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Sedation and Need-Free Salt Intake in Rats Treated With Clonidine

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DE LUCA, L. A., JR., R. L. NUNES DE SOUZA, M. M. YADA AND E. W. MEYER. *Sedation and need-free salt intake in rats treated with clonidine*. PHARMACOL BIOCHEM BEHAV **62**(4) 585–589, 1999.—The effect of intraperitoneal injection of clonidine (9–72 μg/kg) on need-free 1.5% NaCl intake and on performance (defined as percent of a complete trial) in the rotarod test, was studied in normovolemic adult male rats. Clonidine (18 and 36 μg/kg) inhibited the 1.5% NaCl intake in a 2-h test at doses that did not alter the performance in the rotarod test. The dose of 36 μg/kg did not inhibit 10% sucrose intake. Only the highest dose (72 μg/kg) of clonidine inhibited the 1.5% NaCl intake and the performance in the rotarod test, and produced signs of sedation. Sedation was determined either by change in posture (immobility or lack of postural tonus) of the animals during the ingestive test or by their performance in the rotarod test. The results suggest that sedation is not a determinant effect on the inhibition of 1.5% NaCl intake induced by clonidine. © 1999 Elsevier Science Inc.

Salt intake Sodium intake Water intake Food intake Sucrose Adrenoceptors Anxiolytics Rotarod

THE inhibitory effect of noradrenaline on water intake has been well established since the early work by Grossman (13). This effect is dependent on alpha$_2$-adrenoceptor activation (7,11). Recent data show that hypertonic saline intake of sodium-depleted rats also depends on alpha$_2$-adrenoceptor activation (24,25). Evidences for alpha$_2$-adrenoceptor participation in water and hypertonic saline intake is the potent inhibition of these behaviors by the alpha$_2$-adrenoceptor agonist, clonidine, and the inhibition of clonidine by alpha$_2$-adrenoceptor antagonists (24,25).

Hypertonic saline intake also occurs in rats that have regular chow available. This type of saline intake, called natriophilia or need-free sodium intake (20,22), represents an excess intake of sodium because the animal already ingests enough sodium from the chow. Need-free sodium intake is enhanced by multiple sodium depletions (22). Enhanced need-free NaCl intake occurs when the animals have restablished their normal sodium balance and normal plasma concentrations of angiotensin II and aldosterone (22). Although the mechanisms of the enhancement are not known, enhanced intake is useful for acute measurements of need-free NaCl intake when rats show low ingestive activity during the light phase of the day (12).

The inhibition of ingestive behavior by clonidine is preferential for hydromineral fluids in relation to food or sucrose solution (7,24). However, it is not known how much of the sedative properties of clonidine (5,15) is responsible for this inhibition. Pertinent to this question is the enhancement of hypertonic saline intake in water-deprived rats by sedative drugs, such as diazepam (2,3,23). Therefore, it is possible that the inhibition of fluid intake caused by clonidine is independent of its sedative properties.

Deficits in motor coordination, change in posture, and other external signals (5,6,15), can be used as an index of sedation. Performance in the rotarod apparatus is a useful method to measure motor coordination in rodents (6).

The present work was designed to investigate whether the inhibition of fluid intake by systemic injection of clonidine is a

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result of the sedative properties of the drug. The results show that inhibition of need-free sodium intake by clonidine occurs at doses that do not alter performance in the rotarod.

METHOD

General Procedures

Animals. Thirty-nine male Holtzman rats weighing 280–320 g at the beginning of the experimental tests (need-free 1.5% NaCl intake, 10% sucrose intake, and rotarod) were used. They were individually housed in a room on a 12 L:12 D cycle beginning at 0700 h at least 5 days before the experiments began. Standard Purina pellets containing more sodium (0.5–1.0%) than the minimum daily requirement of the rat (the Harvard Bioscience Whole Rat Catalog, Harvard Bioscience-Ealing Division, 1983). Tap water and 1.5% NaCl solution were available ad lib unless otherwise noted. All experiments began between 0800 and 1400 h.

