Pharmacology Biochemistry & Behavior, Vol. 18, Suppl. 1, pp. 537–539, 1983.

Decrease in Ethanol Consumption by Naloxone in Naive and Dependent Rats

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MARFAING-JALLAT, P., D. MICELI AND J. LE MAGNEN. *Decrease in ethanol consumption by naloxone in naive and dependent rats.* PHARMACOL BIOCHEM BEHAV **18:** Suppl. 1, 537–539, 1983.—Acute effects of the opiate antagonist, naloxone, on alcohol intake have been examined and compared in naive and behaviorally dependent rats. In naive rats the aversion to an 8% alcohol solution exhibited in a 30 min presentation was selectively augmented by an IP administration of naloxone (1 mg/kg) 30 min before a morning drinking session. In other rats, behavioral dependence was established by 15 days of IG administration of intoxicating doses of alcohol. This dependence was exhibited by a sustained preference for ethanol for 6 days. Naloxone (1 mg/kg) abolishes the acquired preference for ethanol tested during an 8 hour day time presentation. These effects of naloxone on alcohol intake in ethanol naive and dependent rats are interpreted in relation to a general non-specific action of naloxone on preferred or aversive flavoured solutions.

Ethanol dependence Rats Naloxone Alcohol consumption

THE opiate antagonist, naloxone, has been shown to accentuate taste aversions and to suppress taste preferences [7]. These data suggested a role of opiate receptors and of their endogenous ligands in eliciting an attenuation both of taste nociception or aversiveness and of taste preference or reward.

In order to study further this naloxone effect on ingestive responses, experiments have been undertaken to investigate the acute effect of naloxone administration on oral ethanol and water intakes in rats. The taste aversion of rats to ethanol solution is well documented [3, 5, 6, 9]. However, in rats rendered physically dependent on ethanol, this spontaneous taste aversion may be reversed and a high taste preference for ethanol solution can be exhibited. Thus, the possibility existed to test the effect of naloxone on the spontaneous aversion to and induced preference for the same fluid.

Another purpose of this work was to test the acute effect of naloxone upon alcohol intake in naive compared to dependent rats. The question was raised as to the specific action of naloxone on alcohol intake related to the interaction between naloxone and the neuropharmacological activity of ethanol. Results have been reported which are not consistent with the notion of a specific effect of naloxone on the acute and chronic effect of ethanol. In naive rats, naloxone does not change the acute neurotoxic effect or initial nervous system tolerance to ethanol. In addition, naloxone added to ethanol during a chronic treatment does not change the acquired tolerance [11,12]. However, it has been shown that naloxone, also associated with ethanol in a chronic treatment in mice [2] and rats [1], reduced the signs of the withdrawal syndrome observed at the cessation of the treatment.

METHOD

Experiment 1

Ten adult male Wistar rats were used. Body weight was 299±2 g at the beginning of the experiment. They were individually housed and had free access to their familiar stock diet at all times. Twice a day, a graduated drinking bottle was presented from 10 to 10:30 a.m. and from 3 to 5 p.m. In the latter period, tap water was available throughout the experiment. During the morning presentation, they were offered either an 8% w/v) alcohol solution or tap water on alternate days. After 6 days of habituation to this schedule, an IP injection of saline was administered 30 min before the beginning of the morning drinking session for 8 consecutive days. The liquid intake for the 4 alcohol presentations and the 4 alternate water presentations served as baseline. For the following 8 days, the sessions of alternate alcohol or water presentation were preceded, 30 min before, by an IP naloxone injection (1 mg/kg). Finally, the last 8 presentations were again preceded by a saline injection.

