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# Comparison of relative potencies of i.v. and i.c.v. administered 8-OH-DPAT gives evidence of different sites of action for hypothermia, lower lip retraction and tail flicks

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**Abstract**

8-Hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT)-induced temperature reduction, lower lip retraction and tail flick responses are widely used models of 5-$HT_{1A}$ receptor function. To obtain information about the sites of receptors mediating these effects we measured these responses, parallel over wide dose ranges after intracerebroventricular (i.c.v., 0.6–67 μg/kg) and intravenous (i.v., 3–500 μg/kg) administration. Analysis of the dose–response curves provided evidence for a 9.8-fold ratio of the potency of 8-OH-DPAT following i.c.v. compared to i.v. administration on body temperature reduction ($ED_{50}$ values are 5.1 and 50 μg/kg, after i.c.v. and i.v. administration, respectively) and a 2.9-fold ratio in potency for lower lip retraction ($ED_{50}$ values are 29 and 86 μg/kg, after i.c.v. and i.v. administration, respectively). 8-OH-DPAT was less potent in the induction of tail flicks than of the other responses and had a lower potency after i.c.v. than after i.v. administration ($ED_{50}$ values, the first one extrapolated, are 526 and 246 μg/kg, after i.c.v. and i.v. administration, respectively). In addition, the i.c.v. $ED_{50}$ for temperature reduction was significantly lower than those for lower lip retraction or tail flick responses. The relative potency, that is, the ratio of i.v. and i.c.v. $ED_{50}$, was significantly higher for temperature reduction than for lower lip retraction or tail flick responses ($ED_{50}$ i.v./$ED_{50}$ i.c.v. values are 9.8, 2.9, and 0.47, respectively). These data provide evidence that distinct sites of action are involved in these models. Temperature reduction is mediated mainly by postsynaptic receptors in the close vicinity of the lateral ventricle. Receptors that mediate lower lip retraction are located more distantly in the brain, supporting previous evidence that they are somatodendritic autoreceptors, and receptors in the spinal cord are probably responsible for tail flick responses. 

*Keywords:* Behavior; Body temperature; 5-$HT_{1A}$ receptor; 8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino)tetralin); (Intracerebroventricular administration); Lower lip retraction; 5-HT (5-hydroxytryptamine, serotonin); Tail flick

## 1. Introduction

One of the most extensively studied subtypes of 5-HT receptors are 5-$HT_{1A}$ receptors (Herndon and Glennon, 1993). 5-$HT_{1A}$ receptors in some brain areas (forebrain and midbrain) are located postsynaptically, while those in the raphe nuclei are located presynaptically (Herndon and Glennon, 1993; Hoyer et al., 1994). Activation of 5-$HT_{1A}$ receptors produces a number of behavioral and other pharmacological changes, e.g., the selective agonist, 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT), produces a fall in body temperature, causes motor effects, including several components of the '5-HT behavioral syndrome', changes food intake and endocrine function (Tricklebank, 1985; Aulakh et al., 1988; Bagdy et al., 1989; Wilkinson and Dourish, 1991). Recent studies have shown that, as part of this syndrome, rats exhibit a characteristic change in the musculature of the lower lip which was designated as 'lower lip retraction' (Berendsen et al., 1989; Molewijk et al., 1989). Another effect of 8-OH-DPAT is the induction of spontaneous tail flicks (Millan et al., 1991; Kennedy et al., 1993). 8-OH-DPAT-induced decrease in body temperature, lower lip retraction and tail flick responses are mediated selectively by stimulation of 5-$HT_{1A}$ receptors (Berendsen et al., 1990; Millan et al., 1991; Molewijk et al., 1989; Moore et al., 1993; Thielen and Frazer, 1995). Despite the fact that 8-OH-DPAT-induced temperature reduction, lower lip retraction and tail flick responses have become widely used models of 5-$HT_{1A}$

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receptor function, data about the sites of induction of these responses are still contradictory (Cui et al., 1993; Glaser et al., 1991; Millan et al., 1991, 1993; Berendsen et al., 1994; Wilkinson and Dourish, 1991, for more details see Section 4). To obtain information about the site of 5-$HT_{1A}$ receptors mediating these effects we measured temperature reduction, lower lip retraction and tail flick responses parallel over wide dose ranges after intracerebroventricular (i.c.v.) and intravenous (i.v.) administration of 8-OH-DPAT and analysed the $ED_{50}$ values and equi-effective dose ratios with a powerful statistical method.

