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Hypothermic Effects of Dopamine D_3 Receptor Agonists in the Island of Calleja Magna. Potentiation by D_1 Activation

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BARIK, S. AND R. DE BEAUREPAIRE. *Hypothermic effects of dopamine D_3 receptor agonists in the island of Calleja Magna. Potentiation by D_1 activation.* PHARMACOL BIOCHEM BEHAV **60**(2) 313–319, 1998.—The selective functions of D_3 receptors in the brain are still poorly understood, mainly because all the ligands active at dopamine D_3 receptors have also a high affinity for the D_2 receptors. However, it is possible to study selectively D_3 receptor function because some brain structures, such as the islands of Calleja, contain D_3 and not D_2 receptors. The position of the island of Calleja Magna in the rat brain makes it possible to inject dopamine D_3 ligands into the vicinity of these D_3 receptors, and to study their behavioral role, with no concomitant action on D_2 receptors. We studied the effects on body temperature and on locomotion of unilateral microinjections of D_2/D_3 receptors ligands into the island of Calleja Magna and into the adjacent nucleus accumbens. The results show that D_3 agonists injected into the island of Calleja Magna decrease body temperature and that this effect is potentiated by simultaneous injection of the D_1 agonist SKF 38393. D_3 agonists have no effect on locomotor activity in the island of Calleja Magna. In the nucleus accumbens, the D_3 agonists have only weak effects on body temperature, but, when associated with a D_1 agonist, strongly stimulate locomotor activity. The effects on body temperature of unilateral microinjections of dopamine agonists into unilaterally dopamine-depleted animals are the same as those in nondepleted ones. This indicates that the D_3 receptors are localized postsynaptically in the island of Calleja Magna. © 1998 Elsevier Science Inc.

Hypothermia Microinjection Locomotor activity Nucleus accumbens Quinpirole 7-OH-DPAT Quinelorane SKF 38393

THE dopamine D_3 receptor was cloned in 1990 by Sokoloff et al. (16), but its functional role remains elusive. Several hypothesis have implicated D_3 receptors in locomotor activity (14,17,20), in reinforcement (3), in the regulation of body temperature (10,19,20) and in cardiovascular responses (19,20). However, these studies used intraperitoneal injections of ligands that all have an important affinity for D_2 receptors (even though they have a higher affinity for D_3 receptors), which has made it difficult to differentiate the effects specifically related to D_2 and D_3 receptors.

To overcome this difficulty we have undertaken studies of the effects of dopamine D_2/D_3 agonists and antagonists microinjected in brain areas containing D_3 receptors and devoid of D_2 receptors. This method is warranted by the fact that studies of the expression of the genes encoding for D_2 and D_3 receptors have shown that the two genes are expressed in anatomically distinct areas (2,7). Using this technique, we have previously shown that the dopamine D_3 receptors in the cerebellum are involved in locomotor activity (1). In the present work, we studied the effects of injections of dopamine D_2/D_3 ligands into the island of Calleja Magna, which has the highest density of D_3 receptors in the brain, and which does not contain dopamine D_2 receptors. The island of Celleja Magna is edged by the shell of the nucleus accumbens, a structure that contains D_2 and D_3 receptors. Therefore, a control study with microinjections into the nucleus accumbens was also performed.

Dopamine in the nucleus accumbens is thought to be involved primarily in locomotion and reinforcement, while the functions of the dopamine receptors in the islands of Calleja are not known. We studied the effects of dopamine agonists and antagonists on two specific behaviors related to D_3 recep-

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tor functions, thermoregulation, and locomotor activity. The islands of Calleja and the nucleus accumbens also contain dopamine D_1 receptors (9) and it has been shown that, in certain areas of the brain, dopamine D_1 and D_2 receptors do interact, the D_2 effectiveness being potentiated by concomitant D_1 activation (21). We, therefore, looked for similar interactions in the islands of Calleja and nucleus accumbens by microinjecting simultaneously D_1 and D_3 receptor ligands. We also tried to block the behavioral effects of the D_3 receptor agonists injected into the island of Calleja by peripheral injection of a dopamine D_3 antagonist, nafadotride (14). Finally, we looked for the pre- or postsynaptic localization of D_3 receptors by making microinjections of D_3 agonists into the island of Calleja Magna in dopamine-depleted animals.

