Expert Opinion

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Targeting metabolic and cognitive pathways of the CNS by intranasal insulin administration

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Intranasal administration effectively delivers neuropeptides to the CNS, bypassing the blood–brain barrier and avoiding systemic side effects. Using this route of administration, direct manipulations of central nervous signalling pathways involved in body weight regulation and cognition are possible. Specifically, the subchronic intranasal administration of insulin has been shown to reduce body fat and improve memory function in the absence of adverse peripheral side effects. These results may fuel the future development of therapeutic strategies in disorders such as obesity and Alzheimer's disease that are promoted by dysfunctions of central nervous neuropeptidergic pathways.

Keywords: body weight regulation, central nervous system, cognitive impairments, intranasal administration, neuropeptides, obesity

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1. Introduction

Targeting peptidergic signalling pathways of the CNS in humans is difficult to achieve by systemic administration of neuropeptides because the blood–brain barrier prevents or greatly restricts access to the CNS. Also, neuropeptides can induce potent hormone-like peripheral side effects [1]. Animal studies have indicated that for a multitude of substances, including microorganisms, antibiotics and hormones, a direct passage from the nasal cavity to the brain compartment exists [2]. In humans, the intranasal administration of peptides such as melanocortin$_{4\text{-}10}$ and insulin allows direct access to the cerebrospinal fluid compartment within 30 min, bypassing uptake into the bloodstream (**Figure 1**) [3]. These observations corroborate findings in animals where intranasal administration of peptides and of larger molecules led to an accumulation of the substances in brain tissue [2]. Intraneuronal transport of neuropeptides would face proteolytic obstacles as a result of lysosomal degradation and would probably take several hours for the compound to reach the olfactory bulb. Thus, it is plausible to assume an extraneuronal transport of the peptide molecules passing through intercellular clefts in the olfactory epithelium to diffuse into the subarachnoidal space (for a review, see [2]). Using the intranasal route of administration, biologically effective doses of neuropeptides can be delivered to the human brain without the strong systemic side effects that resorption of the compounds into the bloodstream would entail. Thus, intranasal delivery may become a valuable tool in the treatment of diseases that are known to result, at least in part, from dysfunctions in central nervous neuropeptide signalling, such as obesity and Alzheimer's disease.

Over the past two decades, research on the central nervous control of body weight has made considerable progress, identifying the key players involved in energy homeostasis. In the arcuate nucleus of the hypothalamus, anabolic and catabolic pathways set up a highly integrated neuropeptidergic network (for review see [4]). Anabolic pathways trigger food intake (i.e., they are orexigenic) and decrease energy expenditure – leading to weight gain – while catabolic signals decrease caloric intake

