

The Potential of Intranasal Insulin in the Management of Metabolic Disorders

a report by

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DOI:10.17925/EE.2008.04.02.40

Insulin in the Brain

Clinical Observations and Experimental Studies in Humans

For a long time the brain was believed to be insensitive to the effects of insulin. However, 30 years ago it was shown that insulin and insulin receptors are ubiquitously found in the brain.^{1,2} Insulin accesses the brain from the systemic circulation via a transporter-mediated mechanism.³ The first hints at clinically relevant effects of insulin in the central nervous system derived from observations soon after human insulin had been introduced for diabetes therapy. Having switched their treatment regimen from porcine to human insulin, a lot of patients with diabetes reported on a reduction in their awareness of hypoglycaemic episodes.^{4,5} Experimental studies that scrutinised these more or less anecdotal observations by systematically comparing the effects of intravenous porcine with human insulin infusion on central nervous functions and hypoglycaemia counter-regulation did not yield fully consistent results.^{6–11} However, the idea of insulin playing a pivotal role in the brain that was well established in animal experiments^{12–15} had started to grow also on the clinically orientated scientific community.

In subsequent years, hypoglycaemic clamp experiments demonstrated that high levels of circulating insulin (compared with lower levels)

enhance the neuroendocrine as well as the subjective response to hypoglycaemia in a clear-cut fashion.^{16,17} By infusing insulin directly into the carotid arteries, Davis and co-workers moreover gathered solid evidence that the enhancing influence of insulin on hypoglycaemia counter-regulation is in fact mediated by central nervous action of the hormone.^{18,19} Further studies indicated that insulin not only modulates the response to hypoglycaemia but also exerts distinct effects on neuroendocrine and neurocognitive functions also under euglycaemic conditions. Higher (compared with lower) rates of insulin infusion acutely increase the activity of the hypothalamic–pituitary–adrenal (HPA) axis²⁰ and stimulate the sympathetic nervous system.^{21,22} In order to characterise the temporal dynamics of insulin's central nervous actions, we recorded transcortical direct current (DC) brain potentials before and after a bolus injection of the hormone while blood glucose levels were held constant by additional glucose infusion. A strong shift of the DC potential that occurred within a few minutes indicated an immediate effect of acute changes in systemic insulin concentrations on brain activity.²³

Insulin as an Adiposity Signal

Research in animals has provided an insight into the physiological mechanisms underlying central nervous insulin effects. In particular, the group of Steven Woods has performed a series of seminal studies^{3,12,15,24–27} that have significantly contributed to our understanding of the central nervous regulation of energy homeostasis. Insulin and leptin, which are primarily produced by white adipose tissue, 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.^{28,29} Accordingly, central nervous administration of both hormones reduces body fat stores via negative feedback on food intake.^{12,30} In the arcuate nucleus of the hypothalamus, a highly integrated neuropeptidergic network constitutes the downstream signalling system for these signals, resulting in a balanced regulation of anabolic and catabolic pathways.³¹ Central nervous insulin has been shown in animals not only to serve as an adiposity feedback signal, but also to improve memory functions.^{32,33} Brain insulin receptors apart from hypothalamic nuclei are located in the hippocampus and adjacent limbic brain structures^{34,35} that are essential for the formation of declarative memory, i.e. the acquisition and recall of facts and events.³⁶ Accordingly, euglycaemic intravenous infusion in humans was found to especially improve hippocampus-dependent declarative memory.³⁷

In the past decade, central nervous insulin turned out to play an even broader role in the regulation of peripheral metabolic processes than previously thought. By creating mice with a neuron-specific disruption of the insulin receptor, Jens Brüning and co-workers most poignantly



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showed that defective central nervous insulin signalling results in obesity, peripheral insulin resistance and hypertriglyceridaemia.³⁸ Most recently, the same group has presented evidence that central nervous insulin also contributes to white adipose tissue metabolism.³⁹ Moreover, insulin signalling in the hypothalamus is essential for the suppression of hepatic glucose production.^{40,41}