METHODS

General Procedures

Female Sprague–Dawley rats weighing 180–280 g were used for the experiments [in a previous study we have shown that the effects of hypothalamic microinjections of a pyrogen do not differ in male and female rats (15)]. They were anesthetized with sodium pentobarbital and implanted with a bilateral stainless steel cannula (11 mm long, 0.3 mm inner diameter, and 0.4 mm outer diameter) terminating 1.5 mm above the island of Calleja Magna (coordinates according to the rat brain atlas of Paxinos and Watson: ant. +1.2, lat. 0.5, deep 7 mm), or above the core of the nucleus accumbens (ant. +1.2, lat. 1.5, deep 7 mm). A series of control injections were also made above the island of Calleja Magna (ant. +1.2, lat. 0.5, deep 6.2 mm). After surgery the animals were housed in individual clear plastic cages in a room maintained on a 12D: 12L cycle (lights 0800–2000 h) and with a constant temperature (20°C). All experiments were performed under an approved protocol according to the Declaration of Helsinki.

After the animals had regained their preoperative body weight, they were used for the behavioral experiments. Injections were made through an injection cannula (0.17 mm inner diameter and 0.28 mm outer diameter) connected to a 1 μl Hamilton syringe. The experiments were always conducted at the same time of day. All compounds were injected at the dose of 1 μg, in a volume of 0.3 μl. The compounds used were the following, dopamine D_3 agonists: quinpirole, 7-OH-DPAT and quinelorane (provided by P. Sokoloff, Paris); D_3 antagonists: amisulpride (Synthelabo, Bagneux, France), AJ-76 and UH-232 (Upjohn, Kalamazoo, MI); D_2 antagonist: haloperidol (Janssen, Belgium); D_1 agonist: SKF 38393 (Sigma). When concomitant injections of an agonist and an antagonist were made, the amount injected for each compound was also 1 μg (in 0.3 μl). A group of eight animals had a 6-OHDA lesion of the substantia nigra and ventral tegmental area with two injections of 8 μg 6-OHDA HCl (Sigma) in 4 μl ascorbate solution (0.2 mg ascorbic acid per 1 ml 0.9% saline) over 1 min, one in the substantia nigra (ant. −4.8, lat. 2, deep 8.4 mm) and one in the ventral tegmental area (ant. −4.8, lat. 1, deep 8.4 mm). The effectiveness of the lesions was controlled 2 weeks later by the turning behavior of the animals after a subcutaneous injection of 0.25 g/kg apomorphine (Sigma). The experiments were made 2 weeks later.

Body Temperature Experiment

In the thermoregulation experiment, the animals were habituated to staying for 5 h per day in specially designed "temperature boxes" over the 5 days prior to the experiment. On the day of the experiment they were placed into such boxes, and their rectal temperature was taken immediately before the pharmacological agents or the solvent (distilled water) injection, and then 15, 30, 60, 90, 120, 180, 240, and 300 min after the injection. Another experiment was made using an intraperitoneal injection of a D_3 antagonist, nafadotride (provided by P. Sokoloff, Paris). In this experiment, injections of 7-OH-DPAT + SKF 38393 into the island of Calleja Magna were made 20 min after the peripheral injection of 2.5 mg/kg of nafadotride.

Locomotor Acitivity Experiment

In the locomotor activity experiment, the animals were habituated to an open field (1 meter square with lines on the floor spaced every 0.3 m) for 30 min. They were then injected, placed in the middle of the open field, and the number of lines crossed during 50 min recorded. In all the experiments the animals were used twice, first with an injection on one side, with the drug or the control solution, and then 4 days later with an injection on the other side, according to a counterbalanced schedule, so that all animals acted as their own controls.

