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Low Responsiveness to Agents Evoking 5-HT$_2$ Receptor-Mediated Behaviors in Sardinian Alcohol-Preferring Rats

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CICCOCIOPPO, R., I. PANOCKA, E. STEFANINI, G. L. GESSA AND M. MASSI. *Low responsiveness to agents evoking 5-HT$_2$ receptor-mediated behaviors in Sardinian alcohol-preferring rats.* PHARMACOL BIOCHEM BEHAV 51(1) 21-27, 1995.—The selective NK3 tachykinin agonist senktide evokes in rodents 5-HT mediated behaviors, including 5-HT$_2$ receptor-mediated wet dog shakes (WDS) and head shakes (HS). It was observed previously that genetically selected Sardinian alcohol-preferring (sP) rats show a small number of WDS and HS following intracerebroventricular (ICV) injection of senktide. The present study was aimed at confirming these observations and at providing information on the reasons accounting for the anomalous response of sP rats. Senktide (500–2000 ng/rat, ICV) produced a much lower number of WDS and HS in sP rats than in nonselected Wistar (nsW) rats. Both behaviors were suppressed by the 5-HT$_2$ antagonist ritanserin (1 mg/kg, subcutaneously), confirming that 5-HT$_2$ receptors mediate the response. HS induced by the ICV injection of 5-HT agonists endowed with marked activity at 5-HT$_2$ receptors, such as quipazine (1500–6000 ng/rat) or DOI (500–3500 ng/rat), were much less pronounced in sP rats than in nsW rats. Moreover, WDS following peripheral injection of 5-hydroxytryptophan, 25–100 mg/kg, and carbidopa, 12.5 mg/kg, were less intense in sP and in ethanol-naive sP rats than in nsW and in Sardinian alcohol-nonpreferring rats. These findings suggest that sP rats have an inherent different regulation of central 5-HT$_2$ mechanisms.

Senktide Quipazine DOI 5-HTP Wet dog shakes Head shakes Sardinian alcohol-preferring rats

SENKTIDE (Suc-[Asp^6,MePhe^8]substance P 6–11) is a synthetic tachykinin selective for the NK3 receptor subtype (30). It has been shown to evoke serotonin-mediated behaviors, including head shakes (HS) and wet dog shakes (WDS) that are mediated by the 5-HT$_2$ receptor subtype (5–7,27), both in mice and in rats (23–25). These behavioral alterations are observed both following central and peripheral senktide administration and appear to be due to endogenous serotonin release.

However, in recent experiments in which the effect on ethanol intake of intracerebroventricular (ICV) injections of senktide was investigated, it was observed that the occurrence of WDS and HS in Sardinian alcohol-preferring (sP) rats was very low, at doses known to produce marked responses in genetically nonselected Wistar (nsW) rats.

The present study was aimed a) at documenting the differences in the behavioral response to ICV senktide administration between sP rats and nsW rats, and b) at evaluating whether the differences might be accounted for by different regulation either of the tachykinergic or of the serotonergic mechanisms. A large body of evidence indicates that serotonin plays a major role in the control of alcohol intake (3,9,10, 15,16,26). On the other hand, recent articles have reported that tachykinin peptides can affect alcohol intake in sP rats (4,21). Therefore, interest in the results of the present study was stimulated by the possibility of providing information on

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the regulation of these neurochemical systems in the sP line of rats, genetically selected for alcohol preference.

Moreover, experiments were also carried out in sP rats never exposed to ethanol, which were referred to as naive sP (sPn) rats, and in Sardinian alcohol-nonpreferring (sNP) rats, genetically selected to avoid ethanol, in an attempt to understand whether the differences observed might be due either to genetic selection or to exposure to ethanol.

METHOD

Animals

Male sP rats genetically selected for 20–23 generations were employed. They were bred in the Institute of Pharmacology of the University of Camerino from animals of the 13th generation provided by the Department of Neurosciences of the University of Cagliari. At the beginning of the experiments, the weight of sP rats was 300–350 g. At 60 days of age, one group of sP rats was selected for 8% ethanol preference, then they were allowed free access both to water and to 8% ethanol for all the experimental period; the animals had a stable alcohol preference ranging between 85 and 95%, with a daily alcohol intake ranging between 4.82 and 7.55 g/kg b.wt. Experiments began when they were about 90 days old.