Intranasal Insulin Administration

Transport from the Nasal Cavity to the Central Nervous Compartment

How can the central nervous effects of insulin be safely and easily explored in humans? Intravenous insulin infusion induces a drop in blood glucose that can be prevented by additional glucose infusion. However, the euglycaemic clamp technique is a time-consuming procedure restricted to the laboratory setting, thus precluding prolonged central nervous administration of insulin. Furthermore, transport of circulating insulin into the brain compartment is limited by the blood–brain barrier.³ Our group has shown in humans that the intranasal administration of insulin and of other peptides such as melanocortin_{4–10} bypasses uptake into the bloodstream and allows direct access to the cerebrospinal fluid compartment within 30 minutes.⁴² Most relevant research on intranasal peptide administration in animals has been performed by William Frey II and co-workers, who repeatedly demonstrated an accumulation of intranasally administered substances in brain tissue.^{43–47} 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,⁴³ it is more plausible to assume that after intranasal administration the peptide molecules pass through intercellular clefts in the olfactory epithelium via extraneuronal transport and diffuse into the subarachnoidal space.^{43,47} It has repeatedly been shown that intranasal insulin administration does not alter or only marginally alters blood levels of insulin and glucose.^{42,48–51} Thus, the specific advantage of intranasal insulin administration derives from the fact that with this route, biologically effective concentrations of insulin can be achieved in the human brain without the strong systemic side effects that would be evoked by resorption of the hormone into the bloodstream.

Intranasal Insulin Reduces Food Intake and Body Fat in Men

The first functional evidence for central nervous effects of intranasally administered insulin in humans was gathered in a study demonstrating an acute reduction of the P3 amplitude of auditory evoked brain potentials, especially over frontal recording sites, after intranasal insulin administration.⁵² Subsequently, we examined the effects of eight weeks of intranasal insulin administration on body composition and plasma hormone levels in healthy, normal-weight men who were intranasally administered either insulin (40IU) or placebo four times a day: in the morning, around noon, in the evening (~30 minutes before mealtime, respectively) and before going to bed.⁴⁸ Over the eight-week period, the insulin-treated subjects lost body fat and their waist circumference significantly decreased. Also, leptin levels in the insulin group dropped during treatment, whereas insulin and glucose levels did not differ between groups. Of interest, these catabolic effects were not observed in a parallel sample of insulin-treated women, indicating a gender difference in the central nervous sensitivity to adiposity signals that has

also been found in animal studies.^{53,54} The decline in body adiposity upon insulin administration in the male subjects probably stemmed from reduced everyday food intake, because in a more recent study the acute intranasal administration of 160IU insulin significantly reduced food intake from a breakfast buffet in male subjects, whereas women did not show such an effect.⁵⁰ On the background of animal experiments indicating that enhanced brain insulin signalling may favour hypertension,^{19,22,55} we also assessed the effects of intranasal insulin on

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blood pressure.⁵⁶ Healthy, normal-weight participants received intranasal insulin in an acute setting (total dose of 240IU over a period of 120 minutes) and according to the eight-week administration paradigm described above. In the acute experiments, intranasal insulin slightly increased diastolic and mean arterial blood pressure, but this effect vanished during long-term administration. This outcome may be of considerable relevance for the possible clinical use of intranasal insulin because it excludes a serious adverse side effect of such therapies.

Memory Improvement After Intranasal Insulin

In our long-term experiments we also found an improvement of memory functions by intranasal insulin that was evident in men and women.⁵⁷ In a declarative memory test conducted at the beginning and end of the eight-week insulin treatment period, lists of 30 words were presented to the subjects. In addition to an immediate recall three minutes after presentation of the list, in a delayed recall approximately one week later subjects wrote down all the words they still remembered. Delayed recall of words significantly improved after eight weeks of intranasal insulin administration (words recalled: placebo group 2.92±1.00; insulin group 6.20±1.03), whereas immediate word recall and non-declarative memory functions were not affected. Moreover, the administration of insulin improved feelings of wellbeing and self-confidence after both acute and long-term administration. Beneficial effects of intranasal insulin on memory functions have also been observed in memory-impaired elderly subjects in a series of pioneering studies performed by the group of Suzanne Craft.^{58–61}

Intranasal Insulin Administration in Obesity

In light of the catabolic and anorexigenic effects of intranasal insulin administration in normal-weight men, assessing the potential of intranasal insulin to reduce bodyweight in obese men was of great interest. In these patients, the intranasal approach appeared to be particularly promising because there is some evidence that the transport of insulin across the blood–brain barrier may be hampered in obesity.⁶² However, eight weeks of intranasal insulin treatment in obese men with a cumulative dose of 160IU of insulin per day yielded absolutely no effect on bodyweight and body fat mass.⁴⁹ Nevertheless, we again observed a distinct improvement of memory functions and mood ratings after intranasal insulin treatment. In addition, intranasal

insulin acutely and after prolonged treatment reduced HPA axis secretory activity as assessed by circulating adrenocorticotrophic hormone (ACTH) and cortisol levels. This effect had also been noted to a lesser extent in the foregoing study in normal-weight men,⁵⁷ contrasting with the above-mentioned acute increase in HPA activity during intravenous insulin administration.²⁰ These results point to a state of central nervous insulin resistance in obese subjects that appears to be restricted to insulin effects on energy homeostasis.