Analysis of the Results

Immediately after the end of the experiments, the animals were anesthetized, perfused through a cardiac catheter with 20 ml of isotonic saline, followed by 20 ml of 10% formalin. The brains were removed, fixed in 10% formalin, and later frozen, sectioned at 80 μm, and the point of injection verified.

Injections made in the structures under study were grouped for statistical analysis. In all the experiments, the results were analyzed in groups of eight animals (each treated animal was its own control). Experiments were made in groups of eight animals, but when the point of injection was found to be outside the expected structure in some animals of any series, a new series of eight animals were studied until eight animals injected in the intended site were obtained, which were then kept for the statistical analysis. Student's *t*-tests for matched pairs were made at all the time intervals for the temperature experiment, and every 5 min for the locomotor activity experiment. Two-way ANOVA repeated measures of variance (treatment/time interactions) were made in all the temperature experiments. In the temperature experiment, a comparison of the effects of the D_3 agonists in the island of Calleja Magna was also made: the difference between treated and control animals was first assessed for each compound, two graphs were drawn (the D_3 agonists given alone, and in combination with SKF 38393), and the difference between the three compounds analyzed (as previously: *t*-tests for each time interval, and two-way ANOVA analysis of variance).

RESULTS

Body Temperature Experiment

In the Island of Calleja Magna, injection of the control solution increased body temperature, and the D_2/D_3 dopamine agonists all produced a significant decrease in body temperature in comparison with the controls (Fig. 1A, 1C, and 1E), while the D_1 agonist SKF 38393 had no effect (Fig. 1G). The injection of a combination of SKF 38393 with a D_2/D_3 agonist potentiated the hypothermic response (Fig. 2A, 2C, and 2E). Injections of a mixture of dopamine D_1 and D_3 agonists above the island of Calleja Magna produced no effect (data not shown). Injections of the dopamine antagonists AJ-76, UH-

