Pharmacology Biochemistry & Behavior, Vol. 28, pp. 187–191. © Pergamon Journals Ltd., 1987. Printed in the U.S.A. 0091-3057/87 $3.00 + .00

Benzodiazepines and Putative 5-HT_{1A} Agonists Increase Hypertonic Saline Consumption in Rehydrating Rats

STEVEN J. COOPER AND ASMAWATI DESA

Department of Psychology, University of Birmingham, Birmingham, B15 2TT, U.K.

Received 23 February 1987

COOPER, S. J. AND A. DESA. *Benzodiazepines and putative 5-HT_{1A} agonists increase hypertonic saline consumption in rehydrating rats.* PHARMACOL BIOCHEM BEHAV **28**(2) 187–191, 1987.—Male rats were adapted to a 22 hr water-deprivation schedule, and to a 30 min test of hypertonic (1.8 or 2.7%) NaCl solution ingestion. A novel benzodiazepine, Ro23-0364, recently reported to have anxiolytic activity in rats and squirrel monkeys but to have limited potential to produce unwanted side effects, produced significant dose-related increases in hypertonic saline ingestion. Midazolam, a benzodiazepine full agonist, increased salt intake but the effect was offset at higher doses by the induction of sedation. Three putative 5-HT_{1A} agonists, proposed as nonbenzodiazepine-related anxiolytics, were also tested: the highly selective 8-OH-DPAT, gepirone and ipsapirone (TVX Q 7821). In each case, occasions when hypertonic saline consumption was significantly increased were detected. At 300 μg/kg of 8-OH-DPAT and 10 mg/kg of gepirone, the appearance of a pronounced flattened body posture effectively interfered with drinking responses. It appears possible that a behavioural action shared by benzodiazepines and 5-HT_{1A} agonists may be responsible for the increased hypertonic saline ingestion.

Benzodiazepines Gepirone 8-OH-DPAT Ipsapirone (TVX Q 7821) Midazolam Ro23-0364
5-HT_{1A} receptor Hypertonic saline Rats Water-deprivation

HYPERTONIC NaCl solutions may be aversive to animals not depleted of sodium [16,20] and in acceptance tests [5] the consumption of such solutions by rehydrating rats is reduced below that of water [32]. Hypertonic saline consumption is sensitive to the actions of anxiolytic drugs, and it has been demonstrated that benzodiazepines (e.g., chlordiazepoxide, diazepam, midazolam), and the barbiturate, phenobarbital, increase the acceptance of hypertonic saline in rehydrating rats [6, 7, 21, 25, 26]. It has been suggested that the ingestion of NaCl solutions may be useful in the evaluation of known and putative anxiolytic agents [7]. In support of this possibility, nonbenzodiazepine anxiolytics which act as agonists at benzodiazepine receptors also enhance hypertonic NaCl acceptance. Thus, the β-carboline ZK 93423 [24], the pyrrolopyrazine derivative zopiclone [12], and the triazolopyridazine derivative CL 218,872 [13], all significantly increased the consumption of a 1.8% NaCl solution [2]. It would be particularly important, in addition, to evaluate putative anxiolytics which do not act at benzodiazepine receptors in tests of hypertonic NaCl ingestion to assess the generality of the effect.

There were two aims to the present set of experiments. The first was to investigate the effects of a novel benzodiazepine derivative Ro23-0364 [14], in comparison with midazolam as a reference drug. Ro23-0364 has been reported to have an anxiolytic profile in rat and squirrel monkey conflict tests, but over a broad range of doses to show little evidence of rate depressant effects [22]. It appears to be an effective anxiolytic with only a limited potential to produce unwanted side effects. Testing this compound, therefore, would enable us to determine if increased hypertonic NaCl ingestion is related to, or independent of, side effects typically elicited by benzodiazepine full agonists.