## 2. Materials and methods

### 2.1. Animals and preparation

Male Sprague-Dawley (Crl:$CD^{R}$BR, Charles River, Hungary) rats (300–360 g) were used in the studies. The animals were housed singly in polycarbonate cages (Lignifer, Hungary) under standard condition, with standard food (CRLT/AM, Charles River, Hungary), and water freely available. The temperature was 22 ± 1°C and the 12 h light-dark cycle started at 06.00 h.

A polyethylene i.c.v. cannula was implanted under halothane anesthesia, using a Kopf stereotaxic instrument. The following coordinates were used (bregma 0.0): AP 1.3 mm, L 1.8 mm, DV 4.0 mm (Paxinos and Watson, 1986). Challenges were done between 9.00 and 14.00 h after at least one week for recovery.

### 2.2. Experimental protocol and drug administration

All studies were done in gently restrained rats previously exposed at least 3 times to the experimental conditions. Treatment groups consisted of 6–12 animals. Tail flick and body temperature were measured in separate experiments, lower lip retraction was usually measured parallel to both. The animals were placed into horizontal perforated Plexiglas tubes with partial movement allowed. Plexiglas plates with a V-shaped cut were used to close the open end, allowing the tail to hang freely. For body temperature measurements YSI rectal probes were inserted immediately to a depth of 6 cm and remained there for at least 60 min. Injections of vehicle (saline) or 8-OH-DPAT were administered 15 min after the probes were inserted.

(±)-8-Hydroxy-2-(di-*n*-propylamino)tetralin hydrobromide (8-OH-DPAT, Research Biochemicals International, Natick, MA, USA) was dissolved in physiological saline, and 4–6 μl solution was injected intracerebroventricularly slowly and then flushed in with a volume of saline to a total of 8 μl. For the 67 μg/kg i.c.v. dose, the total volume was 10 μl. 8-OH-DPAT was administered into the tail vein intravenously in a volume of 1 ml/kg. Intracerebroventricular injections were also given on the basis of body weight to facilitate comparisons to i.v. administration. Mean body weights were between 325–340 g for all treatment groups, thus a good estimate of the μg/rat value can be obtained if μg/kg values are divided by 3.

### 2.3. Temperature measurements and behavioral observations

Body temperature was recorded continuously for at least 60 min and at higher doses for 90 min. A fall in temperature was observed within 5 min after injections of 8-OH-DPAT which persisted for at least 30 min, except at the highest dose (500 μg/kg i.v.) where a transient elevation and delayed fall in temperature occurred in most animals. In addition, overt behavioral effects were seen transiently (e.g., extreme motor activity, respiratory problems, bleeding from the nose). At this dose the temperature minimum was reached by 60 min after drug administration, thus values at this time point are given in the figure. Changes in body temperature 30 min after 8-OH-DPAT compared to baseline were calculated and used for statistical evaluation at all other doses.

For a more complete observation of lower lip retraction a mirror was placed below each rat. The animals were scored at 5, 10, 15, 20, 25 and 30 min after injection as follows: 0 = lower incisors are not visible (not different from non-treated rats), 0.5 = lower part of incisors partly visible, 1.0 = major part of incisors clearly visible, 1.5 = lower incisors are completely visible. Thus, a total score of 9.0 per rat was the maximum score achievable. The animals were scored by two observers, both of whom were blind to the treatment.

Spontaneous tail flicks were counted for at least a 30-min period beginning 2 min after drug administration. Tail flicks were defined as the elevation of the tail above the mark (45° compared to the vertical position) on a transparent Plexiglas plate in the coronal plane. The numbers of elevation using the 45° limit were more consistent with less individual variation and higher sensitivity compared to those using the body axis (90°) as a limit. The sum of the elevations counted during the 30 min period was used for further analysis.

### 2.4. Statistical methods

Changes in body temperature compared to baseline (immediately before drug administration), total scores for lower lip retraction and number of tail flicks are given in means ± S.E. for the groups. Comparison of the dose–response curves and simultaneous fitting of i.c.v. and i.v. curves based on the four-parameter logistic equation was done by ALLFIT (version 2.7; for reference, see De Lean et al., 1978). Statistical analysis of temperature data was performed with Super Anova (Brain Powers, CA, USA). One-way analysis of variance followed by the Tukey-Kramer post-hoc test was run for these data. For lower lip retraction and tail flick responses, statistical analysis was

performed with StatViewSE + Graph (Abacus Concepts, Berkeley, CA, USA). The Kruskal-Wallis test followed by the Mann-Whitney rank sum test, including Bonferroni adjustment, was run for behavioral data.