Also, a group of sPn rats, which were never allowed access to alcohol solution before experiments, were employed. After completion of the experiments, they were offered free choice between 8% ethanol and water to check their alcohol preference. Only data from animals showing ethanol preference above 80% were employed.

Finally, also sNP rats were employed, which were selected to avoid ethanol; their body weight was 350–400 g at the beginning of experiments. After a 3-day exposure to both water and 8% ethanol for selection, they were offered just water to drink. Experiments started 4 weeks after selection.

Male Wistar rats, nongenetically selected for alcohol preference, weighing between 300 and 350 g, were purchased from Charles River (Calco Co., Italy). They were offered access to water, but not to the ethanol solution.

Animals were kept in individual cages on a 12 L : 12 D cycle, with food pellets (Diet n. 4RF18, Mucedola, Settimo Milanese, Italy) freely available. Before starting each experiment, animals were made used to the perspex box in which behavioral observation were made.

Surgery

Rats were anesthetized with ketamine (50 mg/kg, intramuscularly) and implanted stereotaxically with a stainless steel cannula aimed at 1 mm above the lateral ventricle. The coordinates were: 0.9 mm posterior and 2 mm lateral to bregma, 2 mm ventral from the surface of the skull. The cannulae were attached to the skull with jewellery screws and dental cement. One week of recovery was allowed before testing began. During this period, animals were handled and mock injected to adapt them to the testing procedure.

Drugs

The following substances were used: senktide (purchased from Peninsula Europe, Merseyside, UK); quipazine, (+)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane hydrochloride (DOI), D,L-5-hydroxytryptophan (5-HTP), and carbidopa (purchased from RBI, Natick, MA); ritanserin (gift of Janssen Pharmaceutica, Beerse, Belgium).

Intracranial Injections

Senktide, quipazine, and DOI were dissolved in sterile isotonic saline and were injected into the lateral ventricle in a volume of 1 μl by means of a stainless steel injector temporarily inserted into the guide cannula and protruding into the ventricle.

Peripheral Injections

Ritanserin was dissolved in a vehicle containing 20% propylene glycol and a few drops of lactic acid. The pH of the solution was adjusted to 5 by adding 2 N NaOH. The drug was injected subcutaneously (SC) in a volume of 1 ml/kg of body weight.

5-HTP and carbidopa were dissolved separately in distilled water containing a few drops of 5 N HCl. The pH of the solutions was adjusted to 6 by adding 2 N NaOH. Carbidopa was injected intraperitoneally (IP), while 5-HTP was given SC. Each drug was administered in a volume of 4 ml/kg of body weight.

Experimental Procedure

Experiment 1. Wet dog shakes and head shakes after ICV senktide injections. Three groups of sP rats (each of seven animals) and three groups of nsW rats (of eight, seven, and eight animals, respectively) were given an ICV injection of senktide, either 500 or 1000 or 2000 ng/rat. Another two groups (21 sP rats and 22 nsW rats), receiving ICV injections of isotonic saline, served as controls. Immediately after ICV injection of senktide or of isotonic saline, each animal was placed in a perspex box and the number of characteristic shakes of neck, head, and trunk (WDS) and shakes of head alone (HS) was recorded for 10 min. Experiments were started at the beginning of the dark phase of the light:dark cycle, and were carried out between 1800 and 2000 h. During experiments animals were not allowed access to food and fluids.

The experiments were carried out according to a randomized design, and animals received either isotonic saline or one dose of senktide.

In this as well as in the following experiments, the observer was completely unaware of the pharmacological treatment received by the animal under observation.

Experiment 2. Effect of ritanserin pretreatment on wet dog shakes and head shakes produced by ICV injection of senktide. Ritanserin (1 mg/kg) was injected SC to sP rats (12 rats) and to nsW rats (15 animals). Sixty minutes after ritanserin pretreatment six sP and seven nsW rats received an ICV injection of senktide, while the others received an ICV injection of isotonic saline.

Another two groups of rats (a group of 12 sP rats and a group of 15 nsW rats) were pretreated with a SC injection of ritanserin vehicle. Sixty minutes later, six sP and eight nsW rats received a central senktide injection, while the others received an ICV injection of isotonic saline.

In nsW rats, 500 ng/rat of senktide was used, as this dose evoked marked WDS and HS responses in these animals in Experiment 1. Since in sP rats ICV injections of senktide were much less effective, these animals were treated with a higher dose of the drug (2000 ng/rat).