Drugs. Clonidine hydrochloride (Sigma, St. Louis, MO) was used. Clonidine was dissolved in 0.9% saline (vehicle) from 9 to 72 μg/kg/ml. The natriuretic/diuretic furosemide (Sigma) was used for sodium depletion.

Statistics. Data are expressed as means ± SEM. Two-way (drug and time as factors) analysis of variance was used for comparisons between groups followed by Student–Newman–Keuls post hoc test. The paired *t*-test was also used where appropriate. Significance level was set at $p < 0.05$ for all tests. The different doses of each drug was injected in a counterbalanced design. Each animal underwent from two to four experimental sessions of each test (described below) separated by a 2- to 3-day interval. Each animal received only one dose of clonidine in each session. Each animal was submitted to only one type of test (need-free 1.5% NaCl intake, 10% sucrose intake or rotarod).

Experimental Protocols

Need-free sodium intake test. Rats consume measurable amounts of 1.5% NaCl for 24 h in the presence of standard food pellets and water, but this behavior is not easily expressed by naive sodium-depleted rats during the few hours of observation in acute protocols. Thus, we used the method described by other investigators (12) to produce need-free intake of NaCl solution for a period of 2 h of testing. This method takes into consideration that need-free intake of NaCl solution is enhanced by multiple sodium depletions (22). Therefore, the animals underwent three sodium depletions and respective sodium appetite tests (described below) every 7 days. Their average body weight was 190 g when they were first depleted. Except during the days corresponding to sodium depletion and to sodium appetite test, 1.5% NaCl, standard food pellets, and water were available ad lib. After the third and last sodium appetite test, the 1.5% NaCl was removed and then only water and standard food pellets became available until the next day. Then, to measure acute need-free 1.5% NaCl intake, this solution was offered in graduated (0.1 ml) burettes fitted with metal spouts every day for 120 min. The wetted tip of the metal spout was brought in contact to the lips of the animals before the burettes were mounted in front of the cages. This procedure was repeated for animals that did not show any intake between two intervals of recording.

The experiments began on the fifth day after the third sodium appetite test. Food was removed, and the need-free 1.5% NaCl intake and water intake were measured at 15, 30, 60, and 120 min. Clonidine (9, 18, 36, or 72 μg/kg) or vehicle was injected intraperitoneally (IP) 20 min before the 1.5% NaCl was offered.

Sodium depletion and sodium appetite test. Sodium-deficient food (powdered corn meal, 0.001% sodium, 0.33% potassium) replaced the regular pellets, and the rats were sodium depleted by combining one injection of furosemide (10 mg/ml/rat) with removal of ambient sodium. This procedure induces an average of 2 mEq of sodium loss in the urine within 2 h (16). At the time of the furosemide injection, food pellets were replaced by the sodium deficient food, the 1.5% NaCl (but not water) was removed, and the rat's cage was thoroughly washed to remove all ambient sodium. Thus, only sodium deficient food and water were available overnight for consumption. The following day (24 h after the furosemide injection) the sodium-deficient food was removed and the 1.5% NaCl was returned to the animals for ingestion for 120 min (sodium appetite test). Standard food was returned to the rat at the end of the test and was available continuously with water and 1.5% NaCl until the next depletion.

Sucrose intake test. This test was used to determine the specificity of the effect of clonidine on ingestive behavior. After 2 days of free access to 10% sucrose, the animals had it available with only water for 2 h daily, for 5 days. They had free access to food and water during the remaining 22 h; therefore, the animals ingested 10% sucrose without being food deprived. On the fifth day, clonidine (36 μg/kg) or 0.9% saline was injected IP 20 min before the sucrose solution was offered. The intake of 10% sucrose and water were measured at 15, 30, 60, and 120 min.

Motor coordination test. Motor performance was measured in a rotarod apparatus (Ugo Basile, Italy). The rotating rod was coupled to an electronic setup for individual automatic recording of the latency to fall off from the rod. On each test day, the animals were submitted to a set of training trials followed by a set of experimental trials.