Central Nervous Insulin Resistance

Experimental Evidence for Reduced Central Nervous Insulin Sensitivity in Obese Humans

Functional evidence for central nervous insulin resistance in obesity was not only gathered in our laboratory but was also found in studies measuring cerebrocortical activity by magnetoencephalography (MEG) under hyperinsulinemic–euglycaemic clamp conditions.⁶³ Insulin infusion increased spontaneous cortical activity in the beta and theta frequency bands, but this increase was significantly reduced in obese subjects compared with normal subjects. Moreover, correlational analyses revealed insulin effects on cortical activity to be negatively related to the amount of body fat and the degree of peripheral insulin resistance. This outcome stands in some contrast to the fact that after eight weeks of intranasal insulin treatment our obese subjects displayed preserved susceptibility to insulin's memory-improving effect as the storage of declarative memory representations also involves neocortical brain areas,³⁶ which underlines the need for further in-depth investigation of central nervous sensitivity in obesity. Nevertheless, taken together these data corroborate the assumption that besides impaired blood–brain transport of insulin^{26,62,64} that can be over-ridden by the intranasal administration of the compound, obesity is associated with central nervous resistance against the adiposity signal of insulin.

The catabolic impact of intracerebroventricular insulin and leptin is also curbed in animals with diet-induced obesity,^{30,65,66} and a partial decrease in insulin receptors selectively pertaining to the hypothalamic arcuate nucleus impairs energy balance and peripheral insulin action in rats.⁶⁷ On a molecular level, a defect in the insulin receptor substrate-phosphatidylinositol 3-OH kinase (IRS-PI3K) pathway is likely to be one mechanism of such local neuronal insulin resistance.^{68,69} Interestingly, a recent study⁷⁰ using positron emission tomography (PET) to measure insulin-evoked responses in brain areas relevant to eating behaviour found a markedly attenuated response to insulin infusion in subjects with peripheral insulin resistance. Thus, central nervous insulin resistance may not be restricted to obese subjects, but may particularly affect subjects with reduced peripheral insulin sensitivity. Therefore, it is tempting to speculate that central nervous insulin resistance as a pathophysiological factor in the development of

diabetes may be a starting point for new approaches in the treatment of the disease.

Intranasal Insulin to Support Weight Loss and Improve Cognition in Insulin Resistance

Approaching central nervous insulin resistance in obese and peripherally insulin-resistant patients by intranasal insulin delivery certainly appears to be an attractive goal because it may attenuate the harmful metabolic and cognitive consequences of obesity and type 2 diabetes. Although apparently ineffective at reducing bodyweight in the obese state, by suppressing HPA axis activity intranasal insulin could counteract the development of peripheral insulin resistance and visceral obesity that are promoted by excessive HPA axis secretion related to chronic stress.^{71,72} Likewise, it is possible that the compound gains impact on weight-regulatory mechanisms after successful weight loss has been achieved (e.g. by caloric restriction and exercise), and in this case may prevent re-gain of weight.⁷³ Animal data^{74–76} and epidemiological findings in humans^{77–80,81} suggest that obesity, insulin resistance and diabetes are tightly linked to neurodegenerative processes. On the background of its beneficial effect on memory functions observed in healthy subjects and patients with cognitive impairments,^{59,82,83} intranasal insulin may be able to reduce the pathological central nervous changes that obesity and diabetes are suspected to entail.^{84,85} A most recent study in a murine model of type 1 diabetes in which intranasal insulin slowed the development of diabetes-induced brain changes compared with subcutaneous delivery of the compound nurtures this promising perspective.⁸⁶ Notably, in healthy young subjects intranasal administration of the rapid-acting insulin analogue aspart exerts a stronger improving effect on memory performance than regular human insulin,⁸⁷ suggesting that the intranasal administration of possible insulin analogues that specifically target neuronal insulin receptors may hold additional potential in the treatment of central nervous insulin resistance.

Conclusion

There is compelling evidence for the notion that the brain is a primary target of insulin effects. Central nervous insulin appears to play a key role in the regulation of whole-body energy fluxes, eating behaviour and cognitive function. Accordingly, central nervous insulin resistance appears to be critically involved in the pathophysiology of type 2 diabetes, obesity and related metabolic diseases, as well as of memory disorders. Therefore, central nervous insulin resistance can be expected to be an attractive therapeutic target to combat these increasingly common and devastating diseases. Although there is some way to go before intranasal insulin administration (which delivers the peptide to the brain in the absence of adverse peripheral side effects) can be routinely used in the clinical setting, in this context intranasal delivery systems may offer a distinct therapeutic potential. ■

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