Regulatory Peptides 149 (2008) 79–83

Contents lists available at ScienceDirect

Regulatory Peptides

journal homepage: www.elsevier.com/locate/regpep

Towards the therapeutic use of intranasal neuropeptide administration in metabolic and cognitive disorders

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ARTICLE INFO

Article history:
Received 18 May 2006
Accepted 1 June 2007
Available online 25 March 2008

Keywords:
Central nervous system
Intranasal administration
Neuropeptides
Body weight regulation
Obesity
Cognition

ABSTRACT

The nose provides an effective way for delivering neuropeptides to the central nervous system, bypassing the blood-brain barrier and avoiding systemic side effects. Thereby intranasal neuropeptide administration enables the modulation of central nervous signaling pathways of body weight regulation and cognitive functions. Central nervous control of energy homeostasis is assumed to rely on hypothalamic neuropeptidergic pathways that are triggered by the peripheral adiposity signals insulin and leptin conveying the amount of body fat to the brain. Melanocortins, including alpha-melanocyte stimulating hormone (alpha-MSH), are essential for inducing anorexigenic/catabolic effects, i.e. for inhibiting caloric intake and increasing energy expenditure. Insulin, in addition to its function as an adiposity signal, also influences memory formation. Here we present a series of studies on the intranasal administration of MSH/$ACTH_{4-10}$, a melanocortin receptor agonist, and of insulin. Prolonged administration of MSH/$ACTH_{4-10}$ induced weight loss in normal-weight, but not in overweight humans. Intranasal insulin reduced body fat and improved memory functions in the absence of adverse peripheral side effects. Our results may contribute to the future development of therapeutic strategies in disorders like obesity and cognitive impairments that derive from dysfunctions of central nervous neuropeptidergic pathways.

1. Introduction

Experimental and therapeutic manipulation of central nervous functions by systemic administration of neuropeptides in humans is limited because the compounds may induce potent hormone-like peripheral side effects while their access to the central nervous system (CNS) is impaired by the blood-brain barrier [1,2]. Our group has shown in humans that the intranasal administration of peptides like melanocortin$_{4-10}$ (MSH/$ACTH_{4-10}$) and insulin allows direct access to the cerebrospinal fluid (CSF) compartment within 30 min, bypassing uptake into the bloodstream [3] (Fig. 1). These observations are in line with findings in animals where intranasal administration of peptides and of larger molecules led to an accumulation of the substances in brain tissue [1,4]. Given that the intraneuronal transport of neuropeptides would face proteolytic obstacles as a result of lysosomal degradation and thus would take several hours for the substance to reach the olfactory bulb [5], it is more plausible to assume that after intranasal administration, the peptide molecules, via extraneuronal transport, pass through intercellular clefts in the olfactory epithelium to diffuse into the subarachnoidal space [1,5]. The specific advantage of the nasal administration of neuropeptides to the CNS, be it intra- or extraneuronal, derives from the fact that with this route, biologically effective concentrations of peptides can be achieved in the human brain without the strong systemic side effects that would be evoked by resorption of the compounds into the blood stream. Intranasal delivery also opens the possibility for treatments of diseases that are known to derive at least in part from dysfunctions in central nervous neuropeptide signaling, such as Alzheimer's disease and obesity [6,7].

Recent years have seen considerable progress in the research on CNS control of body weight regulation [8,9]. Insulin and leptin are commonly considered to be adiposity signals from the periphery that convey to the brain the amount of energy stored as fat tissue because their circulating levels are proportional to body adiposity and decrease during fasting [8,10]. The central nervous administration of both leptin, which is primarily produced by white adipose tissue, and insulin, which is released by pancreatic beta-cells, reduces food intake and body adiposity [11,12]. In the arcuate nucleus of the hypothalamus, a highly integrated neuropeptidergic network constitutes the downstream signaling system for these signals, resulting in a balanced regulation of anabolic and catabolic pathways [9,13]. Anabolic pathways trigger food intake (i.e., they are orexigenic) and decrease energy

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doi:10.1016/j.regpep.2007.06.012