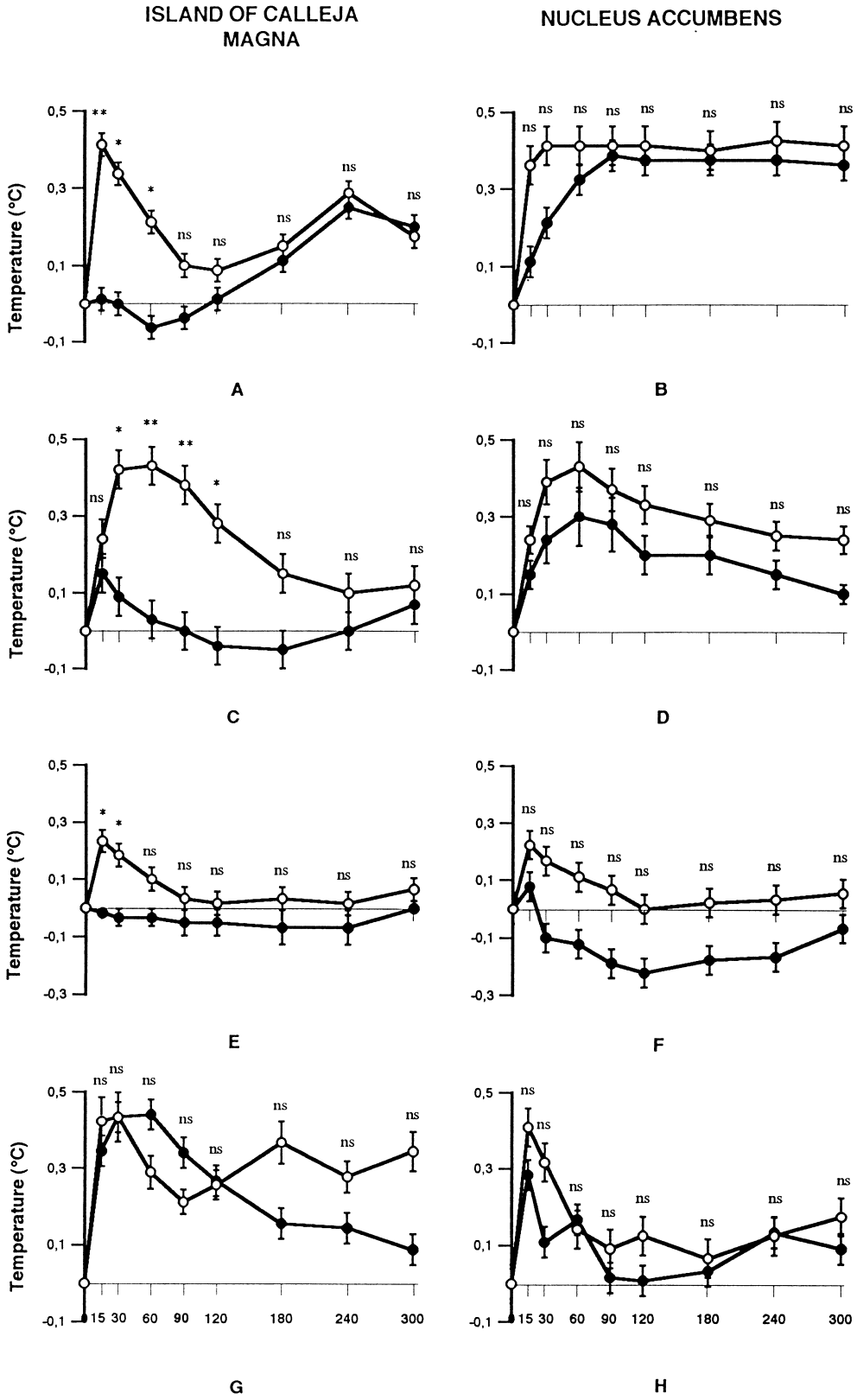

Fig. 1. Thermic effects of injections of dopamine agonists. (A, B) Quinelorane; (C, D) 7-OH-DPAT; (E, F) quinpirole; (G, H) SKF 38393. Left column: in the island of Calleja Magna; right column: in the nucleus accumbens. White dots for controls and black dots for treated animals. Two-way ANOVA analysis: (A) $F = 15.6$, $p < 0.001$; (B) $F = 2.4$, $p < 0.1$; (C) $F = 37.2$, $p < 0.0001$; (D) $F = 7.7$, $P < 0.01$; (E): $F = 6.8$, $P < 0.02$; (F): $F = 4.0$, $P < 0.06$; (G): $F = 0.02$, $P < 0.8$; (H): $F = 0.5$, $P < 0.4$. Student t-tests for all figures: $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.

