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Naloxone and angiotensin-II-induced drinking

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Rats were given one of three doses of angiotensin-II to induce drinking. These same subjects were also given one of five doses of naloxone (.0, .1, 1.0, 5.0, or 10 mg/kg, sc) 15 min before an opportunity to drink for 1 h. Subjects receiving .0 mg/kg of naloxone and angiotensin drank about 6.0 g of water, whereas subjects receiving 1.0, 5.0, and 10 mg/kg of naloxone and angiotensin took only about 1.0 g of water. Naloxone clearly suppressed angiotensin-induced drinking. This finding adds further support to the hypothesis that there is an endorphinergic component in the system regulating drinking.

This brief note is an addendum to, and confirmation of, a preliminary report (Ostrowski, Rowland, Foley, Nelson, & Reid, 1981) indicating that naloxone (NX) suppresses drinking elicited by angiotensin-II (A-II). This note is also a companion to another recent report (Brown & Holtzman, 1981) indicating that NX attenuates drinking elicited by intracerebroventricularly administered A-II. Each of the initial experiments demonstrating that NX attenuates drinking induced by A-II used only a single dose of A-II and only one or two doses of NX. Consequently, we thought it necessary to test more doses of each drug.

METHOD

Sixty-eight experimentally naive male Sprague-Dawley-derived (Taconic Farms, Germantown, New York) rats weighing from 250 to 350 g were used. Each rat was housed individually, with food and water always available. The colony room was maintained at 24°C on a light-dark cycle (12 h of light, with lights on at 2200 h).

To measure water intake, bottles equipped with ball-point sipping tubes were weighed (to the nearest .1 g) before and after a limited opportunity to drink. The drugs used were naloxone HCl (Endo Labs) and isoleucine^5-angiotensin-II (Sigma Chemicals) in a vehicle of .9% saline solution.

After the rats were habituated to their living conditions, they were given a single test at a time when they were typically inactive (between 0100 and 0200 h). On the day of the test, water bottles were removed 45 min before testing. Fifteen minutes before the bottles were put back for 1 h, the rats were injected with NX at doses of .0, .1, 1.0, 5.0, or 10.0 mg of naloxone HCl per kilogram. Immediately before presentation of the bottles, rats were given one of three doses of A-II: .225, .75, or 1.25 mg/kg. Therefore, grams of water consumed in 1 h were the scores, and they conformed to a 3 by 5 factorial design with three levels of A-II and five levels of NX (n = 4/group). Two additional groups were tested following .0 mg/kg of A-II and either .0 or 10.0 mg/kg of NX (n = 4/group). All injections were given subcutaneously in a 1-ml/kg volume.

RESULTS

A-II was effective in eliciting drinking. Subjects receiving 0 mg/kg of A-II and 0 mg/kg NX drank a mean of 1.53 g (SEM = .53), whereas subjects receiving .225, .75, and 1.25 mg/kg A-II and 0 mg/kg NX drank 5.75 g (SEM = 1.21), 3.85 g (SEM = 1.03), and 6.0 g (SEM = 1.91), respectively. A two-sample t test between the data of the control group and the combined scores of the animals receiving A-II yielded $t(14) = 2.53$ ($p < .05$). Animals receiving 0 mg/kg A-II and 10 mg/kg NX hardly drank (mean = .35 g, SEM = .12).

A 3 by 5 ANOVA confirmed that NX reliably reduced drinking induced by A-II [$F(4,55) = 18.69$, $p < .001$]. The doses of A-II did not reliably affect drinking differentially [$F(2,57) = .19$]. The interaction was not a reliable source of variance [$F(8,51) = .35$]. These data are summarized in Figure 1.

DISCUSSION

When NX is given to water-deprived rats, it suppresses but does not eliminate drinking, at even very high doses (10 mg/kg) (Brown & Holtzman, 1979; Holtzman, 1974, 1975; Maickel,

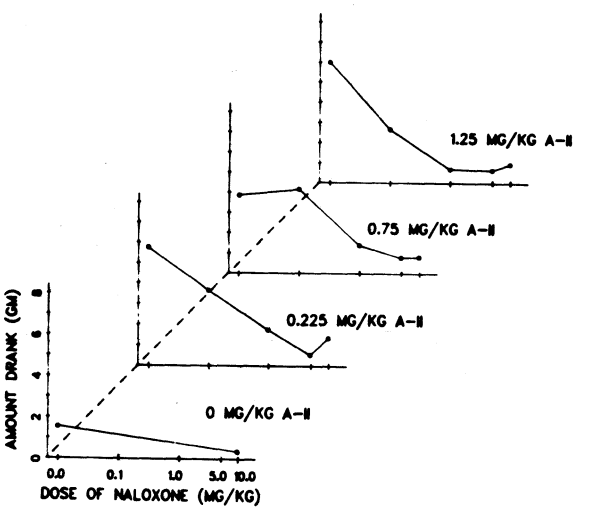

Figure 1. The effects of various doses of angiotensin-II and naloxone on drinking in nondeprived rats. The values represent mean intake (in grams) during a 1-h test.