## 3. Results

8-OH-DPAT caused dose-dependent hypothermia, lower lip retraction and tail flick responses (Fig. 1). The i.c.v. and i.v. $ED_{50}$ values and relative potencies ($ED_{50}$ i.v./$ED_{50}$ i.c.v. values) and their statistical comparisons are given in Table 1.

All dose–response curves showed a good fit for sigmoid curves (all $R^2$ values were $> 0.73$). Analysis of the dose–response curves provided evidence that 8-OH-DPAT

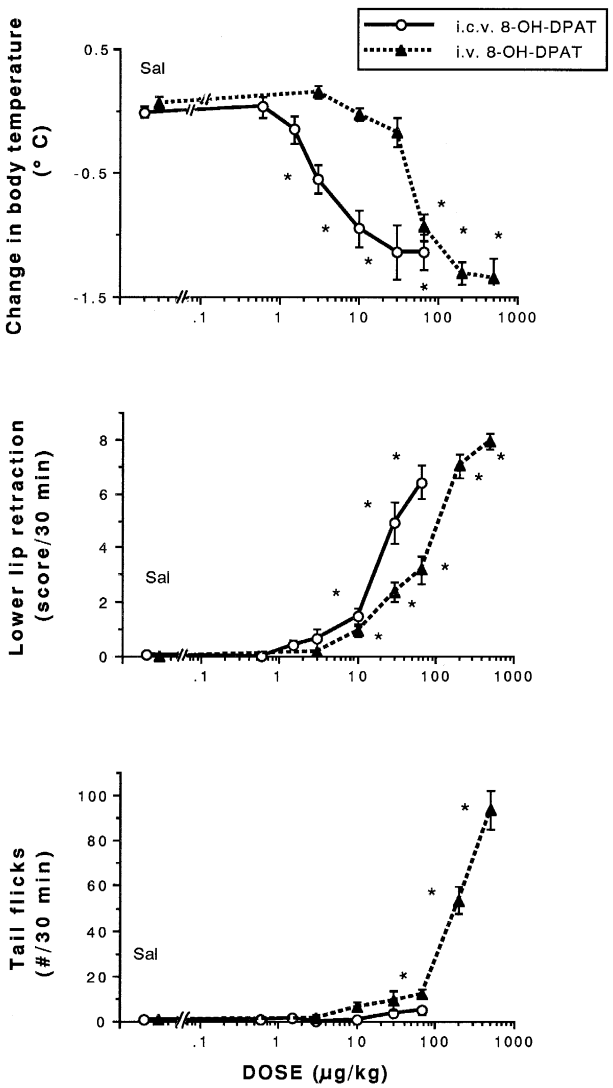


Fig. 1. Effects of i.c.v. (0.6–67 µg/kg) or i.v. (3–500 µg/kg) administered 8-OH-DPAT on body temperature, lower lip retraction and spontaneous tail flicks. * Significant drug effect compared to saline ($P < 0.05$). $ED_{50}$ values and relative potencies ($ED_{50}$ i.v./$ED_{50}$ i.c.v.) and their statistical comparisons are given in Table 1.

Table 1
$ED_{50}$ values and relative potencies (i.v. $ED_{50}$ per i.c.v. $ED_{50}$) of intracerebroventricularly (i.c.v.) or intravenously (i.v.) administered 8-OH-DPAT to induce hypothermia, lower lip retraction and tail flick responses and their statistical comparisons

| | i.c.v. $ED_{50}$ (µg/kg) | i.v. $ED_{50}$ (µg/kg) | Relative potency (i.v. $ED_{50}$ / i.c.v. $ED_{50}$) |
|---|---|---|---|
| Hypothermia | $5.1 \pm 0.9$ [a,b] | $49.9 \pm 4.2$ | $9.78 \pm 1.68$ |
| Lower lip retraction | $29.4 \pm 2.6$ [a,c] | $86.0 \pm 7.6$ | $2.92 \pm 0.36$ [e] |
| Tail flicks | $526 \pm 241$ [a,d] | $246 \pm 43$ | $0.47 \pm 0.17$ [e] |

Values are given as means ± S.E.M. [a] Significantly different from i.v. $ED_{50}$. [b] $F(9) = 18.13$, $P = 0.002$. [c] $F(9) = 10.22$, $P = 0.009$. [d] Extrapolated value, see Section 4, $F(10) = 8.20$, $P = 0.019$. [e] Significantly different from relative potency for hypothermia, $P < 0.05$.

was 9.8-times more potent after i.c.v. than after i.v. administration for induction of temperature reduction and 2.9-times more potent for induction of lower lip retraction. For induction of tail flicks, 8-OH-DPAT was less effective after i.c.v. than after i.v. administration, thus a complete dose–response curve could not be obtained within the i.c.v. dose range studied. In addition, the i.c.v. $ED_{50}$ was significantly lower for temperature reduction than for lower lip retraction (see Table 1).

