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Short communication

Ipsapirone suppresses food intake in food-deprived rats by an action at 5-HT_{1A} receptors

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Abstract

The effects of the 5-HT_{1A} receptor agonist ipsapirone (2.5–10 mg/kg, s.c.) on food intake were investigated in rats that had been fasted for 22 h. Ipsapirone administered immediately prior to presentation of food produced a dose-related decrease in food intake. The effect of ipsapirone (5 mg/kg) was reversed by pretreatment with the 5-HT_{1A} receptor antagonist *N*-{2[4-)2-methoxyl)-1-piperazinyl]ethyl}-*N*-(2-pyridinyl)cyclohexanecarboxamide trihydrochloride (WAY100635) (0.3 mg/kg, s.c.). The results of this study show that ipsapirone has acute dose-dependent depressant effects on food intake in fasted rats, mediated by 5-HT_{1A} receptors.

Keywords: Ipsapirone; 5-HT_{1A} receptor agonist; Food intake; WAY-100635

1. Introduction

5-Hydroxytryptamine (5-HT; serotonin) acts at a number of different receptor subtypes (Hoyer et al., 1994), and it has been generally found that systemic or central administration of 5-HT receptor agonists decrease food intake in mammalian species (Blundell, 1984). An exception to this generalization was the observation that the 5-HT_{1A} receptor agonist 8-hydroxy-2(di-*n*-propylamino)tetralin (8-OH-DPAT) produces an increase in food intake in non-deprived rats (Dourish et al., 1985; Ebenezer, 1992a). Similar results were subsequently obtained for other 5-HT_{1A} receptor agonists, such as gepirone, buspirone and ipsapirone (Gilbert and Dourish, 1987; Fletcher and Davis, 1990; Ebenezer, 1993). Results from electrophysiological, neurochemical, and behavioural studies have suggested that these drugs act at 5-HT_{1A} somatodendritic autoreceptors in the raphe nucleus to decrease 5-HT function in the CNS (Bendotti and Samanin, 1986; Sprouse and Aghajanian, 1987; Hjorth and Magnusson, 1988); thus, their mechanism of action remains consistent with the putative inhibitory role of 5-HT in the control of ingestive behaviour.

In marked contrast, it has been found that doses of 8-OH-DPAT (Ebenezer, 1992b), gepirone (Ebenezer and Tite, 1995) and buspirone (Ebenezer, 1996) that increase feeding in non-deprived rats suppress eating in food-deprived animals. Moreover, this inhibitory effect does not seem to be secondary to the induction of stereotypy or other abnormal 5-HT_{1A} receptor-dependent behaviours (Ebenezer, 1992b). The reason for the anorexigenic action of these drugs in food-deprived rats is not known. Moreover, it remains to be determined whether these agents suppress food intake in hungry animals by an action at 5-HT_{1A} receptors. The present study was therefore undertaken to investigate the effects the 5-HT_{1A} receptor agonist ipsapirone on food intake in food deprived rats and determine whether the hypophagic effect is mediated by an action of the drug at 5-HT_{1A} receptors.

2. Methods and materials

2.1. Subjects

Adult Male Wistar rats (b wt. 250–300 g) were deprived of food for 22 h each day prior to training sessions or drug experiments, but had free access to water at all times. The animals were given 4 training sessions during

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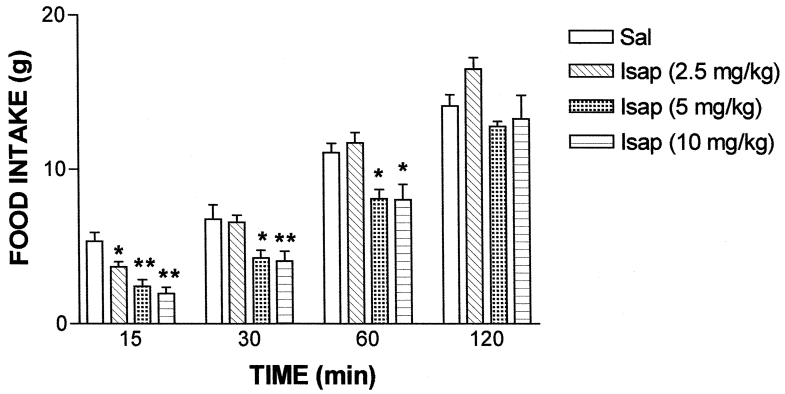

