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Effects of Selective 5-HT_1 Receptor Agonists in Water-Deprived Rats on Salt Intake in Two-Choice Tests

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COOPER, S. J. AND R. CICCOCIOPPO. *Effects of selective 5-HT_1 receptor agonists in water-deprived rats on salt intake in two-choice tests.* PHARMACOL BIOCHEM BEHAV **45**(3) 513–518, 1993.—Twenty-two-hour water-deprived rats were divided into two groups: The first was given access to 1.8% saline and water in a 30-min two-choice test; the second was given access to 0.9% saline and water in the same type of intake preference test. Animals were tested following administration of several selective 5-hydroxytryptamine$_1$ (5-HT_1) receptor agonists. The results indicated a clear-cut distinction between the effects of selective 5-HT_{1A} receptor agonists, on the one hand, and putative 5-$HT_{1B/1C}$ agonists on the other. Ipsapirone, gepirone, and 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT) all showed evidence of increasing the consumption of 1.8% saline (less preferred to water) but had no effect on intake of the more preferred 0.9% saline. In contrast, 1-3-(chlorophenyl)piperazine (mCPP) and 1-(3-(trifluoromethyl)phenyl)piperazine (TFMPP) (5-$HT_{1B/1C}$ agonists) reduced intake of 1.8 and 0.9% saline in the two tests. One interpretation of these results is to assume that the 5-HT_{1A} agonists act at inhibitory autoreceptors to diminish central serotonergic activity, while mCPP and TFMPP act postsynaptically to enhance serotonergic activity. The possibility is discussed that mCPP and TFMPP may act to increase the perceived salt concentration during drinking, whereas the 5-HT_{1A} agonists may have the opposite effect.

Saline-drinking Thirst 5-HT_1 receptor agonists 8-OH-DPAT Ipsapirone Gepirone mCPP TFMPP

RECENT data suggest that there may be a significant serotonergic involvement in the control of salt intake. Thus, we reported that a number of 5-hydroxytryptamine$_{1A}$ (5-HT_{1A}) agonists, 8-hydroxy-2-(di-*n*-propylamino) tetralin (8-OH-DPAT), gepirone, and ipsapirone, increased the consumption of hypertonic saline in rehydrating rats (5). This effect on salt drinking did not reflect a general hyperdipsic effect of the 5-HT_{1A} agonists because they did not increase the drinking of either water- or quinine-adulterated water (8). In contrast, benzodiazepine receptor (BZR) agonists increase hypertonic saline drinking in water-deprived rats, but they also stimulate ingestion of water and isotonic saline (1,2,6,7,9–12,22–24).

Drugs that act as agonists at other 5-HT_1 receptor subtypes reduce salt or water drinking. Thus, the putative 5-$HT_{1B/1C}$ receptor agonist mCPP reduced hypertonic salt drinking at doses (1.0 and 3.0 mg/kg) that did not affect water drinking (19). Moreover, the 5-HT_1C receptor agonist MK-212 also reduced hypertonic salt drinking at doses (1.0 and 3.0 mg/kg) that did not affect drinking water (19). Together, these results suggest a serotonergic component in the mechanisms underlying the control of salt drinking. Recently, it has been demonstrated that the 5-HT_{1C}/5-HT_2 receptor antagonists ketanserin and ritanserin inhibited the salt appetite induced by deoxycorticosterone acetate (DOCA) (13). These data are the first to suggest that serotonergic mechanisms are involved in mineralocorticoid-induced salt appetite.

At present, there is no evidence that bears on the possible effects of 5-HT_1 receptor agonists in two-choice tests, between saline and water, respectively. In some cases, at least, it is not possible to extrapolate from single-choice acceptance tests to predict effects of drugs in preference or aversion tests. For example, while benzodiazepines stimulate hypertonic saline drinking in acceptance tests (2,5,10,12,23) they do not stimulate hypertonic saline drinking in a two-choice test against water (4). Hence, we carried out a series of experiments in which we investigated the effects of a range of 5-HT_1 receptor agonists in two-choice tests, between water and saline, respectively. The drugs tested were: first, the selective 5-HT_{1A} agonists 8-OH-DPAT, gepirone, and ipsapirone; second, the putative 5-$HT_{1B/1C}$ agonists, 1-3-(chlorophenyl)piperazine (mCPP) and 1-(3-(trifluoromethyl)phenyl)piperazine (TFMPP) (17,18). Animals were run in two versions of the