There is currently considerable interest in 5-HT_{1A} agonists as a novel class of anxiolytic compounds [3,19]. Hence, these drugs may be expected to increase hypertonic saline ingestion, if the procedure is sensitive to anxiolytic action and not simply to restricted side effects characteristic only of benzodiazepines and barbiturates. However, in a recent study the only effect of the putative 5-HT_{1A} agonist buspirone [27] was to reduce hypertonic saline consumption when given in large doses (10 and 30 mg/kg) to rehydrating rats [2]. Nevertheless, buspirone is not selective as a 5-HT_{1A} agonist, and also has effects on dopaminergic activity [23]. Therefore, we tested three additional compounds: the highly selective 5-HT_{1A} agonists, 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) [11,15]; ipsapirone (TVX Q 7821) [9]; and gepirone [1,17]. We sought evidence that these 5-HT_{1A} agonists may increase hypertonic NaCl solution consumption.

Most experiments were carried out using a 1.8% NaCl solution, but some compounds were also tested with a 2.7% solution, which depressed drinking to a greater extent.

METHOD

Animals

The subjects were 45 adults, male rats (hooded General strain) which were bred in the Psychology Department, University of Birmingham. They were housed individually in

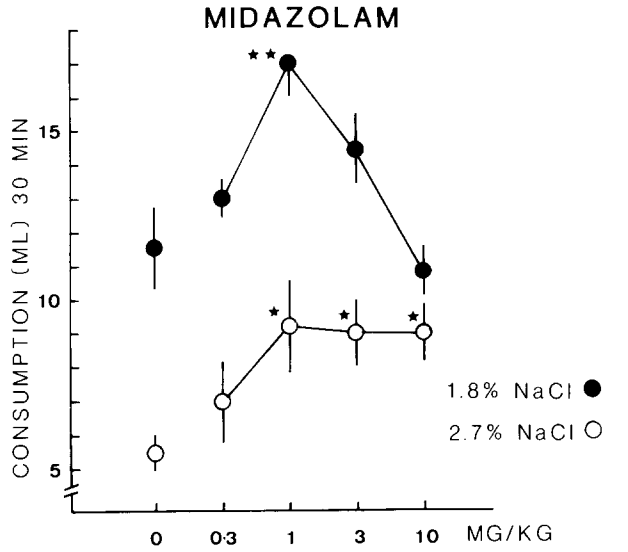

FIG. 1. Effects of midazolam (0.3–10 mg/kg, IP) on consumption of either 1.8% (●) or 2.7% (○) NaCl solution in a 30 min test following 22 hr water deprivation. Results are shown as mean intake (ml) ±S.E.M. N=9 per group. Levels of significance in comparison with control groups: $*p<0.05$; $**p<0.01$ (Dunnett's t-test).

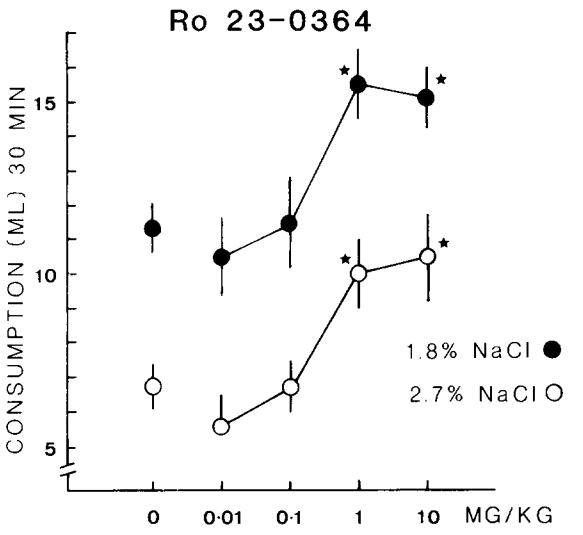

FIG. 2. Effects of the novel, anxioselective benzodiazepine Ro23-0364 (0.01–10 mg/kg, IP) on consumption of either 1.8% (●) or 2.7% (○) NaCl solution. Other details described in Fig. 1 legend.

stainless steel cages with ad lib access to food pellets (modified Diet 41B, Heygate & Sons, U.K.). They were maintained under a 12 hr light-12 hr dark cycle (lights on at 7 a.m.) and the room temperature was kept constant at 20–21°C. The animals were accustomed to being handled, and weighed 300–400 g at the start of the studies.