Fig. 1. The dose-related effects of ipsapirone (2.5–10 mg/kg, s.c.) on food intake in rats fasted for 22 h. Differences between drug and saline treatments at each time interval were determined by Dunnett's *t*-test after a significant ANOVA (one factor with repeated measures). $^{**}P < 0.01$, $^{*}P < 0.05$. Vertical lines represent +S.E.M. Abbreviations in figure: Sal = saline; Isap = ipsapirone; WAY = WAY100635.

which time they were allowed free access to pelleted food (Campden, UK) in experimental cages measuring 32 × 25 × 19 cm for 120 min. The nutrient composition of the food was as follows: protein 20%, oil 4.5%, fibre 5%, ash, 7% plus traces of vitamins and metals. The food was presented to the rats in shallow cylindrical cups and food intake measured, as described previously (Ebenezer, 1992b).

2.2. Experiment 1

Rats ($n = 20$) were injected s.c. with saline ($n = 5$) or ipsapirone (2.5, 5 and 10 mg/kg; $n = 5$ for each dose) and placed separately in the experimental cages with free access to food and water. The amount of food consumed by the rats during the subsequent 120-min test-meal session was measured.

2.3. Experiment 2

Rats ($n = 20$) were injected with either saline followed by saline ($n = 5$), saline followed by ipsapirone (5 mg/kg; $n = 5$), the 5-HT_{1A} receptor antagonist *N*-{2[4-)2-methoxyl)-1-piperazinyl]ethyl}-*N*-(2-pyridinyl)cyclohexanecarboxamide trihydrochloride (WAY100635) (0.3 mg/kg) followed by saline ($n = 5$), WAY100635 (0.3 mg/kg) followed by ipsapirone (5 μg/kg; $n = 5$). Both injections were given s.c.; 30 min separated the two injections. Immediately after the second injection, the rats were placed separately in experimental cages with access to food. Food consumption was measured after 30 min.

2.4. Statistics

The results obtained in both experiments were analysed by two-way analysis of variance (ANOVA).

3. Results

3.1. Experiment 1

Ipsapirone (2.5–10 mg/kg) produced a dose-related decrease in food intake (Fig. 1). Analysis of the data

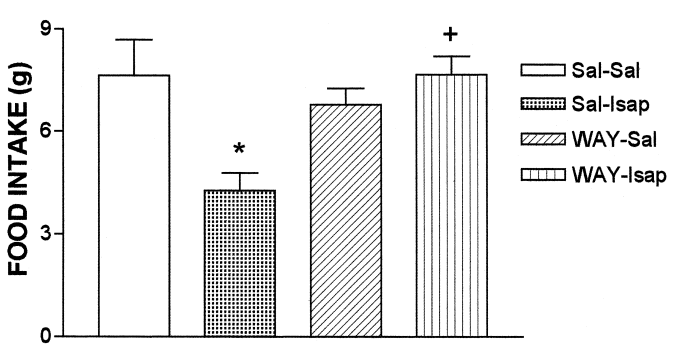

Fig. 2. Effect of WAY100635 (0.3 mg/kg) on the hypophagic effect of ipsapirone (5 mg/kg) in rats fasted for 22 h. Food intake was measured for 30 min. $^{*}P < 0.05$ (vs. saline), + $P < 0.05$ (vs. ipsapirone). Vertical line represents +S.E.M. Abbreviations in figure: Sal = saline; isap = ipsapirone; WAY = WAY100635.

indicated that the 2.5 mg/kg dose only suppressed feeding during the first 15 min after administration ($P < 0.05$) while the higher doses (i.e. 5 and 10 mg/kg) inhibited cumulative food intake during the first 60 min ($P < 0.05$ in each case). None of the doses of ipsapirone used produced overt behavioural effects in the rats compared with controls.

