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BRIEF COMMUNICATION

Diazepam-Induced NaCl Solution Intake: Independence from Renal Factors[1]

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TANG, M., C. BROWN, D. MAIER AND J. L. FALK. *Diazepam-induced NaCl solution intake: Independence from renal factors.* PHARMACOL BIOCHEM BEHAV 18(6) 983–984, 1983.—Rehydrating rats injected with diazepam (8 mg/kg, SC) increased their intake of 2.0% NaCl solution. Neither bilateral nephrectomy nor bilateral ureter ligation interfered with the increased NaCl solution ingestion produced by diazepam. It is concluded that the increased intake of the NaCl solution is not secondary to renal water-electrolyte losses nor dependent upon intact renal benzodiazepine receptors.

Renal factors and drinking NaCl intake Salt appetite Diazepam and drinking

CHLORDIAZEPOXIDE [5], midazolam [16] and phenobarbital [5,13] injections all increase NaCl solution acceptance in the rat. Since these drugs possess punishment attenuation properties [4,7], it has been suggested that the observed increased hypertonic NaCl solution acceptance may be a subclass of this general action [5]. Thus, the increased intake of a noxious NaCl solution might be analogous to the increased drinking of electrified water (e.g., [17]).

Benzodiazepine receptors are found in organs outside the central nervous system, such as the kidneys [1,15], although their functions are unknown. Since changes in renal function can affect sodium appetite [3, 6, 8, 19], it is possible that the kidney might be related to the observed increase in NaCl solution acceptance. The present experiment was designed to delineate the role the kidney might play in benzodiazepine-induced NaCl solution intake.

METHOD

Animals

Twenty-four male, albino Holtzman rats with an initial mean weight of 381 g (range: 352–406 g) were housed individually in standard, Acme stainless-steel cages in a temperature-controlled room with a 12-hr light-dark cycle (lights on 0700 to 1900 hr).

Procedure

All animals were adapted to a 23-hr water-deprivation schedule for 6 days, i.e., water (distilled) was available for only 1 hr each day. Food (Purina Lab Chow, pelleted) was available at all times except during the 1-hr drinking period. At 1330 hr each day food was removed from the cages and all animals were weighed. Water, available from 100-ml Richter drinking tubes, was then placed on the cages. At the end of the 1-hr period, water intakes and any spillages were recorded and drinking tubes removed. Food was then replaced. On the seventh day, animals were randomly divided into 3 groups differing in the type of surgery given: sham, bilateral nephrectomy and bilateral ureter ligation. Half of the animals in each group were given a subcutaneous dose of 8 mg/kg diazepam 4 hours postsurgery while the remaining animals in each group were given a vehicle injection. A 2% NaCl solution (w/w) was made available for 1 hr beginning 15 min after the injection. As during the adaptation days, no food was available during the 1-hr drinking period.

Drugs

Diazepam (generously supplied by Dr. W. E. Scott, Hoffman-La Roche, Nutley, NJ) was suspended in a cornstarch vehicle prepared in the following manner: 2 g of cornstarch was added to 98 ml of distilled water and heated to a rolling boil while stirring. After cooling to room temperature, the mixture was combined with approximately 0.1 ml Tween 80, mixed thoroughly and stored under refrigeration for later use. The diazepam suspension was always prepared prior to injection by gradually adding 1 ml of vehicle (warmed to room temperature) to every 8 mg of drug. Injection volume was a constant proportion of body weight for both drug and vehicle injections and was always less than 0.4 ml.

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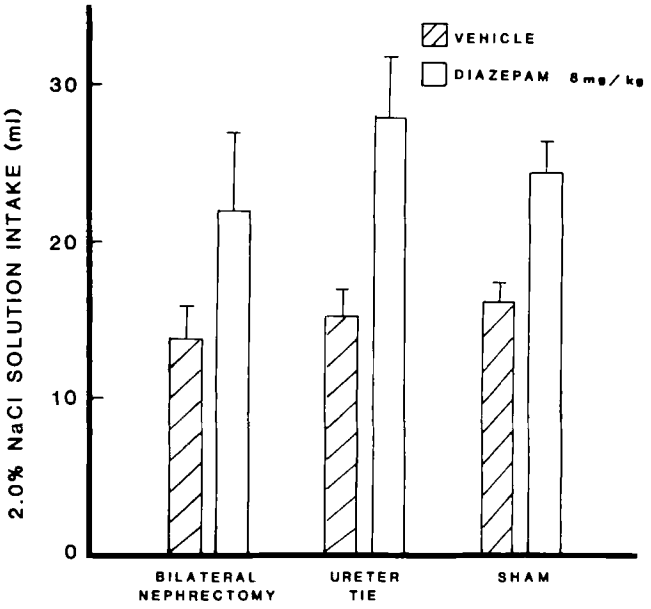

FIG. 1. (Mean (+SE) 1-hr ingestion of 2.0% NaCl solution by rehydrating rats (N=4 each group) as affected by diazepam (8 mg/kg, SC) and renal surgical manipulations.

Surgery

Surgeries were performed under ether anesthesia and lasted 10 min so that ether exposure was equal among the groups. In order to equate the 3 types of surgical procedures, an identical incision was made for all cases. This consisted of a 5 cm ventral midline incision placed between the level of the bladder and the diaphragm. For bilateral nephrectomy, each kidney was decapsulated and the blood supply occluded by placing a hemostat between the kidney and the aorta. The blood vessels were then tied off, with 00 silk suture, central to the hemostat and the kidney was removed immediately lateral to the hemostat. In the case of bilateral ureter ligation, both ureters were tied off with 00 silk suture about 2 cm above the bladder. Sham operation consisted of locating both kidneys but nothing was occluded or removed.

RESULTS AND DISCUSSION

Diazepam significantly increased the 1-hr intake of 2.0% NaCl solution in 23-hr water-deprived rats (see Fig. 1). Overall analysis of variance performed on the intake data yielded a significant F-ratio for drug effects, $F(1,18)=22.20$, $p<0.001$. The F-value obtained for surgical effects, however, was not significant. A one-way analysis of variance on the diazepam groups alone also did not yield significant intake differences among the three surgical groups.

In addition to NaCl solutions, punishment-attenuating agents also have been reported to increase intakes of various other solutions: citric acid [18] tartaric acid [10] and saccharin [10,18], and, on occasion, even water [2, 9, 11, 12, 14]. Thus, it is possible that these drug-induced increases in intakes could be secondary to renal water or electrolyte losses. This possibility, however, is eliminated by the present finding that the enhanced solution intake persisted in animals whose urinary output is blocked by bilateral ureter ligation. The inability of bilateral nephrectomy to abolish the drug effect further demonstrates that intactness of the renal benzodiazepine receptors is not necessary for the full expression of the effect.

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