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Hypothesis paper
Brain talks with fat – evidence for a hypothalamic–pituitary–adipose axis?

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Abstract

The adipose tissue signals to the brain via its secretory products. However, it is unknown whether the brain itself can directly contact the fat tissue. In order to test this hypothesis, the adipocytic expression of receptors for pituitary hormones and hypothalamic peptides was investigated. Besides FSH- and LH-receptors, adipocytes do express the specific receptors for ACTH, TSH, GH, prolactin, oxytocin and the three receptor subtypes for vasopressin. Thus, the adipose tissue might no longer be regarded as an inert and steady tissue but as a fast acting player downstream of and under the control of the brain. Based on this, the potential existence and clinical impact of a hypothalamic–pituitary–adipose axis should further be investigated.

Keywords: Pituitary; Hypothalamus; Adipocyte; Hormone; Receptor

1. Background

For decades, the adipose tissue has been considered as a specialized type of connective tissue that stores energy as triglycerides and releases energy as free fatty acids. However, an increasing body of evidence suggests the adipose tissue as an endocrine organ secreting several highly active molecules (adipokines) such as leptin, adiponectin, resistin, TNF-α, IL-6 and, adipsin (Schäffler et al., 2005). These adipocyte-derived proteins, hormones and cytokines regulate metabolic (insulin sensitivity, fatty acid oxidation, satiety), immunologic (monocyte/macrophage function) and vascular (endothelial cell adhesion molecule expression) processes (Rajala and Scherer, 2003; Havel, 2004).

In the case of leptin, it has been recognized that adipocytes exert a feed back to the brain informing the hypothalamus about the amount of adipose tissue mass and thus regulate appetite/satiety via the ARC-PVN-NPYergic pathway (Wang et al., 1997). Most recently, the adipose tissue-derived adiponectin was demonstrated to act directly in the brain by decreasing body weight and increasing CRF expression (Qi et al., 2004).

However, it is completely unknown whether the brain itself directly contacts the adipose tissue and this hypothesis has not yet been investigated so far (Fig. 1). The known feedback loops between hypothalamus/pituitary gland and peripheral glands (ovary, testes, thyroid

Abbreviations: ACTH, adrenocorticotropin; ACTH-R, adrenocorticotropin receptor; ARC, arcuate nucleus; CRF, corticotropin-releasing hormone; FSH, follicle stimulating hormone; FSH-R, follicle stimulating hormone receptor; GH, growth hormone; GH-R, growth hormone receptor; LH, luteinizing hormone; LH-R, luteinizing hormone receptor; NPY, neuropeptide Y; Prolactin-R, prolactin-receptor; PVN, paraventricular nucleus; TSH, thyroid stimulating hormone; TSH-R, thyroid stimulating hormone receptor; V-1A-R, vasopressin receptor-1A; V-1B-R, vasopressin receptor-1B; V-2-R, vasopressin receptor-2.

