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European Journal of Pharmacology 378 (1999) 149–152

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Short communication

Influence of the non-competitive NMDA receptor antagonist MK-801 on 2-deoxy-D-glucose-induced hyperphagia in rats

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Received 18 March 1999; received in revised form 25 June 1999; accepted 29 June 1999

Abstract

The effects of the glutamate N-methyl-D-aspartate (NMDA) receptor antagonist (5*R*,10*S*)-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclo-hepten-5,10-imine (MK-801) on 2-deoxy-D-glucose-induced hyperphagia were investigated in rats. MK-801 significantly increased 2-deoxy-D-glucose-elicited eating. The facilitating effects of MK-801 on 2-deoxy-D-glucose-elicited feeding were not affected by coadministration of a nitric oxide (NO) precursor, L-arginine. Because NO synthase inhibitors inhibit 2-deoxy-D-glucose-induced hyperphagia and activation of the NMDA receptor leads to NO formation, our results suggest that blockade of the NMDA receptor increases 2-deoxy-D-glucose-induced hyperphagia, which is unrelated to inhibition of NO, and that NMDA receptors may play a role in satiety.

Keywords: 2-Deoxy-D-glucose; Nitric oxide (NO); MK-801; NMDA receptor; N^G-nitro-L-arginine methyl ester; Food intake

1. Introduction

It has been suggested that many neurotransmitters or hormones, including serotonin, neuropeptide Y or glucocorticoids regulate food intake (Bernardis and Bellinger, 1996). Recent findings indicate that nitric oxide (NO) also participates in feeding behaviour. It was demonstrated that NO synthase inhibitors such as N^G-nitro-L-arginine inhibit food intake in food-deprived and genetically obese animals (Squadrito et al., 1993, 1994; Morley and Flood, 1994). We previously found that N^G-nitro-L-arginine methyl ester (L-NAME) inhibits the 5-HT_{1A} receptor agonist 8-hydroxy-2-di-n-(propylamino)tetralin (8-OH-DPAT)-induced increase in food intake in rats (Yamada et al., 1996). Furthermore, L-NAME inhibits hyperphagia elicited by a glucose analogue, 2-deoxy-D-glucose (Yamada et al., 1997). The inhibitory effects of L-NAME on 2-deoxy-D-glucose-elicited hyperphagia are related to NO formation, since they are prevented by a NO precursor L-arginine (Yamada et al., 1997). As the NO synthase mRNA levels or the NO synthase activity of the brain is elevated in hyperphagic animals (Squadrito et al., 1994; Morley et al., 1995), NO formation in the brain may be facilitated in enhanced feeding.

It has been reported that *N*-methyl-D-aspartate (NMDA) increases ingestive behaviour in rats when injected centrally (Stanley et al., 1993a). Moreover, it has been reported that NMDA receptor mRNA is present in the hypothalamus, which area is important in the regulation of food intake (Van den Pol et al., 1994). Activation of the NMDA receptor leads to Ca^{2+} influx and stimulation of NO synthase, resulting in facilitation of NO formation (Dawson et al., 1991). NO formed by stimulation of the NMDA receptor is involved in several brain functions, such as neurotransmitter release or behaviour. Indeed, NO synthase inhibitors can suppress NMDA receptor-mediated effects (Montague et al., 1994; Itzhak, 1996). However, it is not clear whether the NMDA receptor is associated with food intake through NO. In this paper, to study the involvement of NO linked with the NMDA receptor in feeding behaviour, we investigated the effects of the non-competitive NMDA receptor antagonist, (5*R*,10*S*)-(+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclo-hepten-5,10-imine (MK-801), on 2-deoxy-D-glucose-induced hyperpha-

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0014-2999/99/$ - see front matter
PII: S0014-2999(99)00472-0