The animals were removed from their home cages and then put, to a maximum of six, into polypropylene cages (41 × 31 × 17 cm) with wood bedding and a wire mesh cover. Water was available for drinking from a bottle with a metal spout hanging from the top of the cover. The animals rested for 1 h with access to water prior to any other manipulation. Then a set of training trials was executed before each set of experimental trials, at a constant speed of 8 rpm. The animal was defined as "trained" when it showed the same performance (latency of falling off from the rotating rod) in a set of three successive training trials lasting 50 s each. The animals were then randomly assigned to the experimental trials. The performance of each animal in the training trials was similar (±10% of variation) between different experimental sessions.

A set of four experimental trials of 2.5 min each began 1 h after the last training trial. The speed of the turning rod increased from 8 rpm to 20 rpm from the beginning to the end of each experimental trial. Clonidine (18, 36, or 72 μg/kg) or 0.9% saline was injected IP 20 min before the first session. The beginning of the first trial was defined as zero minute, followed by trials beginning at 15, 30, and 60 min. The measurement of performance in each experimental trial was defined as the percent from the total (2.5 min) of the trial completed by the animal. The beginning of the first experimental trial in the rotarod corresponds to the time 1.5% NaCl was offered to animals submitted to the need-free intake test. The animals were returned to their home cages after the last experimental trial.

Recording of other behaviors. The general aspect of the animals during the ingestion tests were recorded by visual inspection. Immobility was defined as the trunk sustained with

the four limbs in the same position while the eyes remained opened and the nostrils were above the plane of the chest (not a sleeping posture). Prostration was defined as the animal laying down, sideways or over its belly, along its longitudinal axis, on the floor of the cage.

RESULTS

Intake of Need-Induced and Need-Free 1.5% NaCl

The animals ingested 13.2 ± 2.2, 22.7 ± 2.2, and 26.0 ± 2.0 ml/120 min of 1.5% NaCl during the first, second, and third sodium appetite test, respectively. There was a significant enhancement of the need-induced intake from the first test to the next ($p < 0.05$, $n = 6$), as expected from the literature (21). Recordings of the need-free 1.5% NaCl intake at 120 min, done one time between 2 experimental days and another 7 days after the last experimental session, were 6.3 ± 1.5 and 6.5 ± 2.5 ml ($n = 6$), respectively. Therefore, the need-free intake between nonexperimental days was not altered by clonidine or saline injection. These intakes are different ($p < 0.05$) from the intakes expressed prior to any depletion (2.0 ± 0.5 ml/120 min, $n = 6$).

Effect of Clonidine on the Need-Free 1.5% NaCl Intake

Clonidine injected IP reduced the need-free 1.5% NaCl intake at the 2-h test, ($F(3, 20) = 20.0$, $p < 0.05$, between vehicle (0.9% saline), 9, 18, and 36 μg/kg). Figure 1 shows that the doses of 18 and 36 μg/kg, but not of 9 μg/kg, inhibited the 1.5% NaCl intake from 60 to 120 min. The dose of 72 μg/kg also inhibited the 1.5% NaCl intake, $F(1, 10) = 228.7$, $p < 0.05$, between vehicle and 72 μg/kg, but the results are represented separately on Table 1 because this dose also altered the performance in the rotarod test. This higher dose, not the lower ones, also induced immobility or prostration that lasted from 15 to 60 min after the injection. These two effects were not observed in any animal that received vehicle. Significant alterations between minutes, $F(3, 75) = 10$, $p < 0.05$, also occurred for all doses of clonidine, but no interaction occurred between time and dose as factors.

