Insulin and cognitive function in humans: experimental data and therapeutic considerations

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Abstract
Data from experimental studies in animals and from epidemiological studies in humans suggest a link between insulin and cognitive performance. Do these results translate into clinical and therapeutic benefit for people with cognitive impairment? Insulin injected peripherally can readily cross the blood–brain barrier. Intravenous insulin can improve aspects of cognitive function in healthy adults and in individuals with Alzheimer’s dementia. Moreover, intravenous insulin increases concentrations of a long form of β-amyloid protein, Aβ42. One potential confounding factor with these data, however, is the need for co-administration of glucose with the insulin to maintain euglycaemia as glucose itself can facilitate memory function. Administration of insulin via the intranasal route is scientifically (and therapeutically) more attractive because the insulin goes directly to the cerebrospinal fluid, with minimal systemic absorption; this obviates the need for a glucose infusion. Intranasal insulin may improve some aspects of memory in healthy individuals, but has yet to be studied in people with cognitive impairment. TZDs (thiazolidinediones) reduce peripheral insulin concentrations by enhancing insulin sensitivity. In adults with Type II (non-insulin-dependent) diabetes, TZD therapy improves memory function, but so does sulphonylurea therapy (which elevates peripheral insulin concentrations). Improved memory is linked to lower blood glucose concentrations, rather than altered insulin levels. However, major trials are currently under way examining the impact of TZDs in people with dementia.

Introduction
There is a considerable amount of scientific data that links insulin to the brain and, in particular, to cognitive function [1–3]. Insulin receptors are found in high concentrations within the limbic system [4]. In vitro, insulin can alter the rate of firing of hippocampal neurons [5] and enhance uptake of neuronal glucose [6]. Intracerebroventricular injection of insulin improves aspects of memory function in rats [7]. In humans, epidemiological studies have demonstrated an association between hyperinsulinaemia and impaired cognitive function and even with an increased risk of Alzheimer’s dementia [8–11]. The apparent paradox between the animal and human data may be explained by the phenomenon of insulin resistance, i.e. hyperinsulinaemia is associated with resistance to insulin at a peripheral tissue level and if neurons are similarly affected then they might be ‘functionally’ insulin-deficient in hyperinsulinaemic individuals [1]. In addition, ‘absolute’ insulin deficiency in the brain may occur, as one small case-control study suggested that serum insulin concentrations were higher and CSF (cerebrospinal fluid) insulin concentrations were lower in individuals with Alzheimer’s dementia, compared with normal subjects [12].

Thus the link between insulin and cognitive function is supported by laboratory and animal studies and by epidemiological data from humans. It offers the intriguing notion that modification of insulin concentrations in vivo may enhance cognitive ability and offer novel routes of treatment for Alzheimer’s dementia and other disorders associated with cognitive impairment. In this paper, the cognitive data from studies in humans, in which insulin concentrations have been manipulated, will be considered critically. There are three main areas of interest: (i) intravenous insulin infusion, (ii) intranasal insulin administration and (iii) the lowering of peripheral insulin concentrations by TZDs (thiazolidinediones).

Intravenous insulin
There is a substantial literature on the deleterious effects of insulin-induced hypoglycaemia on cognitive function, but more recently investigators have examined the effects, on cognitive performance, of peripheral infusion of insulin during a state of euglycaemia. Intravenously administered insulin can actively pass across the blood–brain barrier, via a receptor-mediated saturable transport process, and insulin can also enter circumventricular organs directly as these lack a blood–brain barrier [3]. Kern et al. [13] examined the effects of administration of two different concentrations of intravenous insulin on cognitive function (1.5 and 15 m-units kg⁻¹ min⁻¹) in 30 healthy young adults. After 6 h, recall of a list of 30 words was greater in the group receiving the higher dose of insulin compared with the lower dose (22 ± 1 versus 19 ± 1 words; P < 0.05). There was no control...
arm and so it is not possible to assess the ‘practice effect’ inherent in this task, but the main issue with this study (and indeed any study examining intravenous insulin during euglycaemia) was the obvious need to have a concurrent infusion of intravenous glucose to avoid hypoglycaemia. The authors did not examine word recall during a condition with infusion of intravenous glucose only, but of course that would have stimulated endogenous insulin secretion.

