



Effect of the *N*-methyl-D-aspartate receptor antagonist on locomotor activity and cholecystokinin-induced anorexigenic action in a goldfish model

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ABSTRACT

We have previously identified that peripherally administered cholecystokinin (CCK) exerts an anorexigenic action via the vagal afferent, and subsequently the brain melanocortin- and corticotropin-releasing hormone-neuronal pathways in goldfish. *N*-Methyl-D-aspartate (NMDA) receptors have been shown to be involved in the regulations of locomotor activity and food intake in mammals. Although several neuropeptides and other factors exert similar effects in fish and mammals, the role of NMDA receptor in the control of locomotor activity and feeding behavior in fish is still unclear. In the present study, we examined the effect of the NMDA receptor antagonist, MK-801, on locomotor activity and food intake in the goldfish. Intraperitoneal (IP) injection of MK-801 at 0.15 nmol/g body weight (BW) increased locomotor activity, but did not affect food consumption. IP injection of MK-801 at same dose attenuated peripheral CCK (100 pmol/g BW)-induced anorexigenic, but not peripheral acyl ghrelin (10 pmol/g BW)-induced orexigenic actions. These data show for the first time that the NMDA receptor-signaling pathway is involved in the regulation of locomotor activity and feeding behavior through modulation of the peripheral CCK-induced satiety signal, but not the orexigenic effect of ghrelin.

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N-Methyl-D-aspartate (NMDA) receptors are ionotropic glutamate receptors that act as nonspecific cation channels permeable to sodium, calcium and potassium. NMDA receptors have been shown to be involved in many aspects of synaptic transmission, dendritic integration, synaptic and neuronal maturation, and plasticity throughout the brain [6,9]. Interestingly, excitatory amino acids such as glutamate, or their binding receptors such as those for NMDA, have also been implicated in the regulations of locomotor activity and food intake in rodents [1,4,10].

NMDA receptor antagonist enhances locomotor activity and the nucleus accumbens is an important site of action [1]. With regard to the role of NMDA receptors in feeding behavior, blockade of brainstem vagal afferent neurochemical transmission using the pharmacological NMDA receptor antagonist, MK-801, has been reported to increase meal size [20]. In addition, NMDA receptor blockade attenuates the reduction of feeding induced by peripheral cholecystokinin (CCK) [7,18]. These effects have been studied using rats as an animal model and there has been no report on the ghrelin, a peripherally acting orexigenic hormone. Although several neuropeptides exert similar effects in fish and mammals [16,17] and MK-801 also blocks brainstem NMDA receptors in fish [8,11],

the role of the NMDA receptor in feeding behavior of fish has not been well clarified.

The goldfish (*Carassius auratus*) is rapidly becoming a popular model species for pharmacological and neurobehavioral research. We have been extensively investigating the mechanisms responsible for the regulation of feeding behavior by neuropeptides using a goldfish model [reviewed in 16]. In this species, neuropeptide Y (NPY), orexin A and acyl ghrelin induce orexigenic effects, while corticotropin-releasing hormone (CRH), α -melanocyte-stimulating hormone and CCK inhibit appetite [2,12–16,19]. The aim of the present study was to identify whether the NMDA receptor regulates locomotor activity and food intake in the goldfish model. We examined the effect of IP injection of NMDA receptor antagonist, MK-801, on locomotor activity and CCK- and ghrelin-induced modifications of food consumption. A better understanding of the involvement of NMDA receptor in the regulation of feeding behavior may provide a novel homeostatic mechanism.

All animal experiments were conducted in accordance with the University of Toyama guidelines for the care and use of animals. Young goldfish (6–10 g body weight, BW) of both sexes were obtained from a commercial supplier, and kept for 1 week under controlled light/dark conditions (12-h light:12-h dark) in a temperature-regulated fish tank (20–24 °C) before use. The fish were fed with a commercially available granular diet (Tetragold, Tetra GmbH, Herrnteich, Germany, containing 32% protein, 5%

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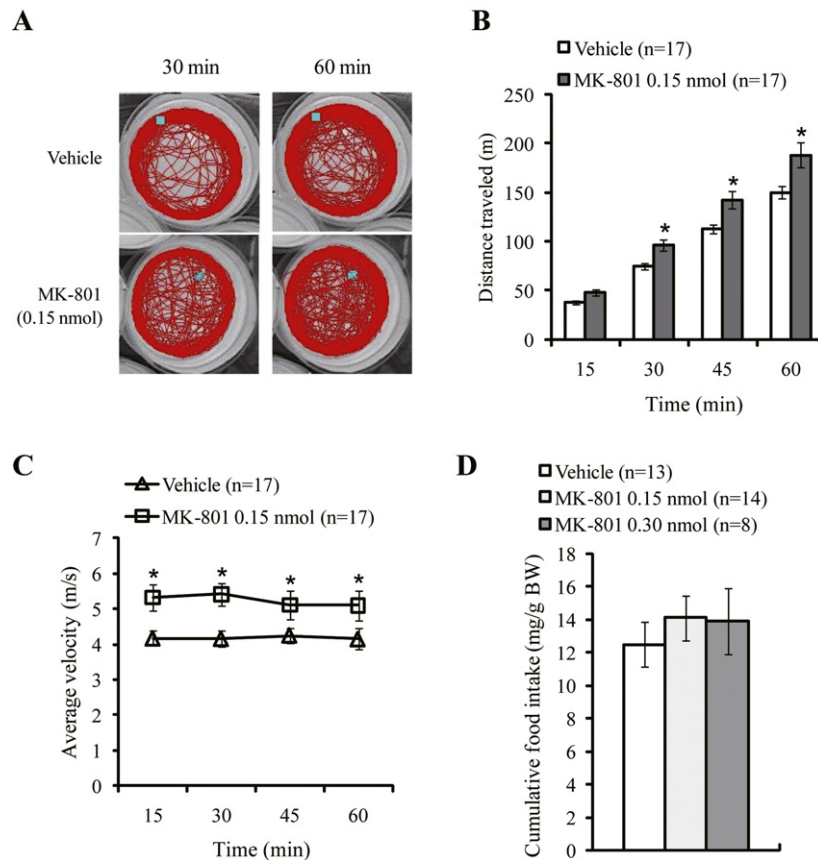