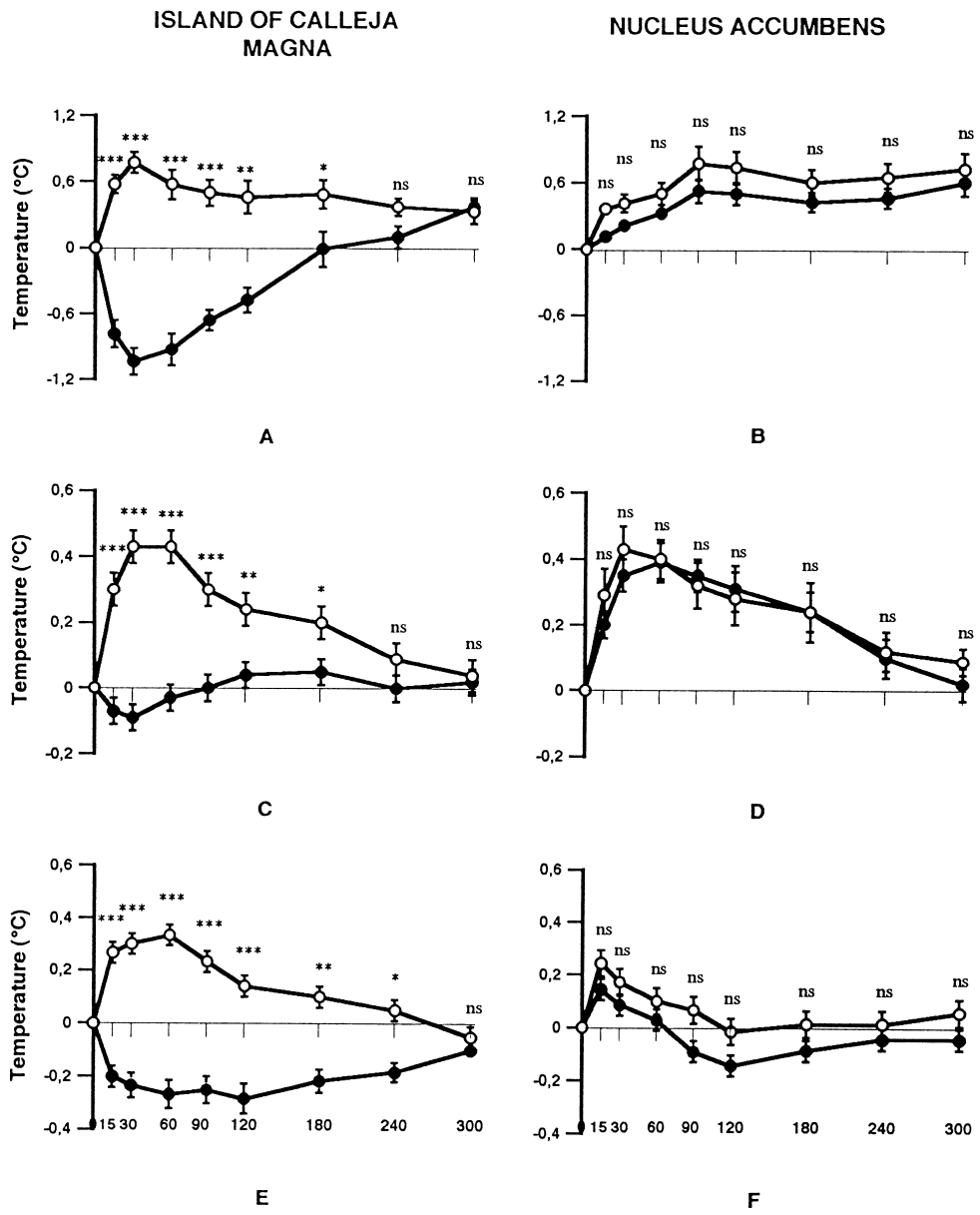

Fig. 2. Thermic effects of concomitant injections of dopamine D_3 agonists and SKF 38393. (A, B) Quinelorane+SKF 38393; (C, D) 7-OH-DPAT+SKF 38393; (E, F) quinpirole+SKF 38393. Left column: in the island of Calleja Magna; right column: in the nucleus accumbens. White dots for controls and black dots for treated animals. Two-way ANOVA analysis: (A) $F = 106.5$, $p < 0.0001$; (B) $F = 9.4$, $p < 0.008$; (C): $F = 97.2$, $p < 0.0001$; (D): $F = 0.4$, $p < 0.5$; (E): $F = 195.5$, $p < 0.0001$; (F): $F = 6.4$, $p < 0.02$.

232, amisulpride, and haloperidol had no effect (data not shown). Injections of quinelorane (in combination with SKF 38393) into the island of Calleja Mgna in dopamine-depleted animals produced a significant hypothermic response (Fig. 3). All but three of the dopamine agonists injected into the nucleus accumbens did not have any thermic effect. The exceptions were 7-OH-DPAT (Fig. 1D), quinelorane + SKF 38393, and quinpirole + SKF 38393 (Fig. 2B and 2F), which all produced a slight hypothermic effect (dopamine antagonists were not tested, and no experiments were made in the nucleus accumbens in dopamine-depleted animals) (Figs. 1 and 2).

Comparison of the abilities of the different dopamine D_3 agonists to decrease body temperature showed that quinelorane is significantly more potent than 7-OH-DPAT and quinpirole, and that 7-OH-DPAT is more potent than quinpirole in decreasing body temperature when the compounds are associated with SKF 38393. The effects of the compounds given alone did not differ significantly (Fig. 4).

