Antagonism of 2-deoxy-D-glucose-induced hyperphagia by naloxone: possible involvement of endorphins

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It has been shown that naloxone inhibits food consumption in rats (Holtzman 1974). Moreover, β-endorphin stimulates food intake in satiated rats after injection into the ventromedial hypothalamus (Grandison & Guidotti 1977) and further evidence has also been presented implicating this endogenous opioid in the development of overeating and obesity in genetically obese mice (ob/ob) and rats (fa/fa) (Margules et al 1978). When 2-deoxy-D-glucose (2-DG) is administered either systemically (Zigmond & Stricker 1972) or centrally in rats (Muller et al 1973) it increases food intake through blockade of glycolysis, though the precise mechanism or neurohumoral factor(s) mediating this response remain unclear, since 2-DG releases a number of hormones (Smith & Root 1969) which are capable of inducing hyperphagia (Bray 1974). β-Endorphin has been shown to be released along with other hormones (Guillemin et al 1977) so the possibility exists that 2-DG induced hyperphagia may be attributable to the release of β-endorphin. Hence the present experiments were designed to test such a possibility by examining the effects of an opiate antagonist on hyperphagia and we report that naloxone antagonizes 2-DG-induced feeding.

Male Wistar rats, 180–200 g, were housed individually in wire mesh cages at constant temperature (22.0 ± 1.0 °C) on a 12 h light-dark cycle at least 3 days before experimentation. They were allowed free access to 41B pellet diet and tap water and were randomly assigned to 3 groups on the day of experiment. Each group received one of the following treatments on a random basis: (i) no treatment (ii) vehicle + vehicle (iii) vehicle + 2-DG or (iv) naloxone + 2-DG and each experiment was separated by 3 days non-treatment.

Experiments were performed between 10.00–16.00 h, when food intake was minimal. At the commencement of each experiment animals were weighed and treated with 2-DG or vehicle intraperitoneally (i.p.) at 10.00 h followed by naloxone (1.0 mg kg⁻¹) or vehicle subcutaneously (s.c.) at 10.45 h. A weighed quantity of food was given at 11.00 h (time zero) and food intake was measured hourly thereafter for at least 4 h.

In an additional investigation, nociceptive sensitivity was assessed by measuring reaction times in seconds over a 4 h period using the cord immersion test at 55 °C (Sewell & Spencer 1976). This test displays sensitivity to a wide range of opiate agents and has the inherent advantage of differentiating agonists from partial agonists.

2-DG induced marked sedation, stupor and ataxia and these behavioural effects were observed for the

initial 2 h after treatment. A significant hyperphagia was produced by all doses of 2-DG in the second hour after injection compared with vehicle treated and non-treated controls and the injection of vehicle did not significantly modify food intake compared with non-treated animals ($P < 0.05$). Administration of naloxone significantly attenuated ($P < 0.001$) 2-DG (325 mg kg⁻¹ i.p.) hyperphagia for the initial 2 h period but in the 3rd h there was no difference in the food intake of both groups. However, in the fourth h the naloxone treated group ate significantly more ($P < 0.001$) than the 2-DG group treated with vehicle. In the group treated with 2-DG (487.5 mg kg⁻¹ i.p.) naloxone significantly reduced ($P < 0.001$) food intake only in the first h, but in the subsequent 3rd h food intake did not vary to any significant degree (see Fig. 1). In the animal group treated with the highest dose of 2-DG (750 mg kg⁻¹
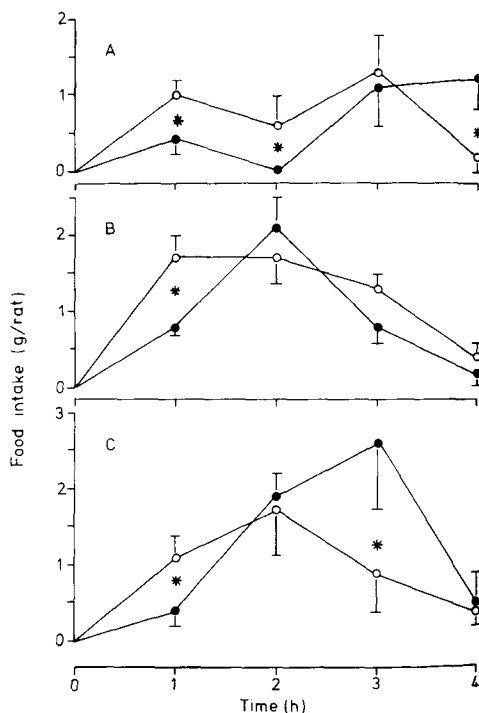