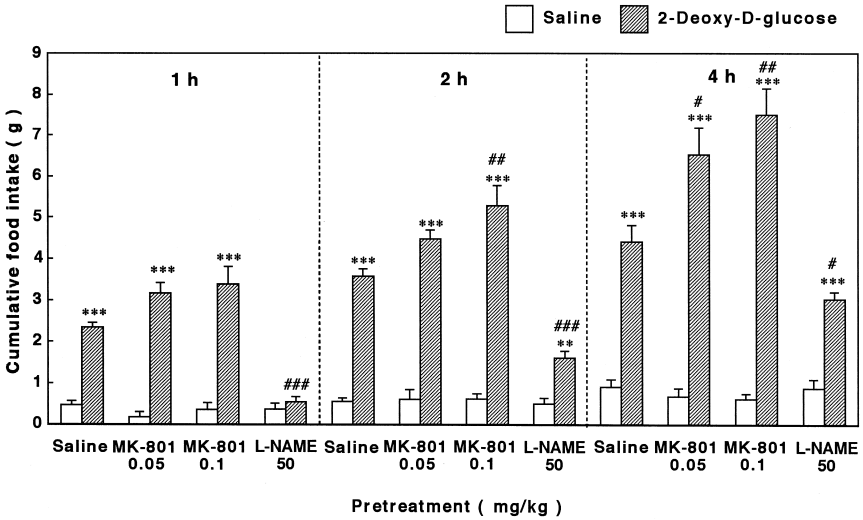

Fig. 1. Effects of MK-801 and L-NAME on 2-deoxy-D-glucose-induced hyperphagia in rats. Results are shown as the means ± S.E. ($N = 5–7$). 2-Deoxy-D-glucose at 750 mg/kg was injected i.p. MK-801 and L-NAME were injected i.p. 30 min before the injection of 2-deoxy-D-glucose. **: $P < 0.01$, ***: $P < 0.001$ vs. saline in the respective group. #: $P < 0.05$, ##: $P < 0.01$, ###: $P < 0.001$ vs. saline + 2-deoxy-D-glucose-treated group.

gia in rats and compared them to the effects of the NO synthase inhibitor.

2. Materials and methods

2.1. Animals

Male Sprague–Dawley rats (200–240 g) were obtained from SLC Japan. They were housed in individual cages and maintained under a controlled 12 h:12 h light/dark cycle (lights on at 0700 h), with room temperature at 23 ± 1°C and humidity at 55 ± 5% for at least 7 days prior to experiments. Rats were given free access to food and water.

2.2. Drug treatment

2-Deoxy-D-glucose and L-arginine were purchased from Wako Pure Chemical (Japan). MK-801 hydrogen maleate and L-NAME hydrochloride were obtained from Research Biochemicals (USA). All drugs were dissolved in saline and injected i.p. MK-801, L-NAME and L-arginine were injected i.p. 30 min before the injection of 2-deoxy-D-glucose. All drugs were administered in a volume of 0.2 ml/100 g.

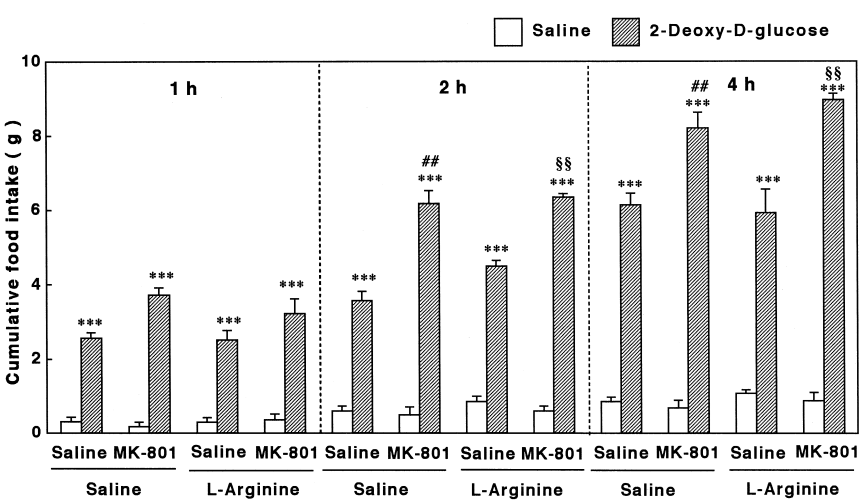

Fig. 2. Effects of MK-801 plus L-arginine on 2-deoxy-D-glucose-induced hyperphagia in rats. Results are shown as the means ± S.E. ($N = 5–7$). MK-801 at 0.1 mg/kg and L-arginine at 1 g/kg were given i.p. 30 min before 2-deoxy-D-glucose. ***: $P < 0.001$ vs. saline of respective groups, ##: $P < 0.01$ vs. 2-deoxy-D-glucose of saline + saline-pretreated group. §§: $P < 0.01$ vs. 2-deoxy-D-glucose of saline + L-arginine-pretreated group.

2.3. Measurement of food intake

Preweighed food was placed in the cage and the amount of food remaining was weighed 1, 2 and 4 h after the injection of 2-deoxy-D-glucose. Drugs were injected between 1300 and 1400 h.

2.4. Statistics

Results were analyzed by two-way analysis of variance (ANOVA) followed by Tukey's test.

