tization of the biting response in *Aplysia* after food is presented is produced by serotonergic neurons that act on the feeding muscle and is apparently also mediated by cyclic AMP (see also K. Weiss, J. Cohen, I. Kupfermann, *Brain Res.* **99**, 381 (1975).

11. In *Aplysia*, as in some other invertebrates, serotonin sometimes produces actions that are mediated by norepinephrine in vertebrates, perhaps because these animals lack the enzyme dopamine-β-hydroxylase and cannot synthesize norepinephrine. An example is the innervation of the heart of *Aplysia*, where inhibition is mediated by acetylcholine (as it is in vertebrates), but where excitation is mediated by serotonin (rather than norepinephrine, as it is in vertebrates) (*7*). In both mollusks and vertebrates, the action of the biogenic amine may be mediated by cyclic AMP. In *Aplysia*, as in vertebrates, sensitization seems to be a component of behavioral arousal [P. M. Groves and R. F. Thompson, *Psychol. Rev.* **77**, 419 (1970); T. J. Carew, V. F. Castellucci, E. R. Kandel, *Int. J. Neurosci.* **2**, 79 (1971)]. Norepinephrine, which increases cyclic AMP in the cerebellum and facilitates its inputs, is thought to have a role in behavioral arousal [F. E. Bloom, *Rev. Physiol. Biochem. Pharmacol.* **74**, 2 (1975); B. J. Hoffer, R. Freedman, D. Puro, D. J. Woodward, *Neurosci. Abstr.* **1**, 204 (1975)]. It is possible that norepinephrine may have a role in the sensitizing component of arousal in vertebrates and that it mediates its action by cyclic AMP.

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Suppression by 1,3-Butanediol of the Ethanol Withdrawal Syndrome in Rats

Abstract. *1,3-Butanediol was tested for its ability to suppress an ethanol withdrawal syndrome. Male Sprague-Dawley rats were rendered physically dependent on ethanol by intragastric administration of ethanol at a dosage of 9 to 15 grams per kilogram per day over a 4-day period. A nonintoxicating oral dose of 1,3-butanediol at 4 grams per kilogram administered after elimination of ethanol from the blood was effective against the tremulous and convulsive components of the ethanol withdrawal syndrome in all animals for 1 to 5 hours. This period coincided with the time of maximum severity of the withdrawal syndrome, as seen in the control animals.*

The clinical management of ethanol withdrawal has to take into account both acute and chronic aspects of ethanol intake. During the early stages of the withdrawal period, a subject displays signs of intoxication similar to those observed during the first drinking episode. As detoxification proceeds and the blood ethanol concentrations decline to approximately 100 mg/dl, a gradual transition develops from depression to hyperexcitability. With the total elimination of blood ethanol, a series of neurological signs and reactions emerge which include general agitation, tremors, convulsions, hallucinations, and delirium tremens (*1*). In addition, a number of side effects resulting from long-term intoxication with heavy doses of ethanol are evident. These may include malnutrition, weight loss, a lessened resistance to infection, hepatitis, cirrhosis of the liver, various vitamin deficiencies, peripheral neuropathy, and general neurological, psychiatric, and clinical deterioration (*1*). Thus, an ethanol withdrawal syndrome can be a serious medical problem and may be fatal if not properly managed. Therefore, the primary aim of treatment is to reduce the neuromuscular and autonomic hyperactivity, thereby preventing exhaustion so that necessary clinical management and treatment can proceed (*1*).

Empirically, any drug that will suppress nervous excitability may ameliorate the severity of the withdrawal reaction. To date, a variety of compounds that are either structurally or pharmacologically similar to ethanol have been effective in treatment (*2*). Among these are aliphatic alcohols and their corresponding aldehydes, paraldehyde, chloral hydrate, barbiturates, phenothiazines, and benzodiazepines (*2*). However, the optimal drug is not only efficacious in controlling the withdrawal syndrome, but is devoid of major side effects. Of the drugs just listed, some are either more toxic than ethanol or have severe side effects, including their ability to induce dependence (*2*).

The availability of a number of animal models of ethanol dependence (*3*) now allows the testing of a variety of potential therapeutic agents for their ability to suppress the signs and responses of the ethanol withdrawal syndrome. Using our model of ethanol dependence in the rat (*4*), we screened a number of compounds listed above and found some effective. In addition, 1,3-butanediol (BD), a compound of low toxicity (*5–7*) suppresses a variety of signs and responses in rats characteristic of the ethanol withdrawal syndrome.

Male Sprague-Dawley rats (200 to 300 g) were rendered ethanol dependent by intubation of a 20 percent solution of ethanol at a dose of 9 to 15 g/kg daily in up to six fractions over a 4-day period (*4*). Since we used the maximum tolerable doses for the induction of ethanol dependence, about one-fifth of the animals usually died as a result of overdosage. On the day of withdrawal, the animals were observed at hourly intervals, initially for the disappearance of ethanol intoxication during the prodromal detoxication phase and then for the onset of a withdrawal syndrome during the ethanol dependence phase. With the onset of signs of the ethanol withdrawal syndrome, blood samples were taken also at hourly intervals from the tail vein; this continued until the complete clearance of ethanol from the blood. Blood ethanol levels were determined by means of an automated adaptation (*8*) of a gas chromatographic method of Roach and Creaven (*9*). At this point, the animals were