Animals employed in this experiments were taken from those employed in the previous experiment. They were tested for Experiment 2 10 days after the first treatment.

Immediately after ICV treatment, each rat was placed in a perspex box and the number of WDS and HS was recorded for 10 min.

Experiment 3. Head shakes following ICV injections of quipazine or DOI. Three groups of sP animals (eight, nine, and nine) were treated with 6000, 3000, and 1500 ng/rat of quipazine, respectively. Another group of nine sP rats received ICV injections of isotonic saline.

Three groups of nsW animals (eight, seven, and seven) were treated with 6000, 3000, and 1500 ng/rat of quipazine, respectively. Another group of seven nsW rats received ICV injections of isotonic saline.

DOI was administered ICV at the doses of 3500, 1500, and 500 ng/rat to seven, nine, and nine sP rats, and to eight, seven, and seven nsW rats, respectively. Two groups of seven sP and nsW rats (controls) received ICV injections of isotonic saline.

Immediately after each ICV treatment animals were placed in a perspex box and the number of HS was recorded for 10 min. The experiment was carried out according to a randomized block design and animals employed for this experiment had never been tested before.

Experiment 4. Wet dog shakes following treatment with 5-HTP and carbidopa. 5-HTP was administered SC at the doses of 100, 50, and 25 mg/kg to: a) 6, 9, and 10 sP rats, b) 8, 6, and 8 sPn rats, c) 6, 6, and 7 sNP rats and d) 5, 10, and 10 nsW rats, respectively. Thirty min before they were IP injected with the peripherally active decarboxylase inhibitor carbidopa (12.5 mg/kg).

Seven sP, 7 sPn, 7 sNP, and 10 nsW rats, receiving IP and SC injections of carbidopa and 5-HTP vehicles, served as controls.

The number of WDS in rats was recorded for 10 min, beginning 2 h after 5-HTP injection, because in preliminary experiments (in which the occurrence of WDS was registered for 6 h after 5-HTP injection) it was observed that the maximum response occurred at 2 h in all the rat lines used. This is in keeping with the findings of Bedard and Pycock (2) who reported the maximum WDS response at 2 h after injection of 5-HTP in rats. The experiment was carried out according to a randomized block design, and animals employed for this experiment had never been tested before.

Statistical Analysis

Data are presented as means ± SEM. Statistical analysis was performed by means of the analysis of variance (multifactor randomized design for between rat lines comparisons and single factor randomized design for within lines comparisons). Post hoc comparisons were performed by means of the Newman-Keul's test.

RESULTS

Experiment 1. Wet Dog Shakes and Head Shakes After ICV Senktide Injections

As shown in Fig. 1, the administration of 500, 1000, or 2000 ng/rat of senktide produced both in nsW rats and in sP rats a dose-related increase in the number of WDS and HS, $F(3, 41) = 62.96, p < 0.01$ and $F(3, 41) = 18.68, p < 0.01$, respectively, in nsW rats; and $F(3, 38) = 16.08, p < 0.01$ and $F(3, 38) = 8.20, p < 0.01$, respectively, in sP rats. Pair-wise comparisons showed that the number of HS and of WDS in nsW rats was significantly increased by senktide even at the lowest dose tested, 500 ng/rat. In sP rats, the effect of senktide became significant at the dose of 1000 ng/rat.

The analysis of variance revealed a statistically significant difference between rat lines in the response to senktide both for HS, $F(1, 79) = 38.92, p < 0.001$, and for WDS, $F(1, 79) = 115.52, p < 0.001$, together with significant line-treatment interactions for both behavioral responses. Pair-wise comparisons showed a significant line difference for WDS at all the doses tested of senktide. The difference in HS response was statistically significant at 500 and 1000 ng/rat.