3. Results

3.1. Effects of MK-801 and L-NAME on 2-deoxy-D-glucose-induced hyperphagia in rats

The effects of MK-801 on 2-deoxy-D-glucose-induced hyperphagia are demonstrated in Fig. 1. 2-Deoxy-D-glucose at a dose of 750 mg/kg induced marked hyperphagia in non-food-deprived rats. MK-801 significantly increased 2-deoxy-D-glucose-induced food intake for 2 and 4 h, although the NO synthase inhibitor L-NAME attenuated it.

3.2. Effects of L-arginine on MK-801-induced increases in 2-deoxy-D-glucose-elicited hyperphagia

The effects of L-arginine (1 g/kg) on the effect of MK-801 (0.1 mg/kg) on 2-deoxy-D-glucose-induced hyperphagia are demonstrated in Fig. 2. Coadministration of L-arginine did not affect the amplifying effects of MK-801 on 2-deoxy-D-glucose-induced hyperphagia.

4. Discussion

It has been reported that glutamate is associated with feeding behaviour (Stanley et al., 1993b). An NMDA type of glutamate receptor has been proposed to be related to food intake and NMDA itself increases eating, which is antagonized by an NMDA receptor antagonist (Stanley et al., 1993a,b). It is well known that activation of the NMDA receptor induces subsequent stimulation of NO synthesis (Dawson et al., 1991). The NO-linked NMDA receptor has been implicated in methamphetamine neurotoxicity because the neurotoxic effects could be blocked by both the NMDA receptor antagonist, MK-801, and NO synthase inhibitors (Ali et al., 1994; Di Monte et al., 1996). To investigate the involvement of the NMDA receptor and NO in food intake, we studied the effects of L-NAME and MK-801 on 2-deoxy-D-glucose-elicited feeding.

Our results showed that MK-801 did not reduce 2-deoxy-D-glucose-induced hyperphagia but dose dependently enhanced it. In contrast, the NO synthase inhibitor, L-NAME, inhibited feeding elicited by 2-deoxy-D-glucose. Furthermore, the facilitating effects of MK-801 on 2-deoxy-D-glucose-elicited hyperphagia were not reversed by coadministration of the NO precursor L-arginine. These results indicate that MK-801 showed opposite effects to those of the NO synthase inhibitor on 2-deoxy-D-glucose-induced hyperphagia and that the facilitating effects of MK-801 on hyperphagia were not associated with NO. We previously demonstrated that the selective neuronal NO synthase inhibitor 7-nitroindazole prevented eating induced by 2-deoxy-D-glucose and that brain NO may be associated with 2-deoxy-D-glucose-induced hyperphagia (Yamada et al., 1997). Therefore, it is likely that NO in 2-deoxy-D-glucose-elicited hyperphagia is unrelated to central NMDA receptors.

It has been reported that direct injection of NMDA into the hypothalamus elicits feeding in rats, a response which is rapidly induced and transient (Stanley et al., 1993a,b). However, we showed that the NMDA receptor antagonist, MK-801, increased the feeding burst elicited by 2-deoxy-D-glucose. 2-Deoxy-D-glucose is known to inhibit glucose utilization and elicits feeding in animals. Our results demonstrate that MK-801 apparently enhanced 2-deoxy-D-glucose-elicited feeding 2 h after its injection but that it did not increase feeding in the early period. In addition, MK-801 did not affect the food intake of saline-treated group, that is, satiated rats. These findings suggest that MK-801 may inhibit satiety. Therefore, taken together with previous reports, the NMDA receptor may have a role both in the initiation of feeding behaviour and in satiety. The NMDA receptor is widely distributed in the central nervous system and modifies the release of other neurotransmitters (Montague et al., 1994). It has been also reported that MK-801 enhances sucrose intake in rats treated with reserpine, which depletes catecholeamines and indoleamines (Bendnar et al., 1994). Therefore, other transmitters may modify the NMDA receptor-mediated effects on feeding behaviour and an interaction between NMDA and other transmitters in regulation of food intake may be present.

In summary, our results demonstrated that the non-competitive NMDA receptor antagonist, MK-801, increased 2-deoxy-D-glucose-induced hyperphagia in rats, an effect which was not reversed by L-arginine. Since NO synthase inhibitors decrease 2-deoxy-D-glucose-induced hyperphagia, NO linked with the glutamate NMDA receptor is not related to the hyperphagia elicited by 2-deoxy-D-glucose. Moreover, the facilitating effects of MK-801 on 2-deoxy-D-glucose-induced hyperphagia suggest that the NMDA receptor may play a significant role in satiety.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Scientific Research (C) from the Ministry of Education, Science, Sports and Culture of Japan.

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