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Rapid communication

Suppression of feeding-evoked dopamine release in the rat nucleus accumbens by the blockade of P_2 purinoceptors

Holger Kittner [a,*], Ute Krügel [a], Ibrahim M. El-Ashmawy [b], Peter Illes [a]

[a] *Rudolf-Boehm-Department of Pharmacology and Toxicology, Universität Leipzig, Härtelstrasse 16-18, D-04107 Leipzig, Germany*
[b] *Department of Pharmacology, Faculty of Veterinary Medicine, University of Alexandria, Alexandria, Egypt*

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Abstract

In order to investigate whether endogenous adenosine 5′-triphosphate (ATP) is involved in the regulation of feeding, the influence of the P_2 receptor antagonist pyridoxalphospate-6-azophenyl-2′,4′-disulphonic acid (PPADS) infused into the rat nucleus accumbens on 18-h food-deprived feeding was tested. PPADS suppressed the feeding-induced dopamine release and reduced the amount of food consumed as well as the time of feeding. These results indicate that activation of P_2 purinoceptors by endogenous ATP facilitates feeding behaviour and contributes to the feeding-associated dopamine release.

Keywords: P_2 purinoceptors; ATP; Feeding behaviour

The mesolimbic–mesocortical dopamine system plays an important role in the regulation of feeding behaviour. There is a considerable evidence for an association between feeding and the release of dopamine in the nucleus accumbens (Westerink et al., 1994; Stratford and Kelley, 1997). Furthermore, feeding can be evoked by dopamine releasing compounds (Winn et al., 1982), whereas lesion of midbrain dopamine neurons may result in hypophagia (Ungerstedt, 1971).

Previous in vivo studies showed that endogenous adenosine 5′-triphosphate (ATP) as well as exogenously applied ATP analogues facilitate dopaminergic mechanisms (Krügel et al., 1999). Infusion of the ATP analogue 2-methylthio ATP into the nucleus accumbens of rats increases the extracellular level of dopamine. The P_2 purinoceptor antagonist pyridoxalphospate-6-azophenyl-2′,4′-disulphonic acid (PPADS) abolished this effect and decreased the basal level of dopamine when given alone.

The aim of the present study was to investigate whether endogenous ATP acting via P_2 purinoceptors is involved in the regulation of feeding. For this purpose, a microdialysis approach monitoring the feeding-evoked release of dopamine in the nucleus accumbens and the feeding behaviour was chosen.

Male Wistar rats (WIST/Lei) weighing 250–300 g were anesthetized with a mixture of ketamine (100 mg/kg) and xylazine (5 mg/kg) and underwent implantation of the microdialysis guide cannulas (CMA 12; CMA, Solna, Sweden). The guides were placed into the left nucleus accumbens at coordinates relative to bregma *A*: +1.7 mm; *L*: 1.5 mm; *V*: 5.2 mm and fixed with dental cement. Microdialysis probes (CMA 12, effective length 2 mm, cut off: 20,000 Da) were perfused with artificial cerebrospinal fluid (aCSF) at a flow rate of 2 μl/min and inserted via the guide cannulas. Samples were collected every 10 min and analysed for dopamine with a HPLC-electrochemical detection system (Antec, Leyden, Netherlands). Details of the method have already been reported (Krügel et al., 1999). All experiments were approved by the Committee on Animal Care and Use of the relevant local governmental body.

Six to seven days after surgery, the rats were trained to eat food pellets (altromin 1326, Altromin, Lage, Germany) after 18 h of food-deprivation, while being given free access to water. At 16.00 h, on the day prior to the first training day, all food was removed from the animal cages. After the first 18-h food-free interval, the animals had the opportunity to eat from 10.00 until 16.00 h, the beginning of the second 18-h food-free period. During the microdialysis experiment on the following day, rats had access to

* Corresponding author. Tel.: +49-341-972-4627; fax: +49-341-972-4609.
E-mail address: kith@medizin.uni-leipzig.de (H. Kittner).