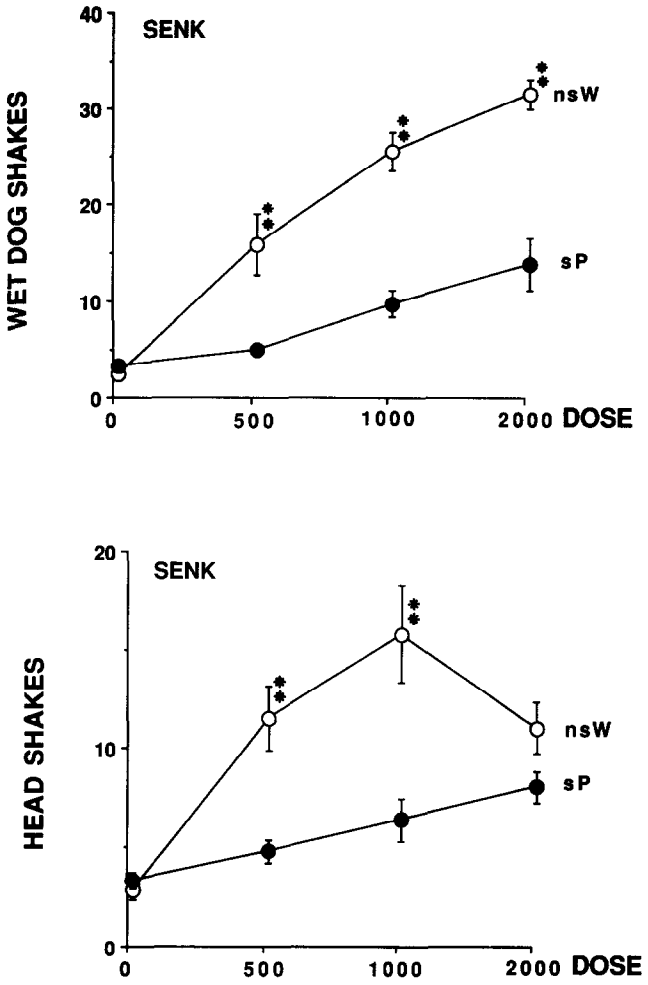

FIG. 1. Wet dog shakes and head shakes in Sardinian alcohol-preferring (sP) and in nonselected Wistar rats (nsW) following ICV treatment with various doses (ng/rat) of senktide (S) or of isotonic saline (0). Data are means ± SEM of the number of observations in 10 min following senktide injection. Statistical difference between sP and nsW rats: $^{**}p < 0.01$; where not indicated, the difference was not statistically significant.

Experiment 2. Effect of Ritanserin Pretreatment on Wet Dog Shakes and Head Shakes Produced by ICV Injection of Senktide

The effect of ritanserin on WDS and HS in nsW rats and in sP rats is reported in Fig. 2. The ICV injection of senktide (500 ng/rat in nsW rats and 2000 ng/rat in sP rats) increased, as expected, WDS and HS. Ritanserin significantly suppressed WDS and HS evoked both in nsW rats, $F(3, 26) = 22.07, p < 0.01$ and $F(3, 26) = 15.14, p < 0.01$, respectively, and in