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Braude, & Zabik, 1977; Ostrowski, Foley, Lind, & Reid, 1980; Ostrowski et al., 1981). Because NX blocks the activity of endorphinergic systems (Goldstein, 1978) and because NX attenuates drinking, the hypothesis is generated that one function of the endorphinergic system is the regulation of ingestion. Since NX only attenuates deprivation-induced drinking, it is possible that the endorphinergic system is involved with only one component of the drinking response. However, NX, as well as other opioid antagonists, is equally effective in reducing intake in response to various physiological stimuli for drinking. NX reduces intake induced by injections of solutions of polyethylene glycol (hypovolemia) (Ostrowski et al., 1981), hypertonic sodium chloride (Brown, Blank, & Holtzman, 1980; Ostrowski et al., 1981), isoproterenol (Brown & Holtzman, 1981), and A-II (Brown & Holtzman, 1981; Ostrowski et al., 1981). Therefore, the idea that NX interferes with the response to a single physiological component related to drinking is not supported.

NX has reduced drinking following intracerebral administration of angiotensin (Brown & Holtzman, 1981), as well as when A-II is given subcutaneously (this paper). Rowland (Note 1) has recently observed NX's suppression of drinking when the A-II was given intravenously, with partial suppression of drinking at doses as low as .01 and .1 mg/kg of NX and nearly complete suppression of drinking at doses as great or greater than 1.0 mg/kg. Doses of NX at or greater than 1.0 mg/kg seem to be capable of yielding close to maximal effect on the particular system being tested. The A-II effect is not dependent on route of administration, and NX is capable of suppressing A-II-induced drinking at relatively small doses regardless of the way A-II is administered.

A possible clue as to why NX reduces drinking arises from the finding that NX does not affect schedule-induced polydipsia (Brown & Holtzman, 1981). One phenomenon associated with drinking induced by schedules is that animals will drink aversive solutions (e.g., alcohol or quinine) that they normally would avoid (Freed, Zec, & Mendelson, 1977). However, intake of quinine-adulterated water has been found to be reduced in rats induced to drink by deprivation, hypertonic sodium chloride, isoproterenol, polyethylene glycol, and A-II (Nicolaidis & Rowland, 1975; Rowland & Flamm, 1977). Therefore, it follows that in situations in which drinking is sensitive to taste, NX exhibits its typical antidipsogenic effect. However, in a paradigm in which the drinking does not appear to be extraordinarily sensitive to taste, NX has no effect. This relationship leads to the suggestion that NX may reduce intake by interfering with some factor associated with determining the stimulus quality of the water. Several lines of evidence support such a possibility. NX has been shown to abolish a preference for sweet solutions as well as to enhance the aversiveness to quinine in deprived animals (LeMagnen, Marfaing-Jallat, Miceli, & Devos, 1980). NX is also quite potent in reducing intake of 10% sucrose solution in nondeprived animals (Ostrowski et al., 1980; Wu, Lind, Stapleton, & Reid, 1981). Finally, when postingestional absorption is prevented while oral factors are left intact, NX still reduces intake of water (Rockwood, Siviy, & Reid, in press).

Deprivation apparently increases the value of certain potentially reinforcing events (Revusky, 1968); in this instance, the reinforcing event is the presentation, or potential intake, of water. As the need for water increases, subjects work harder to be presented with water, the probability of drinking increases, and consummatory behavior is sustained for longer periods. Since NX interferes with the typical sequel following the increment in need or need-related events, we tentatively conclude that the endogenous opioid system serves to modulate the value of water when there is an apparent need. Antagonism by NX dampens the value of water and, hence, decreases the probability of the consummatory responses occurring or being sustained for prolonged periods. In other words, the endogenous opioids are apparently involved with determining the value of certain need-specific stimuli. An issue of some interest, which inspection of these data cannot address, is whether the endorphins function in the hypothesized way with many motivational reinforcement systems or only a few of these systems. Considerable evidence accumulated since 1974, however, does point to a relevant role for the endogenous opioid system in the regulation of water balance.

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