CANNABINOIDS (CB₁) RECEPTOR ANTAGONIST AM 251, CAUSES SUSTAINED REDUCTIONS IN DAILY FOOD INTAKE

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CB₁ receptors are expressed throughout the central and peripheral nervous system including the hypothalamus and gastrointestinal tract. Central and peripheral administration of CB₁ agonists increases food intake while CB₁ antagonists reduce food intake. However, tolerance to the anorectic effects of CB₁ antagonists develops within days. In order to further delineate the role of endogenous cannabinoid signalling in feeding behaviour we studied the effects of the CB₁ receptor antagonist AM 251, the anandamide membrane transport inhibitor (AMT) VDM 11, and the CB₁ agonist methanandamide on food intake.

In experiment I male retired breeder Lewis strain rats (n=8) weighing between 440-500g at the beginning of the study were given either AM 251 (1.25, 2.5 or 5mg/kg), VDM 11 (10mg/kg) or vehicle according to a counter balance design. Food was available from 16:00 to 17:00 hours (pre-feed) and 18:00 to 09:00 hours daily. Water was freely available at all times. Food intake was measured for the next three hours as well as daily for the next seven days. Changes in body weight were also monitored daily. Each animal was given a single dose of each drug each seven days apart. In experiment II a second group of rats (n=8) weighing between 462g and 502g at the beginning of the study were randomly assigned into either methanandamide or vehicle conditions according to a latin square design. Food and water were available as previously described.

AM 251 (5mg/kg) reduced food intake one hour after administration (AM 251 NO INTAKE vs. CONTROL 3.6 g ± 0.6g; p < .05). Reductions in feeding brought about by a single dose of the drug continued to be significant for the next six days (AM 251 47.9 ± 1.3g/day vs. CONTROL 59.5 ± 1.4g/day, p < .05). Reductions in cumulative weight gain were significant for the next seven days (AM 251 2.3 ± 3.4g; CONTROL 23.0 ± 1.4g; p < .05 vs.). Contrary to our initial expectations, VDM 11 transiently reduced food intake during the third hour of testing (VDM 11 12.0 ± 1.6g vs. CONTROL 13.8 ± 1.0g; p < .01). Consistent with previous literature, methanandamide significantly increased food intake after three hours (METHANANDAMIDE 16.2 ± 1.5g vs. CONTROL 11.6 ± 1.5g; p < .05). To confirm the anorectic effect of AM 251 was dose-dependent we administered two additional doses (1.25mg/kg; 2.5mg/kg) of the drug as previously described in rats (n=8) weighing between 469-520g at the start of the study. Rats given a single 2.5 mg/kg dose of AM 251 ate significantly less over the next six days relative to vehicle conditions (p < .05). In contrast rats given 1.25mg/kg of the drug ate significantly less only on the day of administration (p < .01).

A single administration of the CB₁ receptor antagonist AM 251 decreases food intake and body weight much longer than previously reported. The AMT inhibitor only transiently decreased food intake, while the CB₁ agonist methanandamide increased it. These data support a role for endocannabinoids in the control of food intake. Future research will be needed to understand how the effect of AM 251 on food intake is maintained so long after administration.