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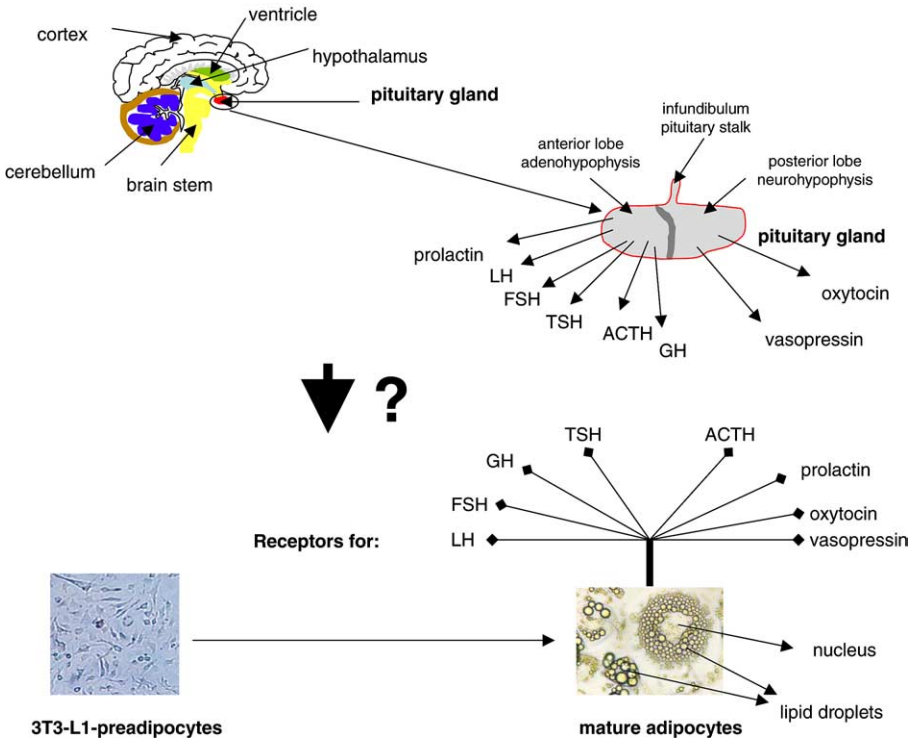

Fig. 1. The hypothesis of a hypothalamic–pituitary–adipose axis.

gland, adrenal gland) are well described and routinely used for diagnosis and stimulation tests in endocrine disorders (Cohen et al., 1986). Based on the current findings by Yong et al. (Qi et al., 2004) cited in *Nature Medicine*, we started to investigate the idea of a hypothalamic–pituitary–adipose axis (Fig. 1).

Pituitary and hypothalamic hormones and peptides exert their action via specific hormone receptors expressed on the target gland. For each hormone, only one highly specific hormone receptor exists, except for vasopressin where three receptor subtypes have been described in the murine system (V-1A, V-1B and V-2).

1.1. Methods and results

mRNA-specific primer combinations were established to detect the specific receptors for the anterior pituitary lobe hormones TSH, ACTH, GH, LH, FSH, prolactin and the hypothalamic peptides oxytocin and vasopressin that are stored in the posterior pituitary lobe. 3T3-L1 preadipocytes and mature, lipid-storing adipocytes were investigated for the complete pituitary and hypothalamic hormone receptor expression profile before and after starting a hormonally induced adipocyte differentiation program. mRNA was isolated from preadipocytes and from mature adipocytes after day 9 of differentiation. The β-actin gene was used as a control. Resistin concentrations in the supernatants of cultured 3T3-L1 adipocytes were measured by ELISA (human Resistin DuoSet-ELISA, R&D systems, Germany). Recombinant prolactin was purchased from Calbiochem, Merck Biosciences, Nottingham, UK. For Western blot analysis, the MA1-611 prolactin antibody from ABR, dianova, Hamburg, Germany was used.

Fig. 2 summarizes the results of the RT-PCR-based expression analysis. The results demonstrate the rather unexpected finding that mature adipocytes do express mRNA for the specific receptors for the anterior lobe hormones ACTH, TSH, GH and, prolactin. In addition, even the specific receptors and receptor subtypes for the hypothalamic peptides vasopressin and oxytocin are expressed in adipocytes. With regard to vasopressin, all three receptor subtypes V-1A, V1-B and V-2 could be detected. Of note, the expression of these receptors in preadipocytes was low and appears to be induced in differentiated adipocytes. Interestingly, mRNA for the TSH-receptor is completely absent in preadipocytes and is induced strongly in mature adipocytes. In contrast, LH- and FSH-receptor mRNA was detectable in control RNA extracted from mouse ovary, but not in preadipocytes or adipocytes.

1.2. Comments and point of view

The results of the present study possibly indicate that there might exist a feedback loop between pituitary gland/hypothalamus and the adipose tissue. These findings could provide the physiological basis for a direct control of adipocyte function by the brain opening a new field of basic and clinical research. Since most of