FIG. 1. Effect of naloxone (1.0 mg kg⁻¹ s.c.) (—●—) or vehicle (—○—) on 2-deoxy-D-glucose (i.p.) induced food intake in satiated rat. Each point represents the mean ± s.e. of 5 animals. (A) 375 mg kg⁻¹ 2-DG, (B) 487.5 mg kg⁻¹ 2-DG, (C) 750 mg kg⁻¹ 2-DG. Significance of difference between points was evaluated using Student's t (* $P < 0.001$)
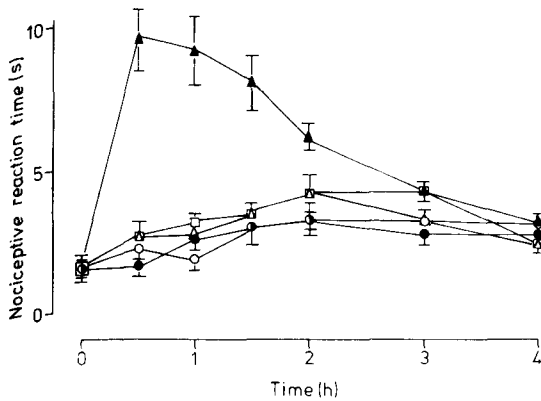
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FIG. 2. Antinociceptive effects of 2-DG (750 mg kg^{-1} i.p.) plus vehicle (s.c.) (—●—), 2-DG (750 mg kg^{-1} i.p.) plus naloxone (1·0 mg kg^{-1} s.c.) (— ○ —), vehicle (i.p.) plus vehicle (s.c.) (—□—), morphine (2·5 mg kg^{-1} i.p.) plus vehicle (s.c.) (— ▲ —), morphine (2·5 mg kg^{-1} i.p.) plus naloxone (1·0 mg kg^{-1} s.c.) (— △ —) in the cord immersion test (55 °C) in rats. Each point represents the mean ± s.e. of 5 animals.

i.p.) naloxone markedly attenuated food intake in the first h ($P < 0.001$) but in the second h there was no detectable difference. However, in the 3rd h the naloxone-treated group ate much more ($P < 0.001$) than the vehicle plus 2-DG group, which represented a compensation for the food lost in the first h. It was also observed that naloxone completely reversed the depressant effects of all doses of 2-DG immediately after its administration.

2-DG (750 mg kg^{-1} i.p.) had no significant effect on nociceptive sensitivity compared with vehicle-treated controls in the cord immersion test and this finding was not modified by combined injection of naloxone (1·0 mg kg^{-1} s.c.) (see Fig. 2). However morphine (2·5 mg kg^{-1} i.p.) produced marked antinociceptive activity which was abolished by naloxone (1·0 mg kg^{-1} s.c.) to levels that were not significantly different from saline-treated controls.

From the results it is possible that, since naloxone antagonizes the hyperphagia induced by 2-DG, some endogenous opioid substance might be involved. This is strengthened by the observation that the pituitary peptide β-endorphin increases food intake, an effect that is antagonized by both naloxone and naltrexone

(Grandison & Guidotti 1977; Margules et al 1978). Thus it is clear that the opiate receptor is involved in the hyperphagic effect of both β-endorphin and 2-DG. Hence it is a possibility that the opioid substance that mediated 2-DG hyperphagia might be β-endorphin. In addition, the depressant effects of 2-DG observed in the present experiments and also of β-endorphin (Bloom et al 1976) are reversed by naloxone indicating a similarity in their depressant activities. Moreover, another resemblance between the actions of 2-DG and centrally injected β-endorphin is that both agents cause marked hypothermia at some stage after administration (Muller et al 1973; Bloom et al 1976).

It is likely that impairment of glucose availability to the cell, as in the case of treatment with 2-DG, might lead to the release of an endogenous opioid. Under these circumstances it is somewhat surprising to discover that 2-DG is not analgesic at the hyperphagic doses employed since β-endorphin produces analgesia (Bloom et al 1976). However, it is possible either that only minimal amounts of endogenous opioid are released which are sufficient to modify food intake but insufficient to gain access to brain areas involved in nociception or that the substance in question is a non analgesic opioid peptide.

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