Experiment 2

In this experiment, 7 rats weighing 325±7 g were used. First, a high ethanol intake was produced according to the procedure described in detail elsewhere [10]. The rats were at first intoxicated by 5 daily intragastric administrations, consisting of 10 g/kg/day of ethanol for 15 days. Twelve hours after the cessation of treatment, the rats (24 hr water deprived) were offered an ethyl alcohol solution (10% v/v) for 1 day, as the only source of fluid. Then they were offered an alternate presentation of ethanol solution and water 8

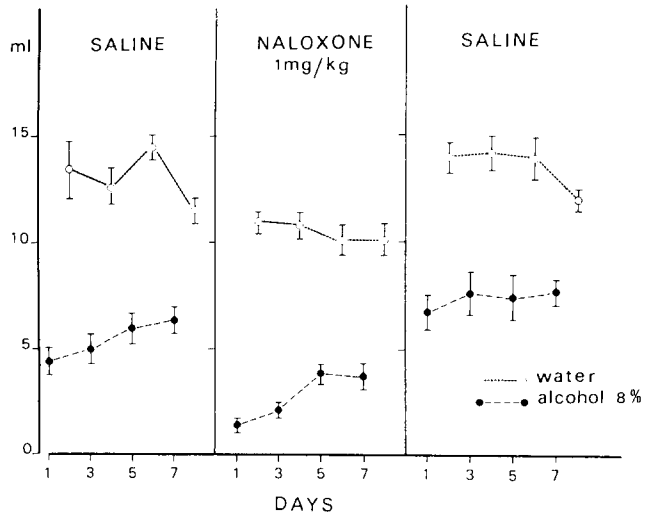

FIG. 1. Thirty min intake of an alcohol solution versus water after an acute naloxone (1 mg/kg) injection (central section) or after an injection of saline (pre and post naloxone controls), in naive rats.

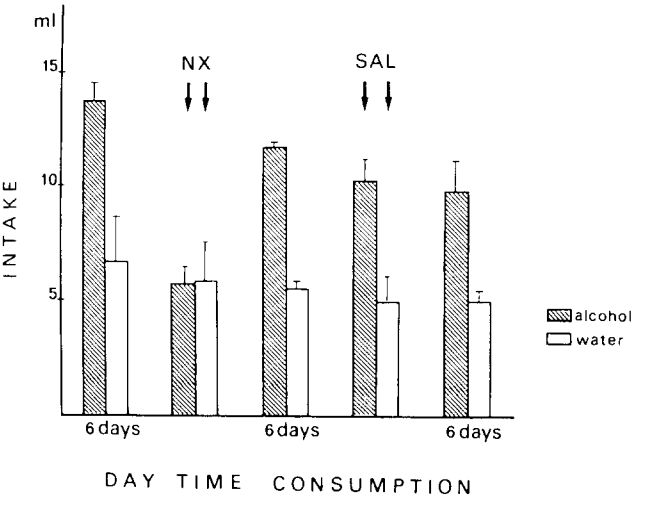

FIG. 2. Histograms of the 10 a.m. to 6 p.m. level of alcohol and water intake (in ml) during baseline, naloxone and saline treatments, in dependent rats.

hours each for 6 days. The acquired behavioral dependence on ethanol was assessed by the preference for the alcohol solution versus water during this period. The day time 8 hour consumption of ethanol solution compared to the water intake on the alternate day was chosen to express this preference and to test further the effect of naloxone. During the subsequent 2 days, rats were injected IP with 0.5 ml naloxone (1 mg/kg) 30 min before the day time presentation, and again in the middle of the 8 hour presentation of ethanol solution the first day and water the other day.

After 6 days, the same day time presentation was preceded by control (0.5 ml) injections of saline for 2 days, followed by 6 further days of periodic presentation.

As a control, 8 rats without previous chronic intoxication were submitted to the same schedule of alcohol and water presentation as the above intoxicated subjects.

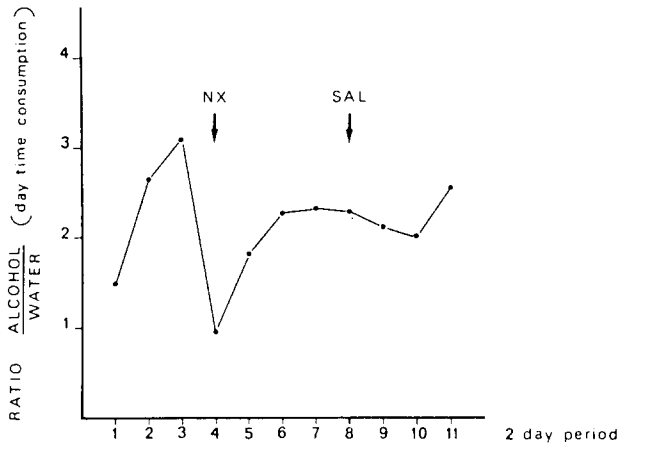

FIG. 3. Ratio of alcohol to water intakes during baseline, naloxone and saline treatments, in dependent rats.