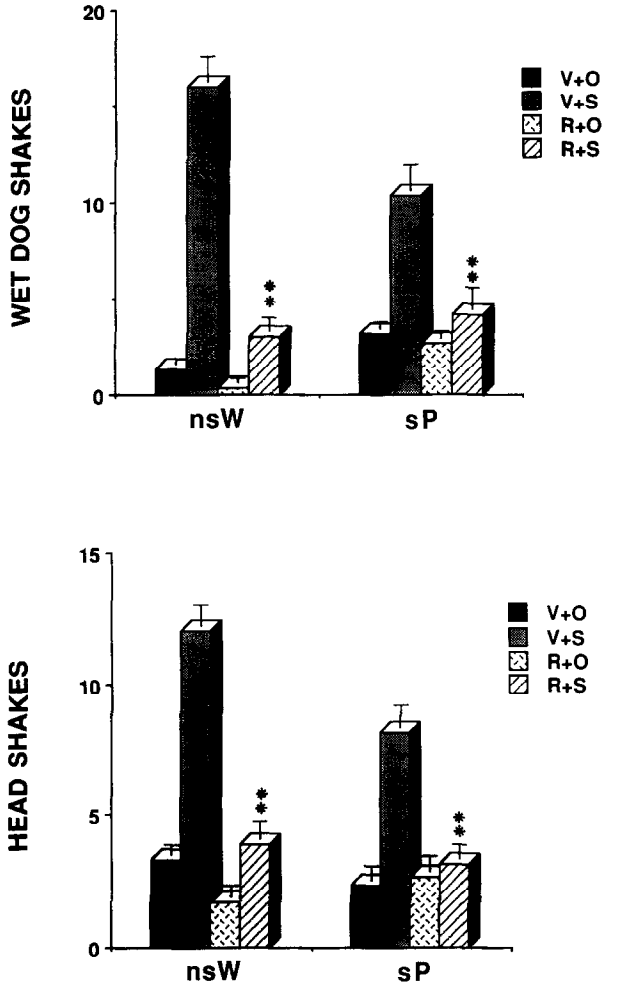

FIG. 2. Wet dog shakes and head shakes in nonselected Wistar rats (nsW) and in Sardinian alcohol-preferring rats (sP) pretreated with ritanserin (R) or with its vehicle (V), and then treated with senktide (S) or with isotonic saline (0). Data are means ± SEM of the number of observations in 10 min following the ICV injection. Statistical difference between V+S and R+S: $^{**}p < 0.01$.

sP rats, $F(3, 20) = 15.11$, $p < 0.01$ and $F(3, 20) = 19.49$, $p < 0.01$, respectively. Post hoc comparisons showed that after ritanserin pretreatment the number of WDS and HS following senktide treatment was not significantly different from that of controls, which did not receive senktide, both in nsW and in sP rats.

Experiment 3. Head Shakes Following ICV Injections of Quipazine or DOI

As shown in Fig. 3, the administration of 1500, 3000, or 6000 ng/rat of quipazine produced a significant dose-related increase in the number of HS, $F(3, 25) = 5.84$. $p < 0.01$, in nsW rats, while the number of HS in sP rats was not significantly affected.

The analysis of variance revealed a statistically significant difference between rat lines in this response to quipazine, $F(1, 56) = 7.18$, $p < 0.01$.

On the other hand, WDS were not significantly modified

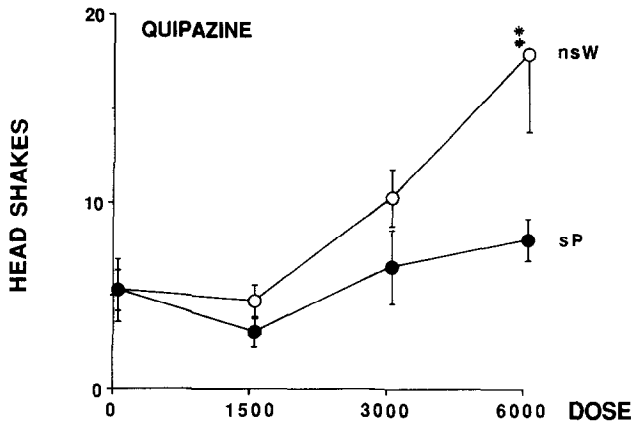

FIG. 3. Head shakes in Sardinian alcohol-preferring rats (sP) and in nonselected Wistar rats (nsW) following ICV treatment with 1500, 3000, and 6000 ng/rat of quipazine or with isotonic saline (0). Data are means ± SEM of the number of observations in 10 min following the ICV injection. Statistical difference between rat lines: $^{**}p < 0.01$; where not indicated, the difference was not statistically significant.

by quipazine treatment either in nsW and in sP rats (data not shown).

As shown in Fig. 4, the administration of 500, 1500, or 3500 ng/rat of DOI produced a significant dose-related increase in the number of HS, $F(3, 25) = 13.62$, $p < 0.001$, in nsW rats, while the number of HS in sP rats was not significantly affected. The analysis of variance revealed a statistically significant difference between rat lines in this response to DOI, $F(1, 53) = 17.47$, $p < 0.001$.

On the other hand, WDS were not significantly modified by DOI treatment either in nsW and in sP rats (data not shown).

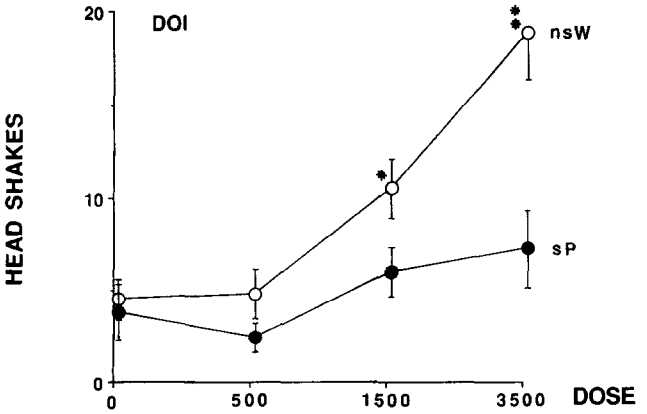

FIG. 4. Head shakes in Sardinian alcohol-preferring rats (sP) and in nonselected Wistar rats (nsW) following ICV treatment with 500, 1500, and 3500 ng/rat of DOI or with isotonic saline (0). Data are means ± SEM of the number of observations in 10 min following DOI injection. Statistical difference between rat lines: $^{*}p < 0.05$; $^{**}p < 0.01$; where not indicated, difference was not statistically significant.