Intraperitoneal injection of nafadotride, given 20 min before the injection of 7-OH-DPAT + SKF 38393 into the islands of Calleja, completely blocks the hypothermic effects of these compounds (Fig. 5).

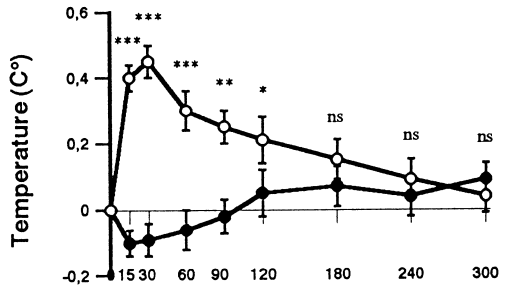

Fig. 3. Thermic effects of injections of quinelorane+SKF 38393 in 6-OHDA lesioned rats. White dots for controls and black dots for treated animals. Two-way ANOVA analysis: $F = 56.4$, $p < 0.0001$.

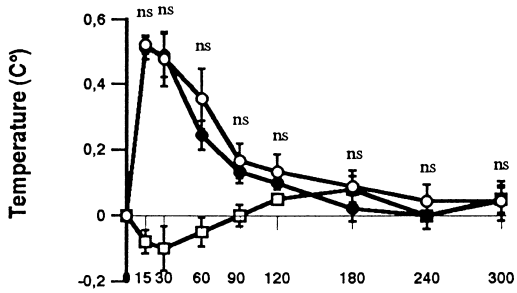

Fig. 5. Effects of a concomitant injection of 7-OH-DPAT and SKF 38393 into the island of Calleja Magna after an IP injection of nafadotride. Empty circles: controls; squares: 7-OH-DPAT+SKF; Full circles: 7-OH-DPAT+SKF after an IP injection of nafadotride. Two-way ANOVA analysis: controls compared to 7-OH-DPAT+SKF: $F = 43.6$, $p < 0.0001$; 7-OH-DPAT+SKF compared to 7-OH-DPAT+SKF in nafadotride-treated: $F = 43.5$, $p < 0.0001$; controls compared to 7-OH-DPAT+SKF in nafadotride-treated: $F = 1.7$, $p < 0.2$.

Locomotor Activity Experiment

None of the compounds injected into the island of Calleja Magna had any effect on locomotor activity. In the nucleus accumbens, concomitant injections of dopamine D_3 agonists and SKF 38393 strongly stimulated locomotor activity, and dopamine antagonists given alone significantly decreased locomotor activity (Fig. 6).

DISCUSSION

These experiments show that injection of dopamine D_2/D_3 agonists into the island of Calleja Magna produced hypothermic effects. Because there are no dopamine D_2 receptors in the islands of Calleja, these effects are most likely related to a stimulation of dopamine D_3 receptors. The fact that injection of a combination of D_1 and D_3 receptor agonists produced a potentiated response indicates a synergy in the activation of the two receptors.

The islands of Calleja have been implicated in the regulation of reproduction, olfactive, and cardiovascular functions, but still only little is known about their functional role (4,6,11,12,18). The finding of their involvement in thermic responses was unexpected. The fact that injection of dopamine D_3 antagonists do not increase body temperature seems to indicate that the island of Calleja Magna is a brain structure more prone to trigger hypothermic than hyperthermic responses. The island of Calleja Magna has a very small size, and this raises a technical concern regarding the volume injected (0.3 μl) because of possible diffusion out of the injected site. This is why we made two series of injections around the Island of Calleja Magna, one laterally (into the nucleus accumbens) and one above. We show that injections of dopamine agonist and antagonists into the nearby nucleus accumbens produce very different effects on locomotor activity. This demonstrates that no diffusion of the injected compounds can preclude the interpretation of the results in the island of Calleja Magna. Furthermore, injections made immediately above the island of Calleja Magna did not alter body temperature, which indicates that the effect was not related to diffusion of the product along the injection cannula tract. We will not discuss the effects of the injections in the nucleus accumbens on locomotor activity because the aim of the study was only to find a selective function for dopamine D_3 receptors, and the D_3 receptors in the island of Calleja Magna do not appear to be involved in locomotor activity.