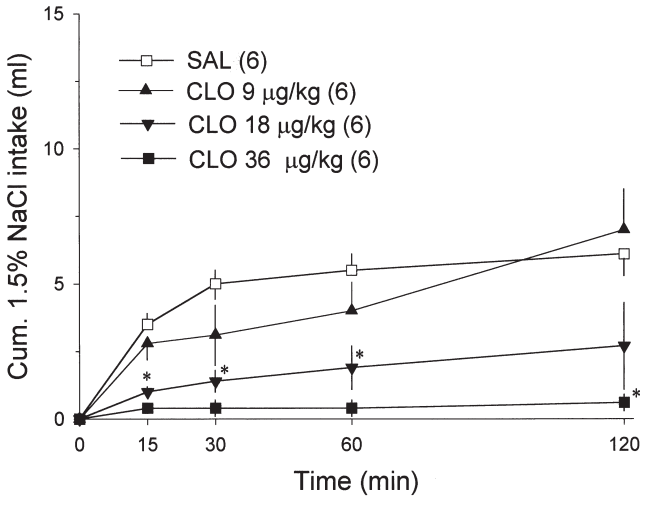

FIG. 1. Cumulative need-free 1.5% NaCl intake of rats that received intraperitoneal injection of 0.9% saline (SAL) or clonidine (CLO, 9, 18, or 36 μg/kg). SAL or CLO was injected at −20 min. *$p < 0.05$ vs. SAL. The number of animals appears within parentheses. Data are expressed as means ± SEM.

TABLE 1

CUMULATIVE NEED-FREE 1.5% NACL INTAKE AND THE PERCENT OF SESSION COMPLETED IN THE ROTAROD TEST BY RATS THAT RECEIVED EITHER 0.9% SALINE OR 72 μg/kg OF CLONIDINE IP

Time (min)	Group	Cum. 1.5% NaCl Intake (ml)	% Session Completed
0	Saline	0 ± 0 (6)	45 ± 9 (13)
	Clonidine	0 ± 0 (6)	26 ± 8 (12)
15	Saline	3.5 ± 0.5 (6)	36 ± 8 (13)
	Clonidine	0 ± 0* (6)	24 ± 6 (12)
30	Saline	5.0 ± 0.5 (6)	45 ± 8 (13)
	Clonidine	0 ± 0* (6)	26 ± 8 (12)
60	Saline	5.5 ± 0.6 (6)	38 ± 7 (13)
	Clonidine	0.1 ± 0.1* (6)	25 ± 7 (12)
120	Saline	6.1 ± 0.8 (6)	—
	Clonidine	0.6 ± 0.4* (6)	—

* $p < 0.05$ compared to saline. $F(1, 10) = 228{,}7$, $p < 0.05$, between treatments, for 1.5% NaCl intake. $F(1, 23) = 8.8$, $p < 0.05$ between treatments, for the rotarod test. The number of animals appears within parentheses.

Animals that received vehicle ingested a maximum of 1.6 ± 0.9 ml ($n = 6$) of water in 120 min of the test. No water intake occurred in the animals treated with doses of clonidine that inhibited 1.5% NaCl intake. Water intake at the lowest dose of clonidine was not different from the group treated with vehicle.

Effect of Clonidine on 10% Sucrose Intake

The two-way ANOVA showed no difference between clonidine (36 μg/kg) and vehicle (0.9% saline), $F(1, 10) = 1.8$. There were differences between minutes, $F(3, 30) = 9.3$, $p < 0.05$, and interaction between drug and time as factors, $F(3, 40) = 3.4$, $p < 0.05$. The animals that received clonidine ingested more 10% sucrose at 120 min of the test (Fig. 2).

Effect of Clonidine on the Performance in the Rotarod Test

The doses of clonidine of 18 and 36 μg/kg, which inhibited the 1.5% NaCl intake, did not alter the performance in the rotarod test, ($F(2, 29) = 1.6$, nonsignificant, between 0.9% saline, 18 and 36 μg/kg) (Fig. 3). These two doses also did not alter the performance when considered individually. The dose of 72 μg/kg, which also inhibited the 1.5% NaCl intake, also inhibited the performance in the rotarod test, ($F(1, 23) = 8.8$, $p < 0.05$, between 0.9% saline and 72 μg/kg) (Table 1). There were no differences between minutes and no interaction between time and dose as factors.

DISCUSSION

The effects of clonidine on need-free 1.5% NaCl intake, on the rotarod test and on general posture of the rats were evaluated in the present work. Clonidine IP inhibited the need-free 1.5% NaCl intake at doses that did not alter the performance in the rotarod test or 10% sucrose intake.