Experiment 4. Wet Dog Shakes Following Treatment With 5-HTP and Carbidopa

As shown in Fig. 5, the administration of 25, 50, or 100 mg/kg of 5-HTP produced a dose-related increase in the number of WDS in the four lines of rats employed; $F(3, 28) = 7.16, p < 0.01$, in sP rats, $F(3, 25) = 4.71, p < 0.01$, in sPn rats, $F(3, 22) = 29.24, p < 0.01$, in sNP rats and $F(3, 31) = 7.29, p < 0.01$, in nsW rats.

The overall analysis of variance revealed a highly significant difference between the four rat lines, $F(3, 106) = 12.41$, $p < 0.01$. Comparison between lines showed no significant difference between sP and sPn rats, as well as no significant difference between sNP and nsW rats.

On the other hand, the WDS response to 5-HTP in sP rats was significantly lower than in sNP and in nsW rats, $F(1, 50) = 20.01, p < 0.001$ and $F(1, 59) = 17.72, p < 0.01$, respectively.

As shown in Fig. 5, the administration of 25, 50, or 100 mg/kg of 5-HTP produced a dose-related increase in the number of HS in sP rats, $F(3, 28) = 3.76, p < 0.05$, in sNP rats, $F(3, 22) = 8.40, p < 0.01$, and in nsW rats, $F(3, 31) = 6.44$, $p < 0.01$, but not in sPn rats.

The overall analysis of variance revealed a highly significant difference between the four rat lines, $F(3, 106) = 8.49$, $p < 0.01$. Comparison between lines showed no significant difference between sP and sPn rats, $F(1, 53) = 0.25$, $p > 0.05$, as well as no significant difference between sNP and nsW rats.

On the other hand, the HS response to 5-HTP in sP rats was significantly lower than in sNP and in nsW rats, $F(1, 50) = 14.36, p < 0.001$ and $F(1, 59) = 8.62, p < 0.01$, respectively.