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TABLE 1

CONSUMPTION OF 0.9% SALINE AND WATER (ml) IN A TWO-CHOICE PREFERENCE TEST FOLLOWING ADMINISTRATION OF SELECTIVE 5-HT_{1A} RECEPTOR AGONISTS IPSAPIRONE, GEPIRONE, AND 8-0H-DPAT

	0	0.1	0.3	1.0	3.0 (mg/kg)*
	0	30	100		(μg/kg)+
Ipsapirone (n = 10)*					
Water intake	8.1 ± 1.6	10.5 ± 1.2	8.0 ± 1.6	7.8 ± 1.1	7.9 ± 1.1
Saline intake	24.4 ± 1.8	24.5 ± 1.6	23.2 ± 1.6	27.6 ± 1.3	27.1 ± 2.2
Gepirone (n = 9)*					
Water intake	13.9 ± 1.4	15.1 ± 1.6	17.1 ± 2.0	12.7 ± 1.9	11.5 ± 1.8
Saline intake	20.8 ± 3.5	21.6 ± 1.9	18.9 ± 3.0	24.1 ± 3.0	23.3 ± 3.2
8-OH-DPAT (n = 9)+					
Water intake	10.0 ± 1.0	9.6 ± 0.8	9.8 ± 0.8		
Saline intake	24.0 ± 2.0	23.1 ± 1.4	27.5 ± 2.1		

Results are shown as mean ± S.E.M. intake in a 30 min period.
*+ Doses for ipsapirone and gepirone are expressed in mg/kg; those for 8-OH-DPAT are expressed in μg/kg.

tonic saline, relate directly to the results of the acceptance tests: In both paradigms, there was a selective increase in the ingestion of hypertonic saline. However, it should be noted that higher doses were required to affect hypertonic saline consumption in the two-choice tests. This may be due, in part at least, to the large difference in the control levels of total fluid intake for the two test paradigms. In the hypertonic saline acceptance test, intake levels were 5–7 ml in a 30-min test (8). In the present two-choice test, fluid intake under control conditions exceeded 25 ml. At smaller doses, 5-HT_{1A} receptor agonists may be less effective in increasing hypertonic saline intake against a high background level of fluid intake.

mCPP and TFMPP, both described as 5-$HT_{1B/1C}$ receptor agonists (17,18), reduced hypertonic saline drinking in the two-choice tests. There was clear evidence for selectivity in their effects because mCPP (0.3 and 1.0 mg/kg) and TFMPP (0.3 mg/kg) decreased saline drinking without affecting concurrent water consumption. At 3.0 mg/kg, neither drug acted selectively and both suppressed both saline and water drinking markedly. In single-choice, acceptance tests, we have previously shown that mCPP (0.3–3 mg/kg) reduced hypertonic saline drinking while leaving water consumption relatively unaffected (19). TFMPP (0.3–3.0 mg/kg) was less selective, however, and reduced both saline and water drinking. Together, these data imply that mCPP and TFMPP can enhance the relative aversion of hypertonic saline drinking, although as doses become larger the effects of these drugs becomes nonspecific and water consumption is affected too. The results for the 5-HT_{1A} agonists and 5-$HT_{1B/1C}$ agonists can be reconciled if it is assumed that the 5-HT_{1A} agonists act selectively at somatodendritic autoreceptors to inhibit central serotonergic activity (16,20,21,25), whereas mCPP and TFMPP act at postsynaptic 5-HT receptors to enhance serotonergic effects.

Both mCPP and TFMPP reduced consumption of the preferred 0.9% saline at doses that did not affect concurrent water consumption (Figs. 6 and 7). This is the first evidence that agonist activity at 5-$HT_{1B/1C}$ receptors may be sufficient to block salt taste preference in rehydrating rats. Nevertheless, they may be acting in some way to reduce saline drinking more generally, at doses that leave water drinking spared, because both drugs also reduced hypertonic saline drinking

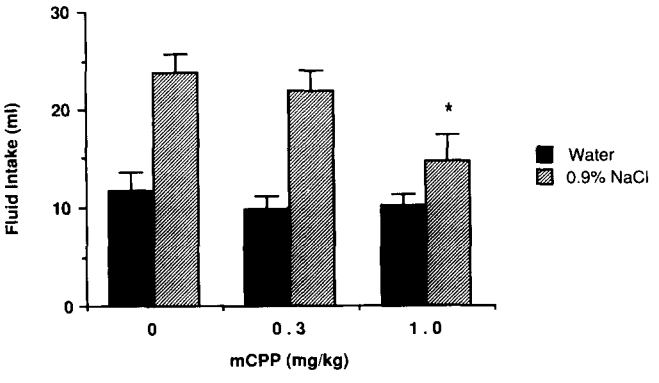

FIG. 6. 1-3-(Chlorophenyl)piperazine (mCPP) (1.0 mg/kg) significantly reduced the consumption of a preferred 0.9% NaCl solution without changing concurrent water ingestion. Other details as described in Fig. 1 legend.