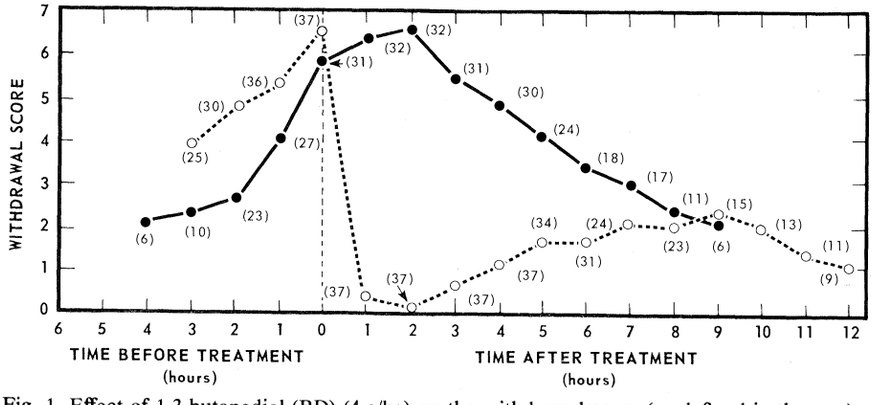

Fig. 1. Effect of 1,3-butanediol (BD) (4 g/kg) on the withdrawal score (as defined in the text). (_____) Untreated ethanol-dependent rats; (-----) BD-treated, ethanol-dependent rats. Time zero corresponds to the point at which all ethanol has been eliminated from the blood, and for BD-treated animals denotes the point at which BD was administered. Numbers in parentheses denote the number of animals observed, while each point refers to the mean of the withdrawal scores. Statistical differences were found for the period 1 to 5 hours after BD treatment using the median test ($P < .05$).

treated (orally) with BD (4 g/kg) or untreated (*10*). In making the behavioral evaluations the experimenter was unaware of which animals were treated with BD. Hourly evaluations continued until the disappearance of the overt signs of the withdrawal syndrome (Fig. 1).

The onset of the withdrawal syndrome was based on visual and tactile evaluation of the intensity of the following signs: tremors of the tail, caudal region, and head, general tremors, tail rigidity, general rigidity, hyperactivity, and convulsions. For the scoring of the effectiveness of BD in suppressing the withdrawal syndrome, only the tremors were used because tremors are observed most frequently in humans (*1*) and are the most easily demonstrated and quantifiable sign in our model. Tremors were rated on a scale of 1, 2, and 3, and were classified into mild, moderate, and severe, respectively (*4*). In general, the severity of tremors of the tail and caudal region ranged from 1 to 3, whereas the maximum score of the head tremors usually was not higher than 2. The severity of the withdrawal is expressed as a total score that represents the sum of the individual scores assessed for four types of tremors observed at each observation session.

The withdrawal tremors usually lasted from 20 to 24 hours in animals that received no treatment (Fig. 1). This period corresponds to the time from the onset of the withdrawal when ethanol was still present in the blood to the total disappearance of the overt signs and responses of the withdrawal syndrome. However, the period of withdrawal corresponding to the time when ethanol was still present in the blood was 4 to 6 hours. The maximum severity of the withdrawal reactions usually occurred when blood ethanol decreased to less than 100 mg/dl and up to 4 hours later.

Administration of single doses of BD reduced the severity of the withdrawal tremors for varying periods of time in different animals. In general, the score dropped to about zero in all treated animals and was statistically different from controls for 1 to 5 hours when compared by the median test ($P < .05$) (Fig. 1). This period also coincided with the time of maximum severity of the withdrawal syndrome as seen in the controls. The tremors reappeared with a severity and time course of recovery similar to that of the untreated animals approximately 6 to 8 hours after administration of BD. No convulsions were observed in any of the 37 BD-treated animals as compared to the five convulsions observed in 32 control rats.

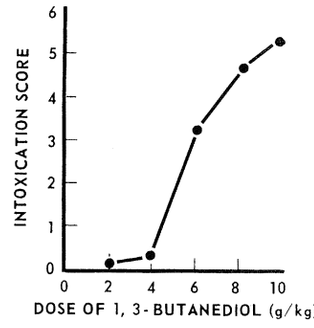

Fig. 2. Effect of 1,3-butanediol on naive rats. Each group contained four animals. The intoxication score was assigned as follows: 0, normal; 1, sedation; 2, ataxia 1; 3, ataxia 2; 4, ataxia 3; 5, loss of righting reflex; and 6, coma (*4*).

The ability of acute doses of BD to induce intoxication was determined with behavioral parameters as described (*4*, *6*, *11*). Doses of 2 to 10 g/kg were administered orally to naive animals deprived of food overnight. Intoxication was observed in a dose-dependent manner (Fig. 2). At the dose of 4 g/kg used for suppressing the ethanol withdrawal syndrome, no significant degree of intoxication was observed.

Our results indicate that BD effectively suppresses the tremulous and convulsive components of the ethanol withdrawal syndrome in the rat. This would suggest the possible use of this compound in treatment of some aspects of the syndrome in humans. Although serious consideration of clinical application is premature, BD has a number of positive attributes. In addition to being able to ameliorate withdrawal signs, it is nonintoxicating in the doses used (Fig. 2) (*10*). Some of its pharmacological and biological properties have been established during the last 30 years in studies with BD as a synthetic source of calories (*5*, *6*). In general, BD is relatively nontoxic in both humans (*7*) and experimental animals (*5*, *6*, *12*), and has little or no toxic effects with doses used in our study. There have been no reports suggesting that long-term consumption of BD can induce physical dependence or intoxication. However, in order to induce physical dependence, highly intoxicating amounts of ethanol must be ingested (*4*, *11*). Until experiments are performed in which intoxication with BD is maintained 24 hours a day for a number of days without the development of a withdrawal syndrome after the last dose of BD, the possibility that BD could be addictive cannot be excluded.

Whether BD can be used in a clinical setting remains to be determined. Also, because of its structural similarity to ethanol, BD and other related compounds may be useful in exploring the specificity of alcohols in inducing physical dependence.

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