RESULTS

Experiment 1

In Experiment 1, during the initial saline control, rats exhibited a statistically significant lower intake of ethanol compared to water, indicating ethanol aversion: $t=13.34$; $p<0.001$ (Student's t-test, Fig. 1). Under the acute effect of naloxone, the intake of the alcohol solution was reduced by 49.35% and the intake of water on alternate days by 20.12%. The difference between alcohol and water intakes was highly significant ($t=18.50$; $p<0.001$).

The aversion, measured by the alcohol to water ratio was 0.41 at saline precontrol and 0.26 under naloxone. This difference is statistically significant (Wilcoxon test, $p<0.01$). During the post-treatment saline control, the initial level of aversion was reestablished (ratio=0.54) (Wilcoxon test, $p<0.01$).

Experiment 2

During the initial 6 days of alternate presentation of alcohol solution and water, physically dependent rats exhibited, as previously demonstrated, a higher intake of ethanol solution compared to water intake during the same 8 hour presentation the subsequent day.

The mean alcohol intake during the day-time, 8 hour presentation was 13.7±0.70 ml (3.48±0.8 g/kg) versus 6.6±1.8 ml of water (Fig. 2).

The alcohol to water ratios for this 10 a.m. to 6 p.m. period were 1.49–2.65–3.10 for the 3 consecutive pairs of days (Fig. 3).

Under naloxone administration a strong decrease in the level of alcohol consumption was observed while water intake remained unchanged. The level of alcohol intake dropped to 5.7 ml versus 5.8 ml for water. Consequently, the alcohol to water ratio decreased to 0.97.

Under saline administration, the consumption of both ethyl alcohol and water were not different from the intake observed during the two preceding days. The alcohol to water ratio was maintained at 2.29. This saline control ratio is statistically different from the naloxone value (Wilcoxon test, $p<0.01$).

DISCUSSION

Results of Experiment 1 demonstrate that naloxone accentuates the aversive ingestive response to an ethyl alcohol solution in ethanol naive rats. The fact that naloxone acutely enhances aversion to ethanol in the same way as it enhances aversion to a quinine solution has several implications. It is a confirmation that the initial aversion of rats to an ethyl alcohol solution is sensory in nature. As such, it provides evidence for a non-specific action of the opiate antagonist on innate aversions, based on oral cues of either alcohol or quinine solutions.

Results of Experiment 2 validate the procedure of induction of behavioral dependence on ethanol [10] as a new method to test the acute effect of a drug on the high intake of ethanol in dependent rats.

In the present study, it is demonstrated that the opiate antagonist abolishes acutely the high preference for alcohol solution acquired by rats after 15 days of administration of high doses of ethanol. This acute effect of naloxone on oral intake could be interpreted as an effect of a disphoric or sickness-producing action of the drug. This acute sickness after naloxone is not supported by the fact that naloxone used as an unconditioned stimulus (U.C.S.) in a conditioned taste aversion paradigm did not induce aversion at a dose higher than employed in this study. However, it has been shown that toxic agents such as LiCl may act to impair ingestive performances at a dose lower than required to induce taste aversion when used as an U.C.S. [4]. Nevertheless, this acute action of naloxone is unlikely since it is observed with ethanol solution and not with water. The differential effect is consistent with other data showing that "flavour" enhances the action of naloxone in reducing fluid intake [8]. This result is in turn consistent with the assumption that naloxone acts on the hedonic, rewarding aspect of oral cues and not on performance. Altogether, the present results indicate that the reduction of intake of ethanol, both in non-preferring naive rats and in preferring dependent rats, is not due to an interaction of naloxone with the neuropharmacological activity of ethanol since the same effect of naloxone was obtained in a previous study with a bitter and sweet solution respectively.

Further work will be needed to see if a chronic naloxone treatment would be an efficient tool to prevent the development of or alleviate behavioral dependence on ethanol of intoxicated rats.

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