The need-free 1.5% NaCl intake is another model of hydrosaline fluid intake inhibited by clonidine. This drug, whether given peripherally or centrally, inhibits water intake induced by different treatments (water deprivation, cholinergic and angiotensinergic activation, hypertonic solutions, solid food intake) and need-induced salt intake [(4,24), for review]. The doses used in the present report are within the range of

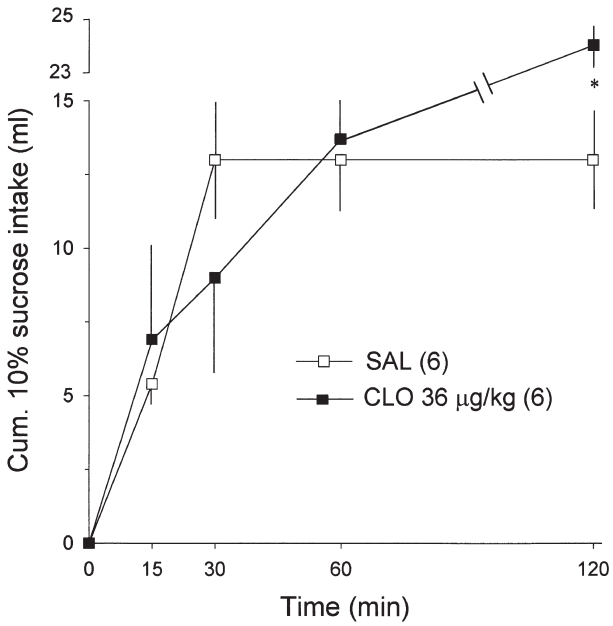

FIG. 2. Cumulative need-free 10% sucrose intake of rats that received intraperitoneal injection of 0.9% saline (SAL) or clonidine (CLO, 36 μg/kg). SAL or CLO was injected at −20 min, $*p < 0.05$ vs. SAL. The number of animals appears within parentheses. Data are expressed as means ± SEM.

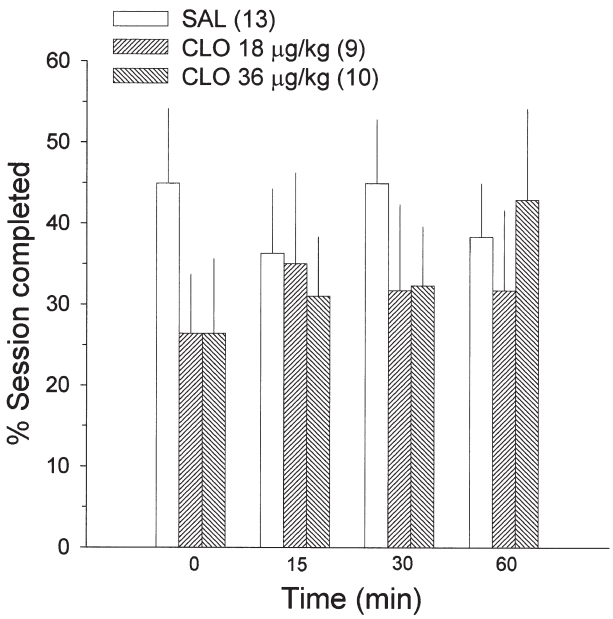

FIG. 3. Percent of trial completed in the rotarod after intraperitoneal injection of 0.9% saline (SAL) or clonidine (CLO, 18, or 36 μg/kg). The drugs or SAL were injected at −20 min. Each time block corresponds to a new trial. $*p < 0.05$ vs. SAL. The number of animals appears within parentheses. Data are expressed as means ± SEM.