Fig. 1. Effect of blockade of the NMDA receptor on locomotor activity and food intake in goldfish. Panel (A) shows representative top view traces for a goldfish using the video tracking system (Ethovision, Noldus, Netherlands). Panel (B) shows the distance traveled by fish during the experiment. Panel (C) shows the average swimming velocity of fish during the experiment. Panel (D) shows the effect of MK-801 on food intake during 60 min. Each column and bar represent the mean and S.E.M., respectively, and the numbers in parentheses in the legend indicate the number of fish used in each group. The significance of differences at each time point, compared to the vehicle-injected group, was evaluated by ANOVA with Bonferroni's method (* $P < 0.05$).

dietary fat, 2% dietary fiber, 6% minerals and 8% water) once a day at 10 a.m.

Detailed descriptions of the methods used for evaluating the feeding activity of goldfish have been reported previously [12–15]. To test the effect of blockade of the NMDA receptor on feeding, fish were IP-injected with 100 μ L of 50 or 100 ng/g (approximately 0.15 or 0.30 nmol/g) BW MK-801, which was a dose that had been determined to block the NMDA receptor in earlier studies with rats [4,10]. Each fish that had received injections was placed individually in a small experimental tank (diameter 24 cm) containing 4.0 L of tap water, and supplied with food equivalent to 3% of its BW. Food intake was measured at 60 min after treatment. The open field test, which started 15 min after IP injection and lasted 60 min, was performed with a video tracking system for automatic recording of goldfish behavior (EthoVision Pro, Noldus Information Technology, Wageningen, Netherlands).

To test the effect of blockade of the NMDA receptor on the anorexigenic action of IP-injected CCK in goldfish, MK-801 (0.15 nmol/g BW) and sulfated CCK octapeptide (CCK-8s) (100 pmol/g BW) were IP-injected together. The dose of CCK-8s used in the present study had been determined previously to induce significant anorexigenic activity in goldfish [12,19]. To test the effect of blockade of the NMDA receptor on the orexigenic action of IP-injected ghrelin in goldfish, MK-801 (0.15 nmol/g BW) and synthetic acyl ghrelin (10 pmol/g BW) were IP-injected together. The dose of synthetic acyl ghrelin used in the present study had been determined previously to induce significant orexigenic activity in goldfish [14]. Control fish in each experiment were injected with the same volume of saline using the same procedure as that for

the experimental group. After IP injection of the test substances or vehicle solution, food intake during 60 min was measured.

All results are expressed as mean $\pm$ S.E.M. Statistical analysis was performed by one-way or two-way ANOVA with Bonferroni's method. Statistical significance was accepted at the $P < 5\%$ level.

Earlier studies in goldfish had shown that blockade of the NMDA receptor by MK-801 impaired spatial learning or passive avoidance [8,11]. In the present open field test, IP-injection of MK-801 at 0.15 nmol/g BW significantly increased the number of visits to the central zone from 30 to 60 min (Fig. 1A). In addition, the distance traveled and the average swimming velocity of goldfish were significantly increased relative to the vehicle-treated group (Fig. 1B and C). By analogy with the plus-maze test in mammals [22], it would suggest that MK-801 also exerts an anxiolytic effect in the goldfish. However, these behavioral changes were less marked in the goldfish treated with 0.30 nmol/g BW MK-801 (data not shown). Therefore, an IP dose of 0.15 nmol/g BW was selected as the pharmacologically active dose of MK-801 for antagonism of the NMDA receptor in the present study. The less marked effect of a higher dose (0.30 nmol/g BW) of MK-801 on the behavior of goldfish might have been attributable to overt antagonism of the NMDA receptor, as had been observed in rats.

Fig. 1D shows the effect of blockade of the NMDA receptor on food intake in goldfish. The doses of MK-801 (0.15 or 0.30 nmol/g BW) used in this study had been shown to block NMDA receptor in earlier studies with rats [4,10]. The cumulative food intake during 60 min did not differ significantly between the vehicle- and MK-801 (0.15 or 0.30 nmol/g BW)-treated groups (Fig. 1D). This observation is contrary to results obtained using rats and may suggest that the

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