

PERIPHERAL INSULIN ACTING ON OXYTOCIN NEURONS IN VIVO.*Luis Paiva¹, Gareth Leng²*¹Centre for Discovery Brain Sciences, University of Edinburgh, UK.²

Insulin is widely known for its role in glucose homeostasis on peripheral tissues, but its central effects are not yet fully elucidated. Once secreted into circulation, insulin is transported into the brain by a saturable transport mechanism. In the brain, several regions have been reported to be sensitive to insulin, including the prefrontal cortex, hippocampus, and hypothalamus. The insulin receptor is abundantly expressed in the supraoptic nucleus of the hypothalamus (SON) which exclusively contains magnocellular oxytocin and vasopressin neurons. In addition to its classical roles in reproduction, oxytocin is also involved in energy homeostasis: both central and peripheral administration exerts anorexigenic effects and increases energy expenditure. Interestingly, clinical reports indicate that patients with diabetes mellitus exhibit lower plasma oxytocin, suggesting a potential relationship between insulin and the secretory activity of magnocellular neurons. This study investigates the effect of systemically administered insulin on the electrical activity of oxytocin neurones *in vivo*. Fasted male Sprague-Dawley rats were anaesthetised with an intraperitoneal injection of urethane (1.25 g/kg); a femoral vein and the trachea were cannulated and the pituitary stalk and right SON were exposed transpharyngeally. A recording microelectrode was placed into the SON to record the extracellular activity of single neurons and a bipolar stimulating electrode was placed on the neural stalk for antidromic identification of SON neurons. Oxytocin neurons were distinguished from vasopressin neurons by their firing pattern and by their opposite response to intravenous (i.v.) cholecystokinin (CCK, 20 µg/kg). Responses to i.v. insulin were analysed by comparing the mean firing rate in the 60-min after insulin with the (basal) firing rate over the 20-min control period, using two-tailed Wilcoxon signed-rank test. I.v. administration of insulin (0.75 IU/kg) increased the firing rate in oxytocin neurons (mean change: 1.6 ± 0.3 spikes/s; $^{**}P < 0.01$; $n = 10$), and this response was prevented by the intracerebroventricular administration of the insulin receptor antagonist S961 (mean change: -0.01 ± 0.1 spikes/s; $P = 1.00$; $n = 8$), but not by the infusion of i.v. glucose (mean change: 1.6 ± 0.4 spikes/s; $n = 5$). These results show that systemic administration of insulin enhances the electrical activity of oxytocin magnocellular neurons of the SON by activation of central insulin receptors.

Financiamiento: This work was supported by the European Commission Seventh Framework Programme for research, technological development, and demonstration (Grant 607310; Nudge-it), and the Biotechnology and Biological Sciences Research Council of the UK (BBSRC; BB/S000224/1).