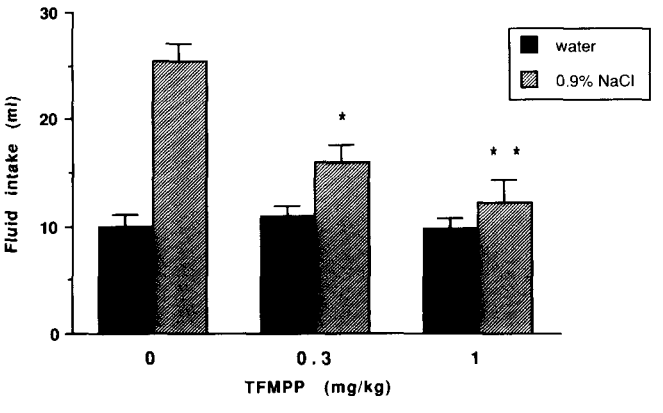

FIG. 7. 1-(3-(Trifluoromethyl)phenyl)piperazine (TFMPP) (0.3 and 1.0 mg/kg) significantly reduced the consumption of a preferred 0.9% NaCl solution without affecting the intake of water. Other details as described in Fig. 1 legend.

(Figs. 4 and 5). It is evident that the effects of these drugs cannot be equivalent to lowering the perceived salt concentration because such an action might be expected to raise the consumption of 1.8% NaCl solution, not reduce it. On the other hand, the effects of these drugs could be to increase the perceived salt concentration so that 0.9% saline becomes less preferred and 1.8% NaCl becomes more unacceptable. Further study should establish if this is indeed the case. According to this analysis, increased serotonergic activity serves to shift the NaCl concentration–intake function to the right, and this could be consistent with the finding that 5-HT$_{1C/2}$ receptor antagonists block drinking responses to induced sodium appetite (12). 5-HT$_{1C/2}$ receptor agonists may act to stimulate drinking responses to induced sodium appetite.

5-HT$_{1A}$ agonists did not significantly increase 0.9% saline drinking in the two-choice test. This, again, stands in contrast to effects of BZR agonists that can strongly enhance the preference for 0.9% saline (4). The increases in hypertonic saline drinking produced by 5-HT$_{1A}$ agonists [present study; (5,8)] do not, therefore, generalise to isotonic saline consumption. The benzodiazepine result suggests that the explanation for the failure of 5-HT$_{1A}$ agonists to increase isotonic saline drinking is not a simple ceiling effect. An alternative view, in line with the argument developed above, is that 5-HT$_{1A}$ agonists inhibit serotonergic activity, causing a shift to the left in the NaCl concentration–intake function. This effect would lead to an increase in hypertonic saline drinking but would not lead to an increase in isotonic saline drinking if this were at or near the optimum concentration for consumption.

In summary, several 5-HT$_{1A}$ receptor agonists and two 5-HT$_{1B/1C}$ receptor agonists, mCPP and TFMPP, were tested in two-choice tests between, on the one hand, 1.8% saline and water and, on the other, 0.9% saline and water. The 5-HT$_{1A}$ receptor agonists increased hypertonic NaCl ingestion without affecting water consumption but did not increase isotonic saline drinking. In contrast, mCPP and TFMPP reduced both hypertonic and isotonic saline consumption selectively, although in both cases a high dose caused nonspecific depression of drinking. These data first establish that the distinctions between 5-HT receptor subtypes are important in determining effects of 5-HT agonists on saline drinking in rats. Second, they are consistent with the pharmacological notion that 5-HT$_{1A}$ agonists may act selectively at somatodendritic autoreceptors to inhibit serotonergic neuronal activity, whereas mCPP and TFMPP may act postsynaptically to enhance serotonergically mediated effects. Behaviourally, the results can be interpreted in terms of changes in the perceived salt concentration brought about by drugs' actions at 5-HT receptors. In more general terms, these data add to existing evidence that implicates serotonergic activity in the control of salt ingestion.

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