Orexigen-sensitive NPY/AgRP pacemaker neurones in the hypothalamic arcuate nucleus

Van den Top M, Lee K, Whyment AD, Blanks AM, Spanswick D
Department of Biological Sciences, University of Warwick, Coventry, UK

The hypothalamic arcuate nucleus (ARC) integrates and responds to satiety and hunger signals and forms the origins of the central autonomic response to perturbations in energy balance. Here we show that orexigens induce pacemaker activity in rat ARC Neuropeptide Y and Agouti-related protein (NPY/AgRP)-expressing neurones, whilst these neurones are inhibited by the anorexigen leptin.

Whole cell patch-clamp recordings were obtained *in vitro* from single neurones maintained in rat hypothalamic slice preparations. We have identified a functionally and pharmacologically distinct subpopulation of ARC neurones henceforth referred to as pacemaker neurones. These neurones were located in the medial ARC, proximal to the third ventricle and were characterised by their unique electrophysiological properties, compared to other ARC neurones. These properties include anomalous inward rectification in conjunction with a transient outward rectifying conductance (I_{TR}). Significantly, and in contrast to other cell types in the ARC (n=88), orexigenic signals ghrelin (100-500 nM) and orexin (50-200 nM) induced characteristic pacemaker-like activity (n=15). Pacemaker activity comprised of regular bursts of action potentials superimposed on underlying oscillations in membrane potential that could be induced by orexigens in the presence of tetrodotoxin (TTX). In contrast to orexigenic signals, the anorectic hormone leptin (50 nM, 30 min) induced a gradual inhibition of pacemaker neurones. Utilising single-cell RT-PCR the expression of receptors for ghrelin, leptin and both orexin receptors was confirmed in pacemaker neurones.

Blocking I_{TR} utilising 4-Aminopyridine (4-AP), increased the frequency of oscillations in the presence of TTX from 34±7 mHz in control to 52±6 mHz (n=3). In the presence of 4-AP, pacemaker neurones were found to express a T-type calcium-like conductance. The application of nickel abolished membrane potential oscillations underlying pacemaker activity in all neurons tested (n=3).

Thus here we demonstrate a neuron-specific signalling mechanism through which central and peripheral hunger and satiety signals engage the central neural anabolic drive.

Marco van den Top, Department of Biological Sciences, Gibbet Hill Campus, University of Warwick, Coventry, CV4 7AL, UK, t 44 2476 572538, e-mail mvandentop@bio.warwick.ac.uk

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