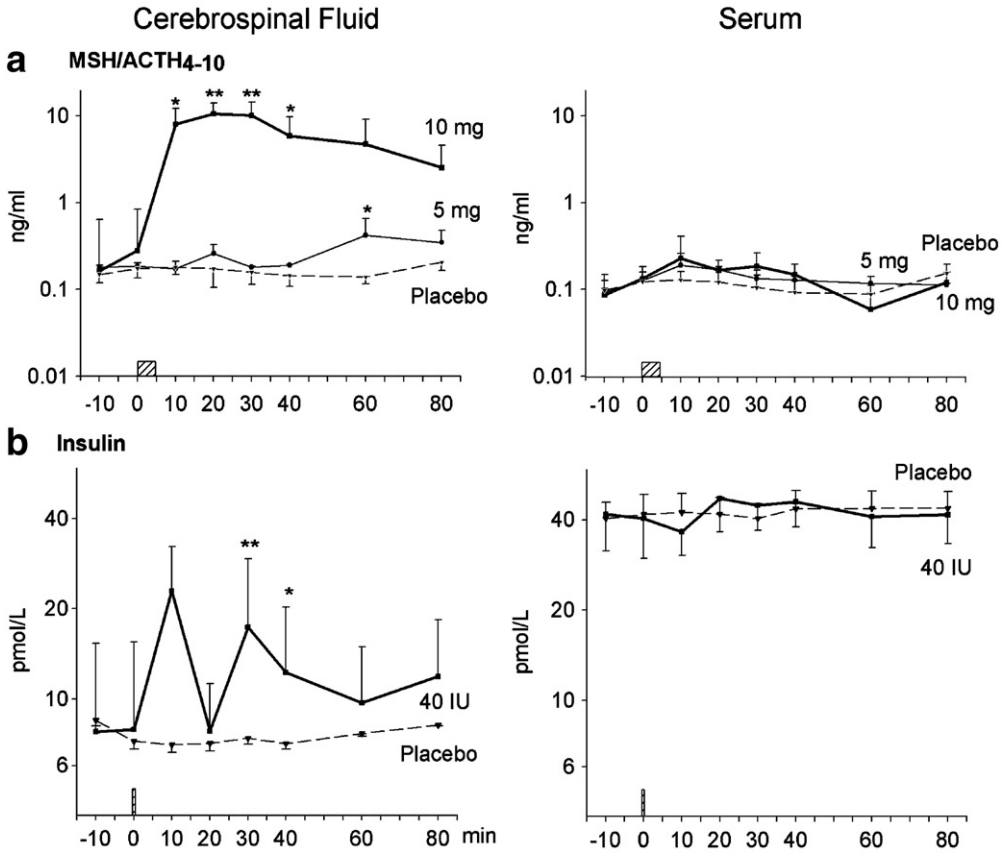

Fig. 1. Concentrations of (a) MSH/ACTH$_{4-10}$ and (b) insulin in CSF (left) and blood serum (right) before and within 80 min after intranasal administration of the peptides in humans (from [3]). Doses of MSH/ACTH$_{4-10}$ were 10 mg (thick solid line, $n=5$) and 5 mg (thin solid, $n=4$), and of human insulin 40 IU (thick solid, $n=8$). Placebo (sterile water) conditions: thin dashed lines. Substances were administered with a nasal spray atomizer. Bars indicate duration of peptide administration. Means, SEM and significance compared to placebo concentration (** — $p \leq 0.01$, * — $p < 0.05$, for baseline adjusted values) are indicated.

expenditure – leading to weight gain – while catabolic signal transduction decreases caloric intake (i.e., is anorexigenic) which in combination with increased energy expenditure leads to weight loss. Neurons synthesizing alpha-melanocyte stimulating hormone (alpha-MSH), a melanocortin derived from prepro-opiomelanocortin (POMC), are essential for catabolic signal transduction [14,15]. It is assumed that the ability of leptin and insulin to reduce food intake relies on the stimulation of arcuate POMC neurons and eventually on the release of alpha-MSH [16], whereas anabolic signaling involves the neuropeptide Y (NPY) and agouti-related protein (AgRP) systems. In-depth accounts of the pathways between hypothalamic nuclei and the caudal brainstem, where control of food intake is established by the integration of neural, endocrine, and duodenal nutrient signals can be found elsewhere [9,13,17]. It is to note that central nervous insulin not only serves as an adiposity feedback signal, but also improves memory functions [18–20]. Brain insulin receptors are located in the hippocampus and adjacent limbic brain structures [21,22] that are essential for the formation of declarative memory, i.e. the acquisition and recall of facts and events [23]. Accordingly, intravenous infusion of insulin in humans in euglycemic clamp conditions was found to improve especially hippocampus-dependent types of declarative memory [20].

The increasing prevalence of both memory related disorders like, e.g., Alzheimer's disease [24] and of obesity [7] underlines the urge to develop therapeutic means that aim at the central nervous pathways involved in the pathogenesis of these diseases. In a series of studies focusing on the intranasal route, we examined the effects of long-term administration of the anorexigenic hypothalamic messenger MSH/ACTH$_{4-10}$ and of insulin on body weight regulation. On the background of the reported beneficial effects of insulin on cognitive functions, we also examined whether long-term intranasal insulin improves cognitive abilities in humans. In addition, intranasal insulin intake was tested for possible side effects on blood glucose levels and on blood pressure.

2. Effects of intranasal MSH/ACTH$_{4-10}$ on body weight regulation in normal-weight and overweight humans

The melanocortin system of the hypothalamic arcuate nucleus is of major importance among the catabolic neurotransmitter networks. In humans, various mutations of the melanocortin receptor 4 (MC4-R) have been identified in extremely obese individuals with BMIs above the 99th percentile [25,26]. Obesity is also a key symptom of human patients and mutant mice with deficient synthesis of melanocortins [27,28]. In the latter animal model, daily treatment with an MSH/ACTH agonist was found to induce weight loss [28]. In two experiments, we examined in normal-weight [29] and in overweight humans [30] the effects of long-term treatment with the MC4-R agonist MSH/ACTH$_{4-10}$ on body weight, body fat, and on plasma concentrations of leptin and insulin.

In the normal-weight study [29], two groups of subjects (6 men and 6 women in each group) underwent a 4-week baseline phase and 6 weeks of treatment with placebo or MSH/ACTH$_{4-10}$ administered intranasally once in the morning and once in the evening at a dose of 0.50 mg. Compared with the effects of placebo, the 6-week treatment with MSH/ACTH$_{4-10}$ decreased body fat on average by 0.99 kg and body weight on average by 0.79 kg (Fig. 2), resulting in a diminished body mass index (BMI). The reduction in body fat was accompanied by a 24% decrease in plasma leptin and by a 20% decrease in plasma insulin concentration (Fig. 2). Cortisol concentrations as well as cardiovascular parameters and routine laboratory measures remained