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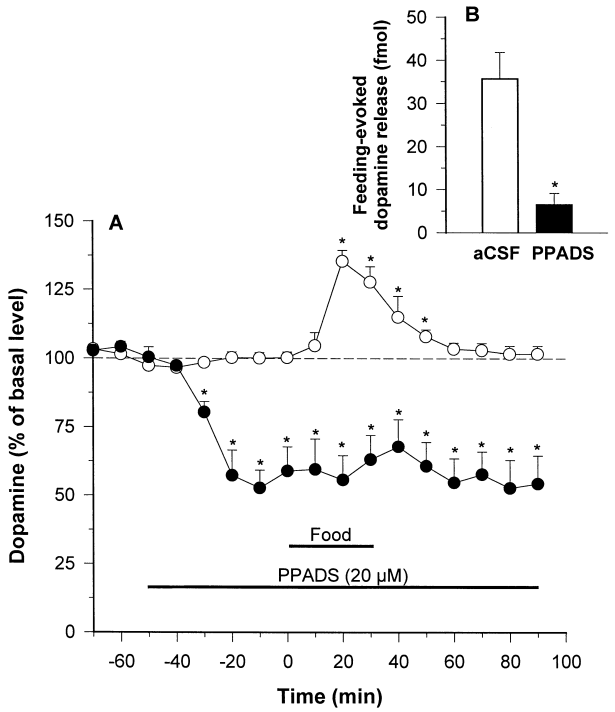

Fig. 1. Effect of PPADS on the feeding-induced dopamine (DA) release in the rat nucleus accumbens. (A) Effect of deprivation-induced feeding on the extracellular concentration of DA in the nucleus accumbens of controls perfused with aCSF (open circles) and during perfusion with PPADS (20 μM; closed circles). Horizontal bars indicate food ingestion or perfusion with PPADS. Data are presented as a percentage of the basal DA level, which was defined as the mean of three consecutive samples differing by less than 10%. The basal value in fmol/DA sample was 41.7 ± 5.5 (means ± S.E.M. of 10 rats). Each symbol represents the mean ± S.E.M. from five animals. $^{*}P < 0.05$; significant differences versus the basal level of dopamine (repeated measure ANOVA on ranks followed by the Student–Newman–Keuls test). Feeding failed to alter the level of dopamine in the presence of PPADS ($P > 0.05$). (B) Total amount of dopamine release induced by feeding during perfusion with aCSF or PPADS. Data are presented as fmol DA recalculated from the respective basal dopamine release (part A, this figure). Each column represents the mean ± S.E.M. of five independent experiments. $^{*}P < 0.05$; significant difference versus the control (Mann–Whitney rank sum test).

food for 30 min. After that, the food was removed while the rats were kept in the cage for the remainder of the experiment.

Under these conditions, the control rats, whose nucleus accumbens were perfused with aCSF consumed 2.3 ± 0.2 g over a mean time of 12.8 ± 0.7 min resulting in an increase of the extracellular dopamine concentration by about 35% of the basal level (Fig. 1A). A significantly increased dopamine level was observed in the second sample during feeding which lasted up to the next three samples (Fig. 1A). Infusion of PPADS (20 μM) into the nucleus accumbens over 50 min prior to feeding and continued throughout the experiment caused a suppression of ingestive behaviour. Food intake as well as the feeding time were significantly reduced to 1.8 ± 0.17 g and 6.9 ± 0.5 min, respectively. PPADS decreased the basal dopamine concentration up to 50% and almost blocked the feeding-induced increase of dopamine release (Fig. 1A). The total amount of feeding-evoked dopamine release was clearly depressed by PPADS (Fig. 1B).

PPADS is a highly selective P_2 purinoceptor antagonist (Lambrecht et al., 1992), which is supposed not to interfere with the effect of nonpurinergic neurotransmitters possibly involved in feeding behaviour. Hence, these results indicate that P_2 purinoceptors activated by endogenous ATP are involved in the regulation of food intake although the underlying mechanisms are still unknown. It has been shown that inhibition of the GABAergic medium-sized spiny projection neurons in the shell region of the nucleus accumbens facilitates feeding (Stratford and Kelley, 1997). It is conceivable that endogenous ATP can inhibit these neurons acting via an enhancement of dopaminergic mechanisms. PPADS may inhibit this facilitatory effect of ATP and may, in addition, shift the balance between ATP and its degradation product adenosine towards the latter compound. Adenosine has been shown to inhibit the release of dopamine in the nucleus accumbens (Krügel et al., 2000) as well as the opioid-induced feeding behaviour in rats (Wager-Srdar et al., 1984).

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