Statistical analysis of the data using ALLFIT revealed that responses at zero dose (effect of saline) for all three responses and the maximal responses (maximal efficacies) for temperature reduction and lower lip retraction were not significantly different after i.v. and i.c.v. administration. The comparison of slopes of i.c.v. versus i.v. dose–response curves yielded a strong trend to a difference only in the case of hypothermia ($F(9) = 4.70$, $P = 0.051$).

## 4. Discussion

The conclusions of studies about the site(s) of action for the pharmacological properties of 8-OH-DPAT now studied and others are often confusing (Wilkinson and Dourish, 1991). Compensatory receptor changes, or more than one site of action, for example, complex interactions between pre- and postsynaptic effects, and the relatively small number of studies using direct central administration of selective 5-$HT_{1A}$ receptor agonists and even fewer comparing their local and systemic effects might account for the confusion (for more details see below).

The methods we used in this study allowed us to make three different comparisons. First, comparison of i.c.v. and i.v. drug potencies for the same action; second, comparison of the potencies of 8-OH-DPAT for the separate pharmacological actions; third, comparison of the relative potencies ($ED_{50}$ i.v./$ED_{50}$ i.c.v. values) between the three parameters.

To eliminate factors as much as possible that could impair the comparisons (e.g., drug permeation and absorp-

tion into the blood) we have used i.v. and i.c.v. administration. Indeed, the start and duration of the actions were similar after the two routes of administration. All these pharmacological actions started within 2–3 min and were evident for at least 20 min.

The four-parameter logistic model has been widely used as the basis for mathematical analysis of concentration-response curves for bioassay, radioimmunoassay and related techniques (De Lean et al., 1978). The logistic equation is mathematically analogous to the Hill equation which has been recommended by the International Union of Pharmacology Committee (Jenkinson et al., 1995). When two or more dose–response curves have been made, the usual practice has been to characterize each one separately and then to compare the slopes and potencies, e.g., in terms of the ratios of the $ED_{50}$ values. More information is provided, however, if one analyzes more curves simultaneously, forcing them to share certain parameters in common, if warranted by a priori considerations and by the data (De Lean et al., 1978). In our studies, analysis of the data revealed that the responses at zero dose (effect of saline) for all three responses and the maximal responses (maximal efficacies) for temperature reduction and lower lip retraction were not significantly different after i.v. and i.c.v. administration, thus we pooled these values in the analysis. Since 8-OH-DPAT behaves as a high-efficacy agonist in all 5-$HT_{1A}$ receptor-mediated behavioral models (Wilkinson and Dourish, 1991) and this is also the case with tail flicks (Millan et al., 1991), we also pooled minimum and maximum values for tail flick responses similarly to the temperature and lower lip retraction data. This allowed us to obtain an extrapolated i.c.v. $ED_{50}$ value for the tail flick response. The use of ALLFIT with these common parameters allowed us to get, e.g., an accurate comparison of relative potencies between two different treatments. Separate or simultaneous analysis of the dose–response curves resulted in very similar $ED_{50}$ values. Standard error values, probabilities and significant differences in ratios, however, would not be obtainable from individual curve analysis.

The data about the site of receptors mediating 5-$HT_{1A}$ receptor agonist-induced temperature reduction are contradictory. In rats, postsynaptic receptors may be predominantly involved, although this is still controversial. 8-OH-DPAT-induced hypothermia can be blocked by 5,7-dihydroxytryptamine administration, or by 2-week (but not after 3-day) pretreatment with *p*-chlorophenylalanine (*p*CPA; Goodwin et al., 1987; Hjorth, 1985; Hutson et al., 1987). In another study, however, lesions with 5,7-dihydroxytryptamine administration 4 and 10 days before 8-OH-DPAT caused similar, partial reduction of hypothermia (Glaser et al., 1991). On the other hand, chemical lesion with the same compound 8 days before the challenge caused a significant effect at low (0.04 mg/kg s.c.) but not high (0.16 and 0.63 mg/kg s.c.) doses of 8-OH-DPAT (Millan et al., 1993). The possibility of compensatory receptor changes in the 5-HT system following amine depletion cannot be ruled out (Wilkinson and Dourish, 1991). Thus, the chemical lesion studies are inconclusive and cannot rule out a role of presynaptic 5-$HT_{1A}$ receptors.