Drugs

The following drugs were used: midazolam bimaleate (supplied by Roche Products Ltd., U.K.) in doses of 0.3–10.0 mg/kg; Ro23-0364 (6-[2-chlorophenyl]-4H-imidazo [1,5-][1,4] benzodiazepine-3-carboxamide), which was generously supplied courtesy of Dr. J. Sepinwall, Hoffmann-La Roche, Nutley, NJ, and which was tested over the dose range 0.01–10.0 mg/kg; 8-OH-DPAT hydrobromide, purchased from Research Biochemicals Inc., Wayland, MA, which was tested in doses from 10 to 300 μg/kg; gepirone hydrochloride (kindly supplied by Bristol-Myers, Evansville, IN), injected in doses 0.1–10 mg/kg; ipsapirone hydrochloride (TVX Q 7821), which was donated by Dr. J. Traber, Troponwerke, Cologne, West Germany, and tested at doses of 0.1–3 mg/kg.

Midazolam, 8-OH-DPAT, ipsapirone and gepirone were dissolved in isotonic saline, and their doses are expressed in terms of their salts. Ro23-0364 was prepared by ultrasonic dispersion in distilled water to which Tween 80 was added (2 drops in 10 ml). Midazolam and Ro23-0364 were injected intraperitoneally, while the 5-HT_{1A} agonists were injected by subcutaneous route (flank). All drugs were administered 25–30 min before the test of hypertonic NaCl ingestion.

Procedure

The animals were first adapted to a 22 hr water-deprivation schedule and to obtaining hypertonic saline from a 25 ml calibrated cylinder clipped to the front of the test-cage (which was identical to the home-cage) in daily 30 min sessions. Following the drinking sessions, the animals were returned to their home-cages for a further 90 min access to water with food. Food was not available in the test-cage. The general procedures was based on those described earlier [2].

Initially, the rats were adapted to drinking 1.8% NaCl solution, and were tested following administration of 8-OH-DPAT (10–300 μg/kg, SC) or isotonic saline vehicle. For this test, the animals were randomly allocated to 5 injection groups (N=9 per group). The rats were then placed in the test-cages with water in place of hypertonic saline for one week, and were re-tested in 8-OH-DPAT following their re-allocation into 5 treatment groups. Completing the 8-OH-DPAT tests, the animals were then adapted to drinking a 2.7% NaCl solution in the test-cages for four days, and on the fifth, were injected with the appropriate doses of 8-OH-DPAT or vehicle.

At weekly intervals, the following tests were carried out: Ro23-0364 (0.01–10.0 mg/kg, IP) and midazolam (0.3–10.0 mg/kg, IP) were tested when animals had access to the 2.7% NaCl solution. Then the animals were re-adapted back to the 1.8% NaCl solution over four days, and were tested with the following sequence of drugs, at a rate of two drugs per week: Ro23-0364, midazolam, ipsapirone (0.1–3.0 mg/kg, SC) and finally, gepirone (0.1–3.0 mg/kg, SC). Although there was no formal test of order effects, it is the case that putative 5-HT_{1A} agonists significantly increased hypertonic saline intake both at the beginning and the end of the series of tests. On each occasion that a drug was tested, a control injection group was included for purposes of statistical comparison. Animals were tested in groups of 8 or 9 for each drug-dose condition. In the intervals between drug testing, the water-deprivation schedule was maintained, and animals continued to receive 30 min daily sessions in test-cages. Throughout the studies, control levels of NaCl solution ingestion remained stable, with the level of 1.8% saline consumption being at a higher level than intake of 2.7% saline, as expected.