The results also show a hyperthermic effect of the injections in the vehicle-treated animals, and it may seem that the D_2/D_3 agonists counteract the hyperthermic effect of the injection rather than produce a real hypothermic effect. But when potentiated by the DI agonist SKF 38393, the effect is clearly hypothermic (while the SKF 38393 does not produce a

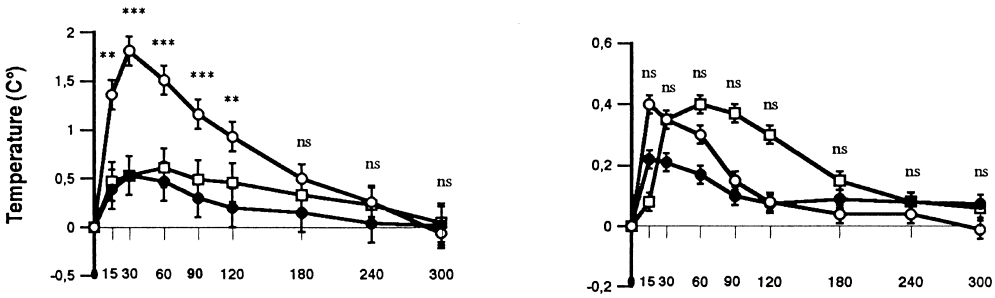

Fig. 4. Comparison of the effects of the three dopamine agonists injected into the island of Calleja Magna (difference between treated and control animals, as shown in Fig. 1 and 2; controls are plotted on zero values on the abscissa). Empty circles: quinelorane; squares: 7-OH-DPAT; full circles: quinpirole. Left figure: concomitant injection of SKF 38393, two-way ANOVA analysis: quinelorane+SKF compared to 7-OH-DPAT+SKF: $F = 22.2$, $p < 0.0003$; quinpirole+SKF compared to 7-OH-DPAT: $F = 0.4$, $p < 0.5$; quinelorane compared to quinpirole: $F = 2.6$; $p < 0.1$; quinpirole compared to 7-OH-DPAT: $F = 3.9$, $p < 0.06$.

