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BRAIN RESEARCH

Research Report

Leptin modulates noradrenaline release in the paraventricular nucleus and plasma oxytocin levels in female rats: A microdialysis study

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ABSTRACT

The neural control and mutual interrelationships among individual factors involved in the regulation of food intake and simultaneously related to reproduction are far from being understood. We have suggested that at least some of the effects of orexigenic and anorexigenic peptides might be mediated via noradrenalin release in the paraventricular nucleus (PVN). The main hypothesis was that leptin has an inhibitory action on oxytocin secretion and hypothalamic release of noradrenalin. Non-pregnant female rats in their diestrus were subjected to cannulation of the carotid artery and a microdialysis procedure with the probes in the hypothalamic PVN. Intra-arterial administration of cholecystokinin-8 (CCK) at the dose of 50 mg/kg was used to induce oxytocin and noradrenalin release. Leptin (10 mg/5 ml) was intracerebroventricularly injected in addition to CCK. Blood and microdialysis samples were collected at 20-min intervals for 80 min. Central administration of leptin significantly reduced both plasma oxytocin and hypothalamic noradrenalin responses to CCK at 20 min following the treatments. In conclusion, leptin may inhibit oxytocin secretion by lowering noradrenergic neurotransmission in the PVN. The modulator effect of leptin on noradrenalin release in the PVN may be related to feeding behavior.

1. Introduction

Oxytocin is a peptide synthesized in magnocellular neurons of the supraoptic (SON) and paraventricular (PVN) nuclei in the hypothalamus, transported to the posterior pituitary and released into the circulation. Oxytocin is produced also in some neurons of the parvocellular subdivision of the PVN (pPVN), which project to other brain regions such as the brain stem, medulla, and cortex. Within the brain, oxytocin is known to act as a neuromodulator or neurotransmitter (Landgraf and Neumann, 2004).

Oxytocin production in the hypothalamus and its secretion from the posterior pituitary is under the control of several brain neurotransmitters. It is well established that brain

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catecholamines and particularly noradrenalin, exert a stimulatory action on magnocellular oxytocin neurons in the SON and PVN. For example, injection of noradrenalin into the lateral ventricle activates oxytocin neurons in the PVN (Ji et al., 1998). In whole cell recordings, noradrenalin administration was found to induce depolarization of magnocellular neurons via α1-adrenergic receptors and to increase the excitatory postsynaptic potential *in vitro* (Daftary et al., 1998). The A2 noradrenergic cell group in the nucleus tractus solitarius (NTS) projects directly to oxytocin neurons in the hypothalamus (Day and Sibbald, 1988), and stimulation of these cells led to specific activation of oxytocin neurons (Raby and Renaud, 1989).

The release of oxytocin is increased not only in parturition and lactation, but also during stress (Jezova et al., 1995) and next to its unambiguous role in processes related to reproduction, oxytocin is nowadays known to influence several other physiological functions, such as the activity of the cardiovascular system (Petersson, 2002; Bakos et al., 2007). Moreover, there is accumulating evidence on the involvement of oxytocin in the control of food intake. As an anorexigenic peptide, oxytocin is thought to participate in neuroendocrine mechanisms leading to hyperphagia during pregnancy (Douglas et al., 2007). Oxytocin influences the food intake in concert with the action of several other peptides involved in central, satiety and/or adiposity signals (Valassi et al., 2008), such as leptin and ghrelin.

Leptin is a peptide secreted from adiposities, which has been shown to participate in the regulation of metabolism, feeding behavior and energy balance (Wolf, 1996; Jéquier, 2002). Leptin can cross the blood brain barrier and easily spread to several brain areas such as cortex, thalamus, hypothalamus and cerebellum (Banks et al., 2000; Kurrimbux et al., 2004). Leptin receptors are localized particularly in the hypothalamus (Matsuda et al., 1999). The reproductive system appears to be another main target for the actions of leptin. It has been reported that leptin has an important role in the initiation of puberty (Mantzoros et al., 1997). A suppression of leptin secretion was observed during lactation (Pickavance et al., 1998; Brogan et al., 1999). Leptin was found to stimulate gonadotropin (Yu et al., 1997; Henry et al., 2001) as well as vasopressin secretion (Yamamoto et al., 1999). However, studies looking into the effects of leptin on oxytocin secretion are quite limited. Previous reports showed either no effects on plasma oxytocin level and oxytocin gene expression in the SON (Yamamoto et al., 1999) or an inhibitory action of leptin on firing of oxytocin cells in the SON in vitro (Honda et al., 2002).