The saline intake data were analysed using a one-way

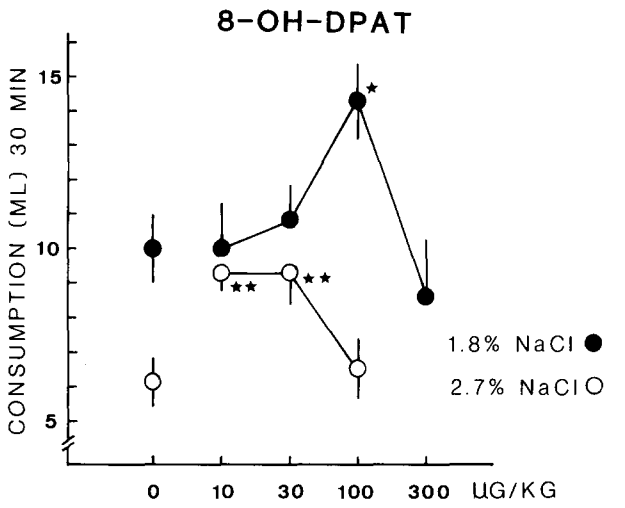

FIG. 3. Effects of the highly selective 5-HT$_{1A}$ agonist, 8-OH-DPAT (10–300 μg/kg, SC) on consumption of either 1.8% (●) or 2.7% (○) NaCl solution. Other details described in Fig. 1 legend.

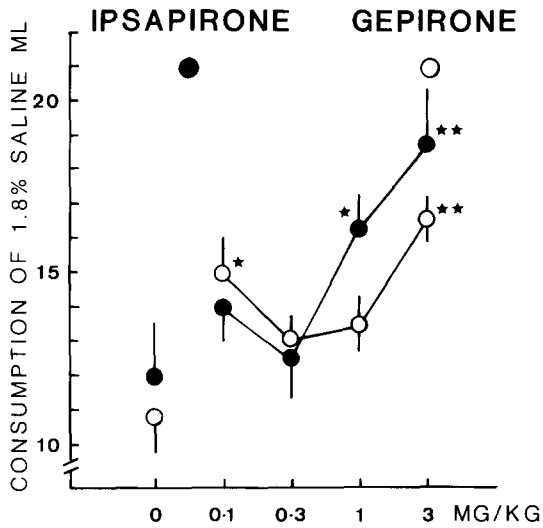

FIG. 4. Effects of ipsapirone (0.1–3.0 mg/kg, SC; N=9 per group) and gepirone (0.1–3.0 mg/kg, SC; N=8 per group) on consumption of a 1.8% NaCl solution in a 30 min test. Other details described in Fig. 1 legend.

analysis of variance for independent groups, followed by Dunnett's *t*-test for comparisons between individual dose conditions and the corresponding vehicle condition [33].

RESULTS

Midazolam

Midazolam had a significant effect on consumption of 1.8% NaCl solution, $F(4,40)=7.32$, $p<0.001$, and of 2.7% NaCl solution, $F(4,40)=2.66$, $p<0.05$. Figure 1 shows an inverted U-shaped dose-effect function for consumption of 1.8% NaCl, with a marked increase in intake occurring at 1.0 mg/kg. Larger doses induced side-effects, and at 10 mg/kg of midazolam, the animals were strongly sedated, with ataxia. Significant increases in consumption of 2.7% saline were produced by midazolam in doses of 1.0 mg/kg and larger, but the effects were not dose-related.

Ro23-0364

The novel benzodiazepine also had significant effects on intakes of 1.8% NaCl solution, $F(4,40)=4.90$, $p<0.005$, and of 2.7% NaCl solution, $F(4,40)=6.39$, $p<0.001$. In both cases, Ro23-0364 produced dose-related increases in consumption, with significant effects occurring at 1.0 and 10 mg/kg (Fig. 2). In absolute terms, the increases in intake were closely comparable in the two conditions, despite the marked difference in baseline levels of consumption. At no dose tested did animals show any sign of motor incapacitation or depression.