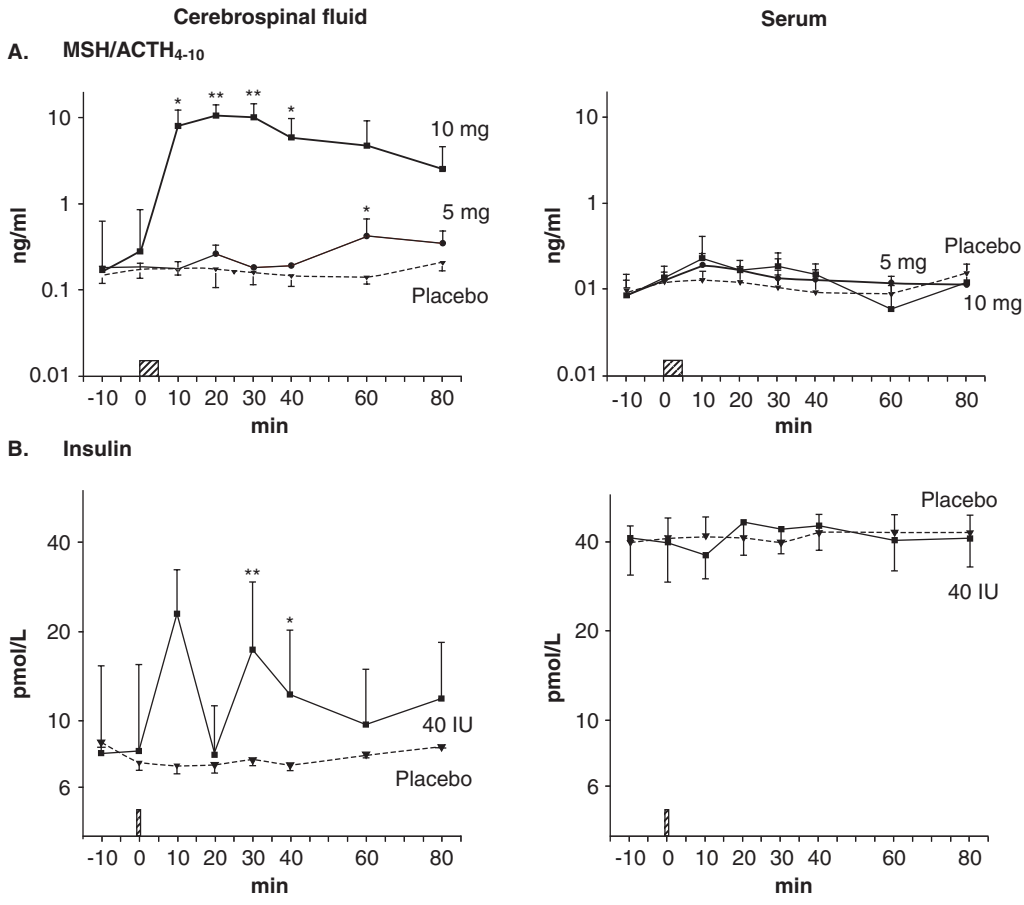

Figure 1. Intranasally administered neuropeptides reach the cerebrospinal fluid compartment [3]. Concentrations of (**A**) MSH/ACTH$_{4-10}$; and (**B**) insulin in cerebrospinal fluid (left) and blood serum (right) before and within 80 min after intranasal administration of the peptides in humans (reproduced with permission 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 atomiser. Bars indicate the duration of peptide administration. Means, SEM and significance compared with placebo concentration (for baseline adjusted values) are indicated.

*$p < 0.05$.

**$p \leq 0.01$.

ACTH: Adrenocorticotropic hormone; MSH: Melanocyte-stimulating hormone; SEM: Standard error of the mean.

(i.e., are anorexigenic) which in combination with increased energy expenditure leads to weight loss. Insulin and leptin, which are peripherally secreted in proportion to body fat stores, provide a negative feedback signal to the hypothalamus that in healthy organisms counteracts excessive weight gain. Of noteworthy, central nervous insulin not only serves as an adiposity signal but also improves memory functions [5]. Declarative memory, (i.e., the acquisition and recall of facts and events), in particular benefits from insulin administration [6]. In a series of studies in humans focusing on the intranasal route, the effects of long-term administration of insulin on body weight regulation and on cognition have been examined in our laboratory.

2. Research so far

In animals, the catabolic effects of central nervous insulin are well documented [4]. Inducing central nervous insulin effects in humans by long-term intravenous infusion is not practicable due to the effect of circulating insulin on glucose metabolism. However, the nasal route provides an effective way of raising brain insulin levels without lowering blood glucose concentrations. In a key study, using intranasal administration, healthy, normal weight men were treated with insulin (40 IU) or placebo four times a day. After 8 weeks of administration, the insulin-treated subjects had lost 1.28 ± 0.71 kg of body weight and 1.38 ± 0.59 kg of body fat (**Figure 2**) [7]. Their waist circumference decreased by 1.63 ± 1.17 cm. In addition, leptin levels in the insulin-treated group dropped, whereas insulin and glucose levels did not differ between groups, which underlines that intranasal insulin does not affect peripheral glucose concentration. The decline in body fat upon insulin administration is assumed to stem mainly from reduced food intake because hunger ratings were also slightly decreased. Studies on long-term