The neural control and mutual interrelationships among individual factors involved in the regulation of food intake and simultaneously related to reproduction are far from being understood. We have suggested that at least some of the effects of orexigenic and anorexigenic peptides might be mediated via noradrenalin release in the PVN. In non-pregnant female rats, we have tested the following hypothese: leptin has an inhibitory action on oxytocin secretion mediated via hypothalamic release of noradrenalin. To evaluate potential inhibitory action of leptin, we have decided to use a model of cholecystokinin-8 (CCK) induced oxytocin release as it is well known that systemic administration of CCK increases electrical activity of oxytocin cells (Leng et al., 1991) and induces oxytocin release into the circulation (Ueta et al., 1993; Onaka et al., 1995). CCK-induced excitation of oxytocin cells is accompanied by concomitant increase in noradrenalin release within the PVN (Kendrick, 1991; Ueta et al., 2000).

2. Results

Noradrenalin concentrations in the microdialysis samples were significantly higher in the CCK group compared to those in the vehicle-treated group at 20 min following CCK injection ($p<0.001$, Fig. 1). There were no significant differences between the values in these two groups at the subsequent time intervals. Central administration of leptin significantly reduced noradrenalin response to CCK at 20 min following the treatments. An inhibitory action of leptin was evident also at 40 min ($p<0.01$). DHPG concentrations did not differ significantly between any of the treatment groups studied and therefore the values are not presented.

Treatment with CCK resulted in increased oxytocin secretion throughout the whole experimental period (Fig. 2). However, these increases were statistically significant only at 20- and 40-min time intervals compared to the vehicle-treated rats ($p<0.05$, Fig. 2). Oxytocin response to CCK was significantly reduced by concomitant ICV treatment with leptin at 20 min ($p<0.05$). No significant differences in oxytocin levels between the groups were observed at the other sampling intervals studied.

3. Discussion

The results of this study obtained in female rats demonstrate that leptin inhibits CCK-induced oxytocin secretion into the

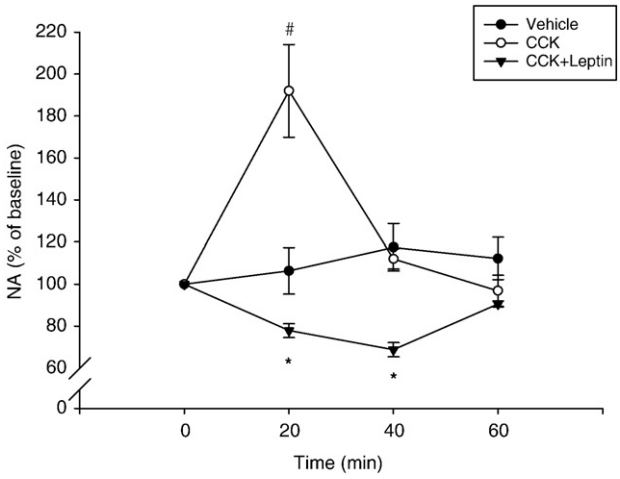

Fig. 1 – Noradrenalin (NA) values of vehicle, cholecystokinin (CCK) and CCK plus leptin groups (Mean ± SEM). #$p<0.001$ by using two-way repeated measures ANOVA with *post-hoc* testing by using the Student–Newman–Keuls multiple range test compared to vehicle group. *$p<0.01$ by using two-way repeated measures ANOVA with *post-hoc* testing by using the Student–Newman–Keuls multiple range test compared to CCK group.