8-OH-DPAT

This compound was active at very small doses. It had significant effects on consumption of 1.8% NaCl solution, $F(4,40)=2.87$, $p<0.05$, and of 2.7% NaCl solution, $F(3,32)=6.80$, $p<0.001$. As Fig. 3 indicates, 8-OH-DPAT significantly increased intake of 1.8% NaCl at only one dose level, 100 μg/kg. However, at the larger dose of 300 μg/kg, animals showed marked signs of a flattened body posture [29,30], which interfered with drinking from the spout. When 8-OH-DPAT was injected prior to the 2.7% saline ingestion test, it produced significant increases at 10 and 30 μg/kg respectively. Intake was not enhanced at 100 μg/kg (Fig. 3), and was completely abolished in all animals tested at 300 μg/kg (for this reason, data for this dose were not included in the statistical analysis). In the test of water drinking, the baseline level of drinking was 16.4±0.8 ml (mean±S.E.M.) in the 30 min period. 8-OH-DPAT (10–100 μg/kg) had no effect on intake, but a 300 μg/kg produced a significant decrease ($p<0.01$) in intake (reduced to 8.9±0.6 ml), coincident with the appearance of the flat-body posture.

Ipsapirone and Gepirone

There were significant effects of both ipsapirone, $F(4,40)=3.74$, $p<0.05$, and gepirone, $F(4,35)=5.97$, $p<0.001$, on consumption of hypertonic saline. As Fig. 4 indicates, ipsapirone stimulated ingestion of the 1.8% NaCl solution at 1.0 and 3.0 mg/kg. Gepirone also increased intake of the hypertonic solution, although the dose-effect relationship was not a simple linear one. Significant increases in intake occurred at 0.1 and 3.0 mg/kg. A group of 5 animals were also tested at 10 mg/kg of gepirone, and consumption of 1.8% NaCl was completely suppressed over the 30 min test period. All the animals exhibited the flat-body posture, which had also been observed in the case of 8-OH-DPAT (300 μg/kg).

DISCUSSION

The results of the present studies allow two main conclusions to be drawn. First, stimulation of hypertonic saline intake by drug action at benzodiazepine receptors appears to be independent of the sedating and ataxic effects which are typically associated with full agonist activity. Sepinwall and his colleagues have recently described the anxiolytic property of Ro23-0364 in rats and squirrels [22]. This ben-

zodiazepine has a greatly reduced potential for producing motor impairment, decreased motor activity or amnesia. To the best of our knowledge, our data are the first to demonstrate significant effects of Ro23-0364 on an ingestional response. It significantly enhanced consumption of either 1.8% or 2.7% hypertonic saline (Fig. 2). In the case of midazolam, a full agonist active at benzodiazepine receptors, there was some indication that the sedation induced at higher dose levels counteracted its effects to enhance saline consumption, resulting in nonmonotonic dose-effect relationships (Fig. 1).

Second, drug action at benzodiazepine receptors is not necessary for significant increases in the ingestion of hypertonic saline by rehydrating rats. Our results show that three selectively-active 5-HT_{1A} agonists, 8-OH-DPAT, ipsapirone and gepirone, produced significant increases in hypertonic saline consumption (Figs. 3 and 4). In the test of 1.8% NaCl consumption, 100 μg/kg of 8-OH-DPAT, 1.0 and 3.0 mg/kg of ipsapirone, and 0.1 and 3.0 mg/kg of gepirone enhanced ingestion. The consistency of the effect across the three compounds suggests strongly that 5-HT_{1A} receptor mediation was responsible. In a recent study of the discriminative stimulus properties of 8-OH-DPAT, Tricklebank and colleagues [31] trained rats with training dose of 50 μg/kg of 8-OH-DPAT, and showed 50% generalisation to the 8-OH-DPAT lever after administration of 1.0 mg/kg of ipsapirone, and 88% generalisation after 3.0 mg/kg. Their extensive pharmacological studies are strongly persuasive that the 8-OH-DPAT cue was mediated by 5-HT_{1A} receptors, and it is striking that doses of ipsapirone which generalised to the 8-OH-DPAT cue produced significant increases in hypertonic salt ingestion in the present experiments. Unfortunately, gepirone was not included in their studies, and so comparisons cannot be made with our present data.