Craft et al. [14–16] have performed a series of investigations examining the effects of intravenous insulin in elderly adults with Alzheimer’s dementia. In an early study [14], 22 adults with mild–moderate Alzheimer’s dementia were studied on three occasions: (i) during euglycaemic hyperinsulinaemia (1.0 m-unit·kg⁻¹·min⁻¹), (ii) during hyperglycaemia and (iii) during infusion of saline. Immediate and delayed recall was improved during the hyperinsulinaemia and hyperglycaemia conditions, with a suggestion that the improvement during the former was greater. In contrast with Kern et al. [13], no change in cognitive function was observed during the experimental conditions in a group of healthy adults. Subsequently, this team demonstrated that infusion of a somatostatin analogue (to suppress endogenous insulin production), abolished the improvement of memory observed during acute hyperglycaemia in adults with Alzheimer’s disease [15]. Craft et al. [16] also examined dose–response effects of insulin on cognitive function. A curvilinear response pattern was observed with the highest and lowest concentrations of insulin associated with the smallest effects on cognitive performance. In addition, there was evidence of individual differences in sensitivity to insulin, with Alzheimer’s disease patients who were non-homozygotes for apolipoprotein E[42] (a susceptibility gene for Alzheimer’s) requiring higher doses of insulin to enhance memory than homozygotes and healthy individuals [16].

More recently, the same team demonstrated in 16 healthy adults that euglycaemic hyperinsulinaemia (1.0 m-unit·kg⁻¹·min⁻¹) was associated with improvements in memory and increased CSF concentrations of insulin and a long form of β-amyloid protein, Aβ42 [17]. β-Amyloid protein aggregates in the plaques that are the neuropathological hallmark of Alzheimer’s dementia and so these results are potentially very interesting. However, what was not clear was whether the increased concentrations of Aβ42 were due to increased neuronal secretion (a potentially favourable scenario for neuronal health) or to reduced breakdown (potentially harmful to neurons). This study also raised the paradox that despite the fact that insulin raised CSF Aβ42 and improved memory, the subjects with the ‘highest’ CSF Aβ42 concentrations following intravenous insulin had the ‘smallest’ improvement in memory.

In summary, the data on the effects of intravenous insulin of cognitive function are promising, but are based on small-scale experimental studies. Aside from the obvious impracticalities of this mode of administration, there are inconsistencies in the data, for example the absence of effect on healthy individuals in some studies, but these may be explained, in part, by differential sensitivity to the infused insulin. A key issue though is whether the effects of intravenous insulin are direct or whether they are secondary to the concurrent intravenous infusion of glucose required to maintain euglycaemia. Physiologically, insulin and glucose are inextricably linked, if the serum concentration of one changes then so will that of the other, and it is, therefore, very difficult to tease apart their individual effects.

### Intranasal insulin

Administration of insulin via the intranasal route is a scientifically and therapeutically more attractive option. The intranasal route is already used for the administration of several different classes of drug, e.g. antihistamines and vasopressin analogues, and is acceptable to patients. Insulin can directly access the CSF compartment by diffusing through the olfactory epithelium [3]. In one study, human insulin was detectable in the CSF 10 min after a dose of 40 units was administered intranasally [18].

Kern et al. [19] have investigated both short- and medium-term effects of intranasal insulin on cognitive function. Eighteen healthy male volunteers aged 18–34 years participated in a double-blind, cross-over study and received 20 units of insulin or placebo every 15 min during the experiment [19]. There was no change in blood glucose or insulin concentrations during the study, confirming the lack of systemic absorption of the intranasal insulin. Auditory evoked potentials following an ‘odd-ball’ task were recorded, i.e. subjects were asked to covertly count infrequent high pitched tones interspersed randomly throughout a sequence of more frequent lower pitch tones. Compared with placebo, intranasal insulin reduced the area under the curve of the P3 wave and prolonged its latency. The P3 wave is a positivity that occurs approx. 300 ms after the ‘odd-ball’ stimulus presentation, but which is absent after the more frequent stimulus is presented. The latency of the peak P3 waveform correlates with psychometric intelligence scores in some studies and is thought to relate to the cognitive processes of stimulus evaluation [20]. Thus intranasal insulin in the short-term appeared to have a deleterious effect on cognitive performance.