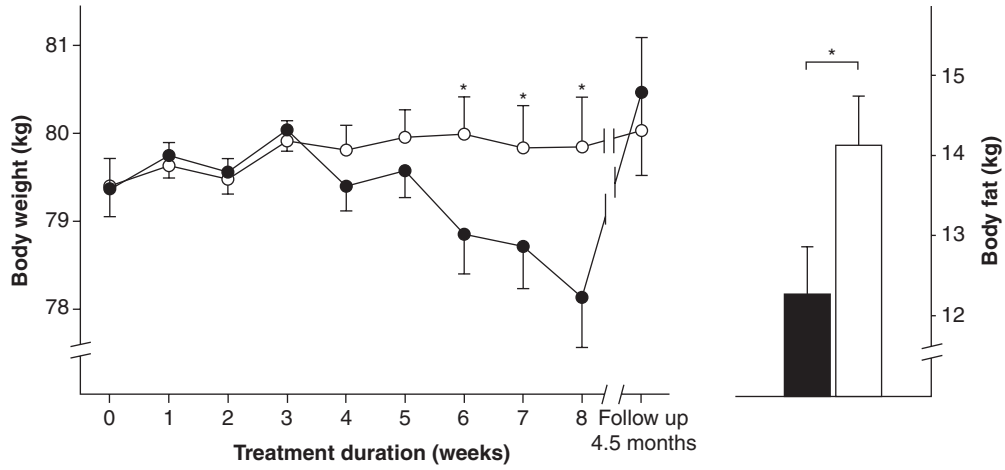

Figure 2. Intranasal insulin decreases body weight and fat in normal weight men. Left: average body weight (± SEM) during 8 weeks of intranasal insulin administration and in a follow-up examination in healthy, normal weight men (reproduced with permission from [7]). Right: body fat (± SEM) after 8 weeks of treatment. One group of subjects received insulin (black circles/bar), the other group received placebo (white circles/bar). Values are baseline adjusted, as derived from analyses of covariance. n = 12 for each group.

*$p \leq 0.05$.

SEM: Standard error of the mean.

central nervous insulin administration in animals indicate a slowly evolving attenuation of 24-h food ingestion [8], fitting the assumption that even small changes in hunger and satiety can down-size caloric intake.

Related experiments have scrutinised the enhancing effects of intranasal insulin on cognition [9]. In one, lists of 30 words were presented to subjects in a declarative memory test conducted at the beginning and end of 8 weeks of treatment, adhering to the experimental paradigm presented above. In addition to an immediate recall 3 min after presentation of the respective list, a delayed recall 1 week later required subjects to write down all the words they still remembered. The delayed recall of words was significantly improved after 8 weeks of intranasal insulin administration (words recalled: placebo 2.92 ± 1.00, insulin 6.20 ± 1.03) [9]. These effects corroborate findings of improved memory function upon acute intranasal administration of insulin in elderly subjects with memory deficits [10]. Most recently, the rapid-acting insulin analogue insulin aspart has been demonstrated to even exceed the beneficial effects on memory of regular human insulin [11]. Based on this, it may be assumed that increases in central nervous insulin not only protect, but also support the development of neural connectivity in hippocampal brain regions known to be essential for declarative memory formation. It is of note that animal experiments have hinted at a hypertensive effect of enhanced brain insulin signalling by sympathoexcitation via central nervous autonomous centres [12]. Importantly, except for an acute but very transient increase in blood pressure, intranasal insulin administration has been shown not to have a long-term effect on blood pressure when used chronically in human subjects [13] – an outcome that is of considerable relevance for the possible clinical use of the compound.

3. Conclusion

Increasing evidence indicates that intranasal administration of neuropeptides such as insulin bypasses the blood-brain barrier and enables effective delivery to the CNS without inducing peripheral effects of the compounds. Data from other and the present authors' own laboratories convincingly demonstrate that intranasal insulin in particular modulates central nervous pathways of energy homeostasis and memory formation, reducing body fat stores and improving declarative memory function in the absence of adverse side effects. As disorders such as obesity and Alzheimer's disease are assumed to be promoted by dysfunctions of central nervous insulin signaling, intranasal insulin administration may contribute to the development of centrally active therapeutic agents against these disorders.

4. Expert opinion

The promising results on intranasal insulin briefly outlined here demonstrate that the central nervous networks of body weight regulation and memory formation can be targeted by nasal administration of insulin and other neuropeptides. Besides an impaired central nervous sensitivity to insulin, decreased blood-to-brain transport of the peptide possibly contributes to the development of obesity – a defect that could be overridden by adequate intranasal insulin substitution. Furthermore, epidemiological findings in humans [14] suggest that obesity and neurodegenerative dementia have a common

pathophysiological mechanism in disturbed insulin signalling. Thus, intranasal insulin might be able to counteract cognitive impairments that are suspected to concur with obesity [15]. Recent studies not only provide the basic proof that intranasal neuropeptides successfully improve brain functions, but they also suggest their potential as therapeutic options in brain disorders such as Alzheimer's disease [10]. Nevertheless, there is still some way to go before intranasal neuropeptide administration can be routinely used in the clinical setting. Considering the global obesity epidemic, the list of possible intranasal therapeutics will have to be extended. Most recently, the safety and tolerability of intranasal peptide YY, a compound whose intravenous administration is assumed to exert anorexigenic effects [16], have been investigated in obese humans [17]. At the same time, the field becomes increasingly diverse as increasing numbers of peptides come under scrutiny and new directions are explored. Intranasal oxytocin, a promising candidate for improving social abilities [18], is just another example of the increasing interest in this compelling route of administration. Thus, it does not come as a surprise that increasingly sophisticated technologies for intranasal delivery are being developed [101,102] for use in research and therapeutic settings. Therefore, it seems likely that the first major clinical trials of intranasal delivery will occur in the near future.

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