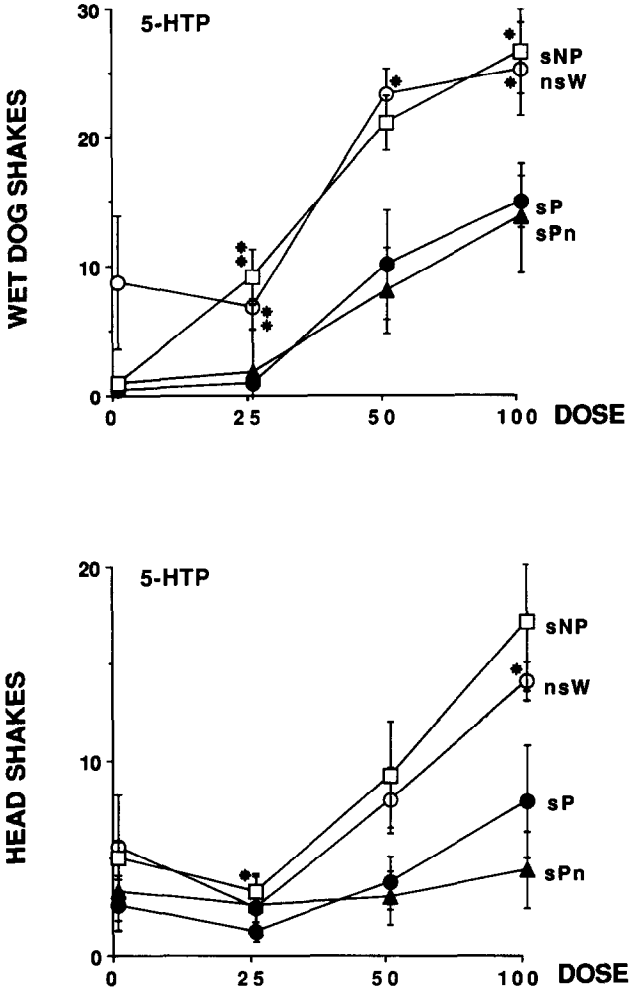

FIG. 5. Wet dog shakes and head shakes in Sardinian alcohol-preferring rats (sP), in ethanol naive sP rats (sPn), in Sardinian alcohol-nonpreferring rats (sNP) and in nonselected Wistar rats (nsW) following SC treatment with 25, 50, or 100 mg/kg of 5-HTP (plus carbidopa, 12.5 mg/kg) or with vehicle (0). Data are means ± SEM of the number of observations in 10 min, beginning at 2 h following the SC injection of 5-HTP. Statistical difference between animal lines: $*p < 0.05$, $**p < 0.01$; where not indicated, difference was not statistically significant.

DISCUSSION

The results of the present study clearly show that the number of WDS and of HS following ICV administration of the tachykinin senktide is much lower in sP rats than in nsW rats.

It has been reported that NK3 tachykinin receptor agonists, such as neurokinin B and senktide, can stimulate 5-HT release in the central nervous system of rats and mice (23–25), and/or can enhance the behavioral response to endogenous 5-HT by increasing the binding affinity of 5-HT for its receptors (1). On the basis of these findings, it might be speculated that the lower response to senktide in terms of WDS and HS in sP rats might be due: either a) to a different regulation of the tachykinergic mechanisms in sP rats, or b) to a lower 5-HT content in the central nervous system of sP rats, resulting in a lower release following senktide administration, or c) to altered regulation of 5-HT receptor mechanisms.

To throw some light on the problem, we thought it interesting to evaluate the effect of direct serotonergic agonists endowed with pronounced activity at 5-HT_2 receptors, such as the rather selective 5-HT_2 agonist DOI and the nonselective serotonergic agonist quipazine. The use of these agonists was related to the fact that a large body of evidence indicates that 5-HT_2 receptors mediate both WDS and HS induced by serotonergic agents (5–7,27); moreover, also the results of Experiment 2, showing that the 5-HT_2 antagonist ritanserin almost completely suppresses WDS and HS induced by senktide, support the idea that the 5-HT_2 receptor subtype mediates these responses. Finally, also 5-HTP was employed; the drug acts by generating serotonin in the central nervous system and, therefore, lacks any selectivity for 5-HT receptor subtypes; however, it was considered interesting to use this drug in relation to its ability to evoke WDS (2), thus complementing experiments with DOI and quipazine, which predominantly evoke HS.

The results of Experiments 3 and 4 clearly show that also in response to direct serotonergic agents the 5-HT_2 receptor-mediated behaviors are significantly less intense in sP rats than in nsW rats. These findings strongly point to strain differences in the 5-HT_2 mechanisms that mediate the response. Moreover, the finding that sPn rats do not differ from sP rats in WDS and HS response to 5-HTP strongly suggests that the low reactivity of the 5-HT_2 mechanisms in sP rats results from genetic selection, rather that from recent exposure to ethanol.

Interestingly, after submission of this manuscript, a marked reduction in the number of 5-HT_2 receptors has been

reported by McBride and colleagues (8) in several brain regions of alcohol-preferring rats of the P line. On the basis of these results, it might be hypothesized that the low reactivity of 5-HT_2 mechansims in sP rats might be due to 5-HT_2 receptor downregulation.

However, just on the basis of the present study, it cannot be ruled out that, at least in part, the altered response to senktide might be due to differences in tachykinergic mechanisms or to a lower release of 5-HT in sP rats. Indeed, several studies have reported that central 5-HT levels are reduced in rats and mice genetically selected for ethanol preference (14,28,29); but this information is not available yet for the sP line of rats.

In previous studies, it has been reported that 5-HT_2 antagonists, such as ritanserin and risperidone, markedly reduce ethanol intake in nsW rats (11,12,17,18,20) with developed preference for 3% ethanol and reduce the craving for alcohol in chronic alcoholics (13). The effect in nsW rats is long lasting, well reproducible, and behaviorally selective. However, the same 5-HT_2 antagonists do not reduce ethanol preference (both to 3% and to 8% ethanol solution) in sP rats (19). The results of the present study suggest that the ineffectiveness of these drugs in reducing alcohol intake in sP rats might be related to altered regulation of the 5-HT_2 mechanisms in the central nervous systems of this line of rats.

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