More recently, Kern and co-workers studied longer-term effects of intranasal insulin [21]. A total of 38 healthy adults, aged 18–34 years, were randomly allocated to receive intranasal insulin (40 units four times daily for 8 weeks) or placebo in a double-blind fashion. Cognitive function and mood were assessed at three time points – at baseline, 60 min after the administration of the first dose of insulin or placebo (to investigate acute effects) and after 7 weeks of treatment. In addition, to assess long-term memory recall, additional sessions took place 1 week after each of the three main sessions. Peripheral blood insulin and glucose concentrations were again unaffected by intranasal insulin therapy. Acute administration of intranasal insulin had no effect on cognitive function, but subjects reported significantly lower levels of anger and greater self-confidence and well-being. Chronic insulin administration was associated with enhanced...
delayed recall of a list of 30 words compared with placebo (6.2 ± 1.0 versus 2.9 ± 1.0 words; \( P = 0.04 \)). Well-being, self-confidence and extroversion were enhanced, while levels of depression were reduced.

There is obviously an unexplained disparity between the effects of acute administration of intranasal insulin on auditory evoked potentials and directly measured cognitive performance. However, the data on chronic administration of intranasal insulin are intriguing and if replicated in larger studies and in older people with cognitive decrements, offer a novel means of improving cognitive performance.

**Insulin-sensitizing agents**

TZDs reduce blood glucose concentrations by increasing hepatic and peripheral (muscle and adipose) tissue sensitivity to insulin, i.e. they are insulin-sensitizing agents that reduce peripheral blood insulin concentrations. TZDs bind to and activate the nuclear PPAR\(\gamma\) (peroxisome proliferator-activated receptor-\(\gamma\)), modifying transcriptional regulation of factors involved in the control of insulin secretion [22].

The effects of rosiglitazone, a TZD, on cognitive performance have been examined in patients with diabetes and in patients with early Alzheimer’s dementia. These studies have not, as yet, been published in peer-reviewed journals and so only limited data are available in the public domain. Ryan et al. [23] randomized 145 adults with Type II (non-insulin-dependent) diabetes, in a double-blind fashion, to receive either rosiglitazone or glyburide (a sulphonylurea agent which increases blood insulin concentrations). Both agents predictably lowered blood glucose concentrations over 24 weeks of therapy and blood insulin concentrations were significantly higher in the glyburide-treated subjects. Significant improvements in working memory (~0.7 S.D., a moderate effect size) were observed at the end of the study. However, there was no difference between subjects treated with rosiglitazone or glyburide, i.e. both drugs improved working memory to the same extent. The greatest improvements in working memory were observed in those subjects with the largest fall in blood glucose concentrations, but there was no significant correlation between change in blood insulin levels and cognitive function.

Individuals with dementia were actively excluded from this study and thus subjects did not have significant cognitive impairment at baseline [23]. In addition, Type II diabetes is a very complex metabolic disorder and it is likely that the origin of any cognitive impairment in affected individuals is multifactorial [24], i.e. any effect of insulin on cognition may be overwhelmed by other factors such as hyperglycaemia, hypertension, hyperlipidaemia and vascular disease. However, this was by far the largest investigation to date in which the link between insulin and cognition has been examined and its null result should carry significant weight.

Craft and co-workers found that rosiglitazone preserved cognitive function in adults with early Alzheimer’s dementia [25]. A total of 30 adults with mild cognitive impairment or early Alzheimer’s dementia were randomized to receive rosiglitazone (20) or placebo (10). At the end of 24 weeks of therapy, the subjects receiving rosiglitazone showed less of a decline in memory function than those receiving placebo. In addition, concentrations of plasma \(\beta\)-amyloid protein declined in subjects receiving placebo, but remained unaltered in those receiving rosiglitazone [26]. No data on changes in blood glucose concentrations have been provided in this study to date and it may be that the improvement in cognitive function observed with rosiglitazone was a manifestation of better glycaemic control (in a group of elderly individuals with a likely high prevalence of diabetes or impaired glucose tolerance) rather than to changes in insulin concentrations. Indeed, TZD agents have anti-inflammatory actions as well as effects on blood pressure and serum lipids, which could also have impinged on cognitive performance.

**Conclusions**

The data from humans examining the link between insulin and cognitive function are inconsistent. In general, the studies have been small, with usually far less than 50 subjects participating, and only short-term effects have been examined. The largest study showed no impact at all of manipulating blood insulin concentrations on cognitive function, but this was in people with diabetes and so the results may not be applicable to other patient groups. Large-scale studies of TZDs are currently under way in people with Alzheimer’s dementia and there is a clear need for large studies with inhaled insulin in people with cognitive impairment. Manipulating brain insulin levels offers an intriguing new therapeutic avenue for cognitive impairment, but as yet the Scottish legal verdict of ‘not proven’ should be applied to its clinical utility.

**References**


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