A greater suppression of drinking occurred, as expected, when a 2.7% NaCl solution was provided instead of a 1.8% solution. Drug effects were affected to some degree, at least, when dose-response relations are compared (Figs. 1–3). 8-OH-DPAT, which enhanced 1.8% NaCl ingestion at 100 μg/kg, increased consumption of the more concentrated salt solution at the very low doses of 10 and 30 μg/kg. It is interesting to note that 8-OH-DPAT did not increase water intake. Midazolam had significant effects at doses 1.0–10 mg/kg on intake of 2.7% NaCl, although they were not dose-related. In the case of Ro23-0364, there was a very close similarity in the dose-response relations for the two salt concentrations. This last result suggests that when benzodiazepine side effects are absent, stimulation of hypertonic saline ingestion may be relatively unaffected by differences in baseline.

It has been argued that putative 5-HT_{1A} agonists may be effective anxiolytics [3,19]. There are behavioural data from animal models of anxiolytic activity which support this idea. Significant anticonflict activity has been reported in a punished licking test following 125 and 250 μg/kg of 8-OH-DPAT [4]. Furthermore, 8-OH-DPAT and gepirone display anticonflict effects in a Cook-Davidson procedure using rats (D. Bennett, personal communication). Traber and colleagues reported recently that ipsapirone increased the number of punished responses in a punished drinking test, and reduced aggressive and fear-related behaviour [28]. Nevertheless, using an elevated plus-maze test, File and her colleagues failed to detect anxiolytic activity of 8-OH-DPAT (62.5–250 μg/kg) or ipsapirone (2.5–10 mg/kg) [8]. Clearly, the nature of the anxiolytic paradigm appears to be critical in detecting appropriate effects of putative 5-HT_{1A} agonists. Set against these reports, our data show that the test of hypertonic saline consumption is sensitive to their behaviourally-enhancing effects.

Tricklebank and co-workers described a behavioural syndrome produced by subcutaneous administration of low doses of 8-OH-DPAT to rats: hyperlocomotion, head-weaving, a flat-body posture and reciprocal forepaw treading [29,30]. Of these behaviours, they presented evidence that the latter two effects (flat-body posture and forepaw treading) are probably mediated at 5-HT_{1A} postsynaptic sites. In our work, we observed clear evidence of flattened body posture at 300 μg/kg of 8-OH-DPAT and 10 mg/kg gepirone. In both cases, ingestion of hypertonic saline was severely attenuated or abolished entirely. It seems very probable that the flattened posture interfered with the act of licking at a drinking spout, on the basis of our observations during the drinking tests. It is not surprising therefore to find that at 10 mg/kg, gepirone decreased food intake and general activity in rats, as recently reported [18].

In summary, our data indicate that benzodiazepine agonists that have a reduced potential for producing side-effects can be particularly effective in increasing hypertonic saline ingestion. Furthermore, our results describe increases in saline intake produced by putative 5-HT_{1A} agonists, 8-OH-DPAT, gepirone and ipsapirone. 5-HT_{1A} receptors are thought to be located both pre- and postsynaptically [3,10], but our data are not sufficient to indicate which sites may be more relevant to the increases in saline consumption. The present evidence indicates that it would be fruitful to search for a common behavioural mechanism underlying effects of benzodiazepines and 5-HT_{1A} agonists on saline ingestion. Future experiments could investigate possible relationships between these two classes of anxiolytic drugs on the consumption of salt solutions.

ACKNOWLEDGEMENTS

A. Desa is supported by a grant from the Malaysian government. We thank Jo Neill and David Barber for their help.

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