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Research Report

Effects of central gastrin-releasing peptide on glucose metabolism

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ABSTRACT

Gastrin–releasing peptide (GRP) mediated signals in the central nervous system (CNS) influence many functions associated with energy metabolism. The purpose of the present study was to investigate the central effect of GRP on glucose metabolism in the male rat. Intracerebroventricular (icv) administration of GRP caused an immediate hyperglycaemia which was sustained till the end of the infusion. The rise in plasma glucose levels was accompanied by an increase in endogenous glucose production (EGP), as well as increases in plasma glucagon and insulin concentrations. Furthermore, no differences in plasma corticosterone levels were noted between control and GRP treated rats. These results demonstrate that central GRP increases plasma glucose levels, probably by stimulating pancreatic glucagon release and concomitantly or subsequently endogenous glucose production.

1. Introduction

The plasma glucose concentration results from a coordinated regulation of glucose input (food intake, hepatic glucose production) and its utilization (uptake by skeletal and cardiac muscles, brain and adipose tissues). Plasma glucose concentrations show a daily rhythm that is maintained by the circadian clock in the suprachiasmatic nuclei of the hypothalamus (SCN), in both nocturnal and diurnal mammals (Kumar Jha et al., 2015). The SCN transmit their timing signals via the

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autonomic nervous system through hypothalamic relay structures, such as the hypothalamic paraventricular nucleus (PVN) and the orexin-containing neurons in the perifornical area (PF). Activation of these nuclei by SCN signals causes hyperglycemia via sympathetic inputs to the liver (Kalsbeek et al., 2004; Yi et al., 2009). Therefore, time-of-day dependent excitatory and inhibitory signals from the SCN to PVN and PF help to maintain the daily rhythm of plasma glucose concentration (Alam et al., 2005; Kalsbeek et al., 2008; Yi et al., 2009).

In addition to orexin, many other neuropeptides have been implicated in the brain control of glucose homeostasis (Brown, 1981; Plamondon and Merali, 1993; van Loon and Appel, 1981). Also the SCN itself contains a number of neuropeptides that show a daily rhythm in their release pattern, such as arginine vasopressin (AVP) and vasoactive intestinal peptide (VIP), but also gastrin-releasing peptide (GRP) (Aoyagi et al., 2007; Bechtold et al., 2008; Chun et al., 1998; Francl et al., 2010; Kalsbeek et al., 2010; Karatsoreos et al., 2006; Nagai, 2004). These neurotransmitters might communicate time-cues to metabolic organs via nervous and humoral signals in order to regulate metabolic homeostasis and its daily rhythmicity. Indeed, deletion of the AVP receptor V1a leads to impaired glucose homeostasis in these knock-out mice, whereas mice lacking VIP or the VIP receptor VPAC2 express disrupted behavioral and metabolic rhythms (Aoyagi et al., 2007; Bechtold et al., 2008; Hannibal et al., 2011). GRP is a 27-amino acid neuropeptide and is a mammalian homolog of the amphibian tetradecapeptide bombesin (Bn). It acts by binding to the GPR receptor (GRP-R, a G protein-coupled receptor also known as BB2). The GPR-R preferentially binds GRP (Roesler and Schwartsmann, 2012). GRP-mediated signals influence many functions in the central nervous system, including food intake, glucose metabolism and body weight. In particular, intracerebroventricular (icv) infusions of Bn and Bn-like peptides have been shown to induce anorexia, hypothermia and hyperglycemia in rats (Brown et al., 1977a, 1977b; Plamondon and Merali, 1993; Plamondon et al., 1998; Tsushima and Mori, 2005). GRP-containing neurons originating in the SCN project to the PVN, which is an integrator of SCN signals and other metabolic cues (Kalsbeek et al., 1993). Additionally, both peripheral and central administration of Bn strongly activates PVN neurons, as shown by increased c-FOS staining (Li and Rowland, 1996; Kallingal and Minz, 2014). This Bn-induced activation of PVN is lacking in GRP-R KO mice (Ladenheim et al., 2002). In addition, both GRP-R levels and its binding exhibit a daily rhythm in the mouse SCN, with an acrophase at the beginning of the activity period (Karatsoreos et al., 2006).

In the present study, we investigated the possible involvement of GRP in the control of the plasma glucose homeostasis using icv infusions of GRP and the stable isotope dilution technique to determine endogenous glucose production (EGP).

2. Results

Experiments were conducted according to the experimental protocol outlined in Fig. 1. The icv infusion of GRP resulted in a marked elevation of blood glucose levels (*Infusion* $F_{1,140}=16.143$, $p=0.001$; *Time* $F_{10,140}=9.677$, $p<0.001$; *Infusion*Time* $F_{10,140}=5.537$; $p<0.001$, Fig. 2). Post-hoc analysis showed that GRP administration increased blood glucose levels at all-time points ($t=130$ to $t=270$) from the beginning till the end of the infusion ($p<0.05$).

The observed GRP-induced hyperglycemia could be established via different mechanisms. In order to better understand this mechanism, we simultaneously determined endogenous glucose production (EGP), using the stable

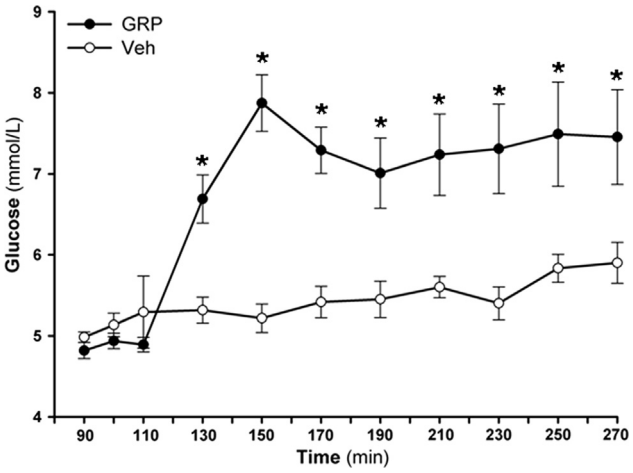

Fig. 2 – Changes in blood glucose concentration during icv infusion of GRP. The icv infusion of GRP significantly increases blood glucose levels. Veh, vehicle. Data are presented as mean ± SEM. *$p<0.05$.

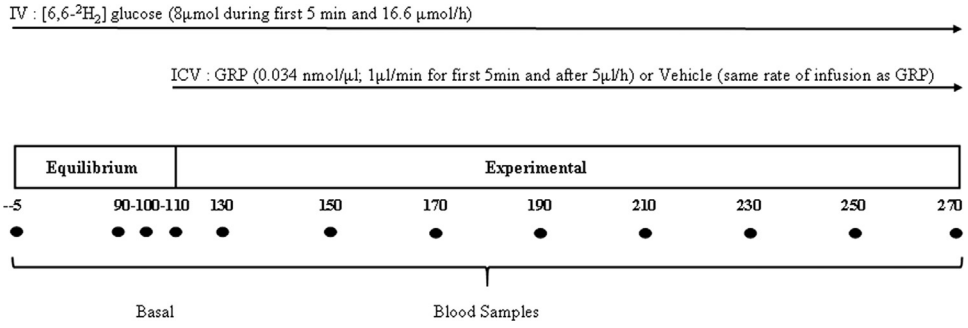

Fig. 1 – Experimental protocol showing the time line of the infusions (IV and ICV) and the timing of blood sampling. The numbers above the black dots indicate the timing of blood sampling in minutes.