (in preparation). Further, levemopamil may exert a taste aversion effect that could lead to attenuation of alcohol intake. This speculation, as well as the possible action of levemopamil on reinforcing properties of ethanol, needs to be further investigated.

Usually, the appearance of ethanol withdrawal symptoms occurs following an abrupt cessation of chronic ethanol intake and elimination of ethanol from the system. Chronic exposure to ethanol leads to what is called neuronal adaptation; when ethanol is not available to the organism any longer, the adaptation leads to maladaptive function (hyperexcitability) of the neuronal system (30). Several hypotheses have been proposed for the development of withdrawal symptoms. Both GABAergic systems and NMDA receptors have been implicated in ethanol withdrawal. The upregulation of the NMDA receptor-coupled ion channels and an increase in NMDA receptor sensitivity have been suggested to be involved in ethanol withdrawal. MK-801, a noncompetitive NMDA antagonist, inhibited the expression of audiogenic seizures in rats 12 h after withdrawal from chronic ethanol treatment (17).

Evidence also has been presented to indicate that the upregulation of voltage-sensitive Ca^{2+} channels in the brain is the underlying mechanism of ethanol physical withdrawal symptoms (2,9,10,11). It has been shown that ethanol withdrawal-induced hyperexcitability is a consequence of an increased number and functional activity of dihydropyridine-sensitive Ca^{2+} channels in the brain (3,9–11). Several dihydropyridine

L-channel antagonists have been found to antagonize the handling-induced ethanol withdrawal seizures in mice when they are given during ethanol withdrawal (6). Further, concurrent chronic administration of nitrendipine, a dihydropyridine Ca^{2+} channel antagonist, prevented the ethanol-induced upregulation of dihydropyridine recognition sites (15). There is no data available on other Ca^{2+} channel inhibitor binding sites, such as phenylalkylamine sites, with respect to alcohol withdrawal. However, one can speculate that, similar to dihydropyridine sites, phenylalkylamine-sensitive Ca^{2+} channels in the brain may also be involved in CNS hyperexcitability observed during alcohol withdrawal states.

Overall, levemopamil, given acutely, caused a rapid and significant reduction in both alcohol intake and preference. Further, this drug diminished the severity of ethanol physical withdrawal symptoms in rats. It is likely that levemopamil exerts its inhibitory action on ethanol preference by interfering with serotonergic and/or other neurotransmitter systems in the brain. The ability of levemopamil to diminish the severity of ethanol withdrawal might be due to its direct interaction with neuronal Ca^{2+} channels. Experiments are underway to further investigate these speculations.

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