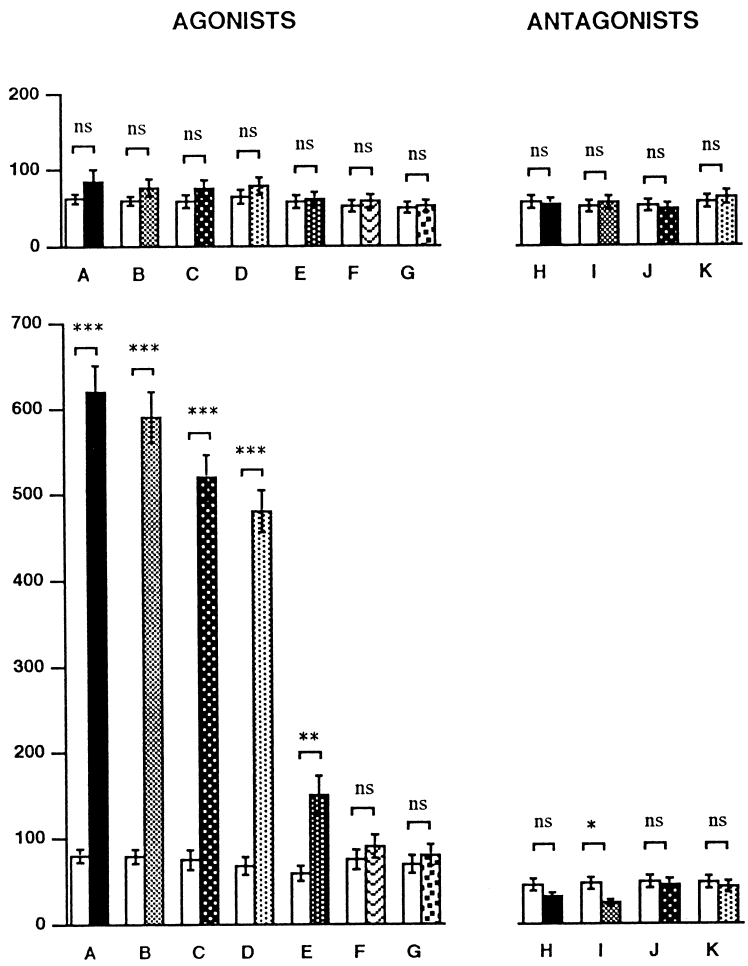

Fig. 6. Effects on locomotor activity of injections of dopamine agonists and antagonists (Student *t*-tests). Number of lines crossed during 50 min after the injection of: (A) quinelorane+SKF 38393; (B) 7-OH-DPAT+SKF 38393; (C) quinpirole+SKF 38393; (D) quinelorane; (E) SKF 38393; (F) 7-OH-DPAT; (G) quinpirole; (H) amisulpride; (I) haloperidol; (J) AJ-76; (K) UH-232. Upper figures: in the island of Calleja Magna; lower figures: in the nucleus accumbens. Empty bars = controls.

hypothermic effect by itself). It is, therefore, likely that the hypothermic effects are related to an action of the D_2/D_3 agonists on a central mechanism of body temperature regulation. The hyperthermia in vehicle-treated animals is probably related to a stress effect of the injection, as is usually the case after intracerebral injections [see, for instance, (15)]. However, further experiments testing the effects of D_2/D_3 injections in the island of Calleja Magna in animal models of stress will be necessary.

The pre- or postsynaptic localization of D_3 receptors in the brain is a matter of controversy. D_3 receptors are often considered as autoreceptors (presynaptic receptors); however, dopamine denervation downregulates dopamine D_3 receptors (8). We explored the pre- or postsynaptic localization of the D_3 receptors in the island of Calleja Magna by studying the effects of injections of a mixture of D_1 and D_3 agonists in dopamine-depleted animals. The results show that animals with lesions of the dopaminergic systems react in the same way as nonlesioned animals. It is, therefore, probable that in the case of the island of Calleja Magna, the D_3 receptors are localized postsynaptically. Furthermore, the similarity of the effects in lesioned and in nonlesioned animals indicates that the D_3 receptors in the island of Calleja Magna do not present denervation hypersensitivity. According the Diaz et al. (5), D_3 receptor binding and mRNA are abundant in the granule cells of the islands of Calleja. These cells are postsynaptic to dopaminergic projections, they make sparse contacts with dopaminergic axons, and they contain D_1 receptors. Such histochemical organization corresponds to our findings of a postsynaptic effect and interaction with D_1 receptors.

The blockade of the hypothermic effects of a D_1/D_3 agonists in the island of Calleja Magna demonstrates a great selectivity of the experimental procedure. The dopamine D_2/D_3 agonists used do not all have the same affinity for D_3 receptors. According to the studies published in the literature, in terms of selectivity compared with D_2 receptors, quinelorane is a more potent D_3 agonist than 7-OH-DPAT and quinpirole, and 7-OH-DPAT more potent than quinpirole (according to Sautel et al. (13), the functional selectivity [EC_{50} (D_2)/EC_{50}(D_3)]

of the agonists are the following: quinpirole 3.3, 7-OH-DPAT 7.0, quinelorane 21.4). We found that, in synergy with the D_1 agonist, quinelorane is more potent than 7-OH-DPAT and quinpirole, and 7-OH-DPAT more potent than quinpirole to trigger the hypothermic responses. Therefore, our results do correspond to the potencies found in vitro by Sautel et al., so that the ability of dopamine D_3 agonists (associated with a D_1 agonist) to decrease body temperature when injected into the island of Calleja Magna, may provide a behavioral test for measuring the agonist potencies of D_3 ligands.

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