previous reports showing inhibition of water intake by peripheral clonidine (1,10,19). Water intake of 24-h water-deprived rats is larger than the 10% sucrose intake, but doses of clonidine within that range produce a percent inhibition of water intake (10) that is similar to the percent inhibition of need-free 1.5% NaCl intake observed in the present work. Nevertheless, similar doses of clonidine do not reduce sucrose solution intake [(9), and present results]. In addition, clonidine (36 μg/kg) fully inhibits the need-free 1.5% NaCl intake for 120 min, which is similar to the inhibition of 3% NaCl intake of sodium depleted rats when it is injected centrally (24). If the amount of fluid ingested by control animals, which could be reflecting motivational states, were important for the inhibitory effect of clonidine, then this drug should have inhibited the 10% sucrose (high palatable solution) intake during at least the first 15 min of the sucrose test, when the intake of 10% sucrose of every group was similar to the need-free intake of 1.5% NaCl of controls (saline injection) at 60 and 120 min (Figs. 1 and 2). When depleted of sodium, rats ingest more of 1.5% NaCl (present results) and more of the otherwise aversive 3% NaCl (24) than the need-free 1.5% NaCl, yet clonidine potently inhibits the intake in depleted animals [(24) for central injections; unpublished results for peripheral injections]. Thus, the inhibition of fluid intake by clonidine is not related to differences in the amounts of different types of fluid ingested by controls or to motivational states (e.g., dehydration or palatability). The failure to inhibit 10% sucrose intake by IP clonidine at a dose (36 μg/kg) that inhibits need-free 1.5% NaCl intake is consistent with the idea that the inhibitory action of clonidine 1) depends on the nature of the fluid ingested (9), and 2) is preferential for hydro-saline fluid intake (7,24).

Clonidine injected into the brain inhibits preferentially water and salt intake in relation to food and 10% sucrose (24). Animals that received clonidine IP in the present experiments ingested the same amounts of 10% sucrose the controls did until 60 min, but they ingested more 10% sucrose at 120 min. This is a possible explanation for the significant interaction between treatment (clonidine vs. vehicle) and time for 10% sucrose intake. Although we used satiated rats in the present experiments, the results are more consistent with the enhancing effect of clonidine on sucrose intake of food-deprived rats (9). However, unpublished results from our laboratory with the dose of 72 μg/kg indicate that sucrose intake is partially inhibited by this higher dose at the initial part (15 to 30 min) of the test. Thus, unspecific effects of clonidine on ingestive behavior may appear at higher doses.

The present work does not assess listed symptoms (5,15), other than motor incoordination, immobility, or prostration, induced by clonidine. We considered that an animal was sedated if it showed at least one of these symptoms. Nevertheless, the main point to be considered is the more potent and longer-lasting inhibitory effect clonidine has on hydrosaline fluid intake than on the intake of other commodities like food or sucrose [(7,24), present results].

The normal or even enhanced intake of sucrose solution in animals treated with clonidine suggests that this drug is not altering the coordination of oral movements. The sedation induced by the highest dose (72 μg/kg) of clonidine could also be an additional factor that inhibits fluid intake. To completely demonstrate that sedation is not important to alter fluid intake we need a drug that sedates but has no effect (inhibition or activation) on intake.

The inhibition of angiotensin-induced water intake by systemic clonidine and its antagonism by centrally injected yohimbine, an α_2-adrenergic antagonist, indicates that clonidine acts on brain α_2-adrenoceptors to inhibit fluid intake (11). This indication has been confirmed for need-induced water or

salt intake (7,25) and demonstrated to be independent from the effects of clonidine on arterial pressure (24). The inhibition of fluid intake induced by clonidine is probably not related to production of anxiogenesis, because clonidine has anxiolytic-like properties (14,18).

The inhibition of need-free sodium intake by systemic injection of clonidine has the counterpart of systemic injection of yohimbine in normovolemic rats inducing sodium intake (8,17). The mechanism of this natriorexigenic effect of yohimbine is still not understood (8), but the opposite effects of agonist and antagonist suggest that endogenous α_2-adrenoceptors are part of an inhibitory system of sodium intake.

In conclusion, there are doses of clonidine that inhibit need-free salt intake without altering the motor mechanisms of fluid intake and independent of sedation. Therefore, sedation is not an important mechanism for the inhibition of fluid intake by clonidine.

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