3.2. Experiment 2

The results are shown in Fig. 2. The selective 5-HT_{1A} antagonist, WAY100635 (0.3 mg/kg), had no effect on food intake in 22 h food-deprived rats when administered on its own. However, pretreatment with WAY100635 (0.3 mg/kg) completely abolished the hypophagic effect of the 5 mg/kg dose of ipsapirone.

4. Discussion

It has previously been found that the 5-HT_{1A} receptor agonist, ipsapirone, increases food intake in non-deprived rats (Fletcher and Davis, 1990). By contrast, the results from the present study show that ipsapirone inhibits food intake in food-deprived rats in a dose-dependent manner. The present findings confirm and extend the results of previous studies in rodents (Ebenezer, 1992a), and suggest that ipsapirone has complex effects on feeding behaviour, increasing food intake in satiated or non-deprived rats (Fletcher and Davis, 1990), while producing a short-term reduction in food intake in food-deprived animals.

The hypophagic effects of ipsapirone (2.5–10 mg/kg, s.c.) on food intake in the food-deprived rats was most apparent in the first 15–30 min after administration. These results are consistent with the early depression of operant and non-operant food intake observed in fasted rats after systemic administration of 8-OH-DPAT (Ebenezer, 1992a), buspirone (Ebenezer, 1996) or gepirone (Ebenezer and Tite, 1995) at doses that do not cause stereotypy or motor incoordination. Moreover, the observation in this study that the selective 5-HT_{1A} receptor antagonist, WAY100635 (Vickers et al., 1996), abolished the hypophagia induced by ipsapirone (5 mg/kg), suggests that its inhibitory effect on feeding in hungry rats is mediated by 5-HT_{1A} receptors. It is widely acknowledged that enhanced central 5-HT activity has an inhibitory effect of food intake (Blundell, 1984), and it has been suggested that the 5-HT_{1A} receptor agonists increase food intake by acting at 5-HT_{1A} somatodendritic autoreceptors in the raphe nucleus to decrease 5-HT function in the CNS (Bendotti and Samanin, 1986; Sprouse and Aghajanian, 1987; Hjorth and Magnusson, 1988). While such an interpretation may explain the hyperphagia caused by 5-HT_{1A} receptor agonists in non-deprived animals, it does not explain the hypophagia observed in food-deprived rats following administration of these agents. Although the mechanism by which these drugs decrease food intake in hungry animals is not known, the present study has shown that ipsapirone does this by an action at 5-HT_{1A} receptors. However, WAY100635 will block both 5-HT_{1A} somatodendritic autoreceptors as well as post-synaptic 5-HT_{1A} receptors. It is therefore not possible to predict from this study whether the hypophagic action of ipsapirone in food-deprived rats is mediated by an action at pre- or post-synaptic 5-HT_{1A} receptors. Experiments in our laboratory with 1-(2-methoxyphenyl)-4-(4-succinimidobutyl)piperazine (MM-77), a drug with supposedly high selectivity for postsynaptic 5-HT_{1A} receptors (Mokrosz et al., 1994), also appears to have high selectivity for other receptor subtypes (Arkle and Ebenezer, unpublished results). It has been found to depress food intake at low doses (Arkle and Ebenezer, unpublished results), making it unsuitable to investigate the possible role of post-synaptic 5-HT_{1A} receptors in mediating the hypophagic effect of ipsapirone. Thus, until good selective antagonists for 5-HT_{1A} pre- or post-synaptic receptors become available, it will be difficult to provide an unequivocal answer to this question as to whether the hypophagic action of ipsapirone in food-deprived rats is mediated by an action at pre- or post-synaptic 5-HT_{1A} receptors.

In conclusion, the results of this study are the first to show that ipsapirone has acute dose-dependent depressant effects on food intake in food-deprived rats. Furthermore, the results indicate that this effect is mediated by an action of the drug at 5-HT_{1A} receptors.

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