Prokineticin 2 potently inhibits food intake in rodents and is a potential new target for the development of anti-obesity drugs

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Background: The prokineticins are cysteine-rich secreted proteins involved in regulating gastrointestinal motility, spermatogenesis, neurogenesis and circadian rhythms. Prokineticin 2 (PK2) is highly expressed in the suprachiasmatic nucleus and prokineticin receptors are expressed in hypothalamic regions involved in energy homeostasis, including the arcuate nucleus (ARC) and paraventricular nucleus (PVN). However, the role of PK2 in the regulation of food intake and body weight is not known.

Aim: To investigate the role of PK2 in appetite regulation.

Methods/Results: Intracerebroventricular (ICV) administration of PK2 (1.5nmol per rat) reduced 0-1 hour food intake by 86% in ad libitum fed rats and induced a significant reduction in 24 hour food intake. This effect was specific; ICV PK2 did not affect locomotor activity or behaviour nor did it alter energy expenditure. Immunoblockade of PK2 by ICV administration of anti-PK2 IgG resulted in a 6-fold increase in food intake at 2-4 hours post-injection. Fasting reduced hypothalamic PK2 mRNA expression by 45% in 12-hour fasted and 44% in 24-hour fasted rats suggesting a physiological role for PK2 in appetite regulation. ICV administration of PK2 in rats resulted in c-fos expression, suggesting neuronal activation, in the supraoptic nucleus, ARC, PVN and anterior hypothalamic area. Direct injection of PK2 into these hypothalamic sites potently reduced food intake, suggesting that the anorectic effects of PK2 may be mediated via these hypothalamic areas. Treating hypothalamic explants with PK2 significantly increased α-melanocyte stimulating hormone (α-MSH) release. ICV co-administration of PK2 and agouti-related protein (AgRP) (an antagonist of α-MSH receptors) attenuated the anorectic effect of PK2, suggesting that the ARC melanocortin system mediates the anorectic effects of PK2. In accord with this, following ICV PK2 administration, 64% of c-fos-expressing neurones in the ARC were α-MSH-producing neurones. Peripheral administration of PK2 twice daily for 5 days in lean and obese mice significantly reduced food intake with no evidence of tachyphylaxis, resulting in a significant reduction in body weight in both types of mice.

Conclusions: We have shown for the first time that PK2 potently reduces food intake and that endogenous PK2 may play a physiological role in appetite regulation. Our work identifies PK2 as a novel target for the development of anti-obesity agents.