The previous observation that direct introduction of 8-OH-DPAT into the dorsal raphe nucleus evokes hypothermia favors the involvement of presynaptic sites (Higgins et al., 1988; Hillegaart, 1991; Glaser et al., 1991). However, the doses of 8-OH-DPAT used in these studies were relatively high. In comparison, our dose–response curve shows that i.c.v. administration of 8-OH-DPAT was more potent than direct injection to the dorsal raphe nucleus to causing hypothermia. These data provide evidence that receptors in the close vicinity of the lateral ventricle (e.g., hippocampus, septum) may play a predominant role in these responses.

Other data point to the complexity of the 5-$HT_{1A}$ receptor-mediated effects. For example, in the case of a postsynaptically mediated hypothermic response induced by intraseptal 5-HT injection, the fall in core temperature was associated with two separate effects: decrease in heat production and increase in heat loss (Cui et al., 1993). Other data suggest that inhibitory effects of 8-OH-DPAT on the dorsal raphe firing rate might be mediated indirectly by the frontal cortex (Ceci et al., 1994). In addition, the presynaptic effect of 8-OH-DPAT that leads to a reduction in 5-HT turnover may modulate its direct postsynaptic effect on temperature. Thus, tonic activation of other 5-HT receptor subtypes may interfere with selective 5-$HT_{1A}$ receptor-mediated hypothermia and other responses. Furthermore, the overt behavioral effects after systemic administration of 5-$HT_{1A}$ receptor agonists complicate the analysis of hypothermic effects (Wilkinson and Dourish, 1991). Indeed, in our study, statistical analysis showed a strong trend to a difference between the slopes of i.c.v and i.v. temperature dose–response curves. Our data suggest that, because of its high potency for temperature reduction, i.c.v. administration of 8-OH-DPAT is a useful model for the analysis of the hypothermic response in the rat. At low doses (2–10 $\mu$g/kg) significant decreases in core temperature occurred without any behavioral effects.

The conclusions from previous studies about the site of 5-$HT_{1A}$ receptors mediating lower lip retraction are controversial. RU 24969 (5-methoxy-3-(1′,2′,3′,6′,tetrahydro-4-piridinyl)-1*H*-indole) induces lower lip retraction in the rat (Berendsen et al., 1989, 1990) but has no effect in the mouse (Bill et al., 1989) following systemic administration. Recently, the autoreceptors in the median raphe nucleus have been suggested as a site responsible for the mediation of lower lip retraction (Berendsen et al., 1994).

There has been a lack of studies about the sites of 5-$HT_{1A}$ receptors mediating tail flick responses. Data from a recent study demonstrate that tail flicks in rats are mediated by postsynaptic 5-$HT_{1A}$ receptors localized in the lumbar spinal cord, and primary sensory (nociceptive)

mechanisms are likely to be involved (Bervoets et al., 1993).

Our study allowed us to compare i.c.v. and i.v. dose–response curves for the same effect and among the three pharmacological effects, and to contrast relative potencies between the three actions. Thus, our data are in agreement with previous results showing that hypothermic and lower lip retraction responses to 8-OH-DPAT are generated within the brain (Wilkinson and Dourish, 1991; Berendsen et al., 1994). Tail flick responses, however, are mediated by receptors in the spinal cord (Bervoets et al., 1993). The extremely high potency of i.c.v. 8-OH-DPAT on body temperature compared to that after intradorsal raphe injection found in previous studies suggests that the site of this action is much closer to the lateral ventricle then to the raphe nuclei, thus postsynaptic site(s) are predominantly involved in this action. Receptors in the median raphe nucleus have been suggested as a site of action for lower lip retraction (Berendsen et al., 1994). The much higher relative potency of 8-OH-DPAT for hypothermia than that for lower lip retraction suggests that the site of receptors for temperature reduction is much closer than the raphe nuclei. This comparison, again, points to the role of postsynaptic receptor sites in the action of 8-OH-DPAT that leads to temperature reduction. In addition, our data suggest that, because of the high efficacy, i.c.v. administration of 8-OH-DPAT is a useful model for the analysis of 5-$HT_{1A}$ receptor-mediated responses where overt behavioral effects may confuse the conclusion (e.g., hypothermic or blood pressure responses).

In conclusion, our data provide evidence that the availability, thus also the sites of receptors for 8-OH-DPAT to mediate temperature reduction, lower lip retraction and tail flick responses are different.

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