Insulin and insulin-like growth factor I signalling in neurons

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1. ABSTRACT

Insulin-like peptides are an ancient acquisition in phylogeny, suggesting a crucial biological role for these family of peptides. Indeed, a key function of these hormones in cell metabolism and growth has been firmly established. However, their significance in neuronal physiology is less characterized, although progress in recent years on the neuroactive properties of insulin and insulin-like growth factor I (IGF-I) supports an important role for these hormones in brain function. During development, appropriate IGF-I input is critical in brain growth while the role of insulin at this stage, although not well defined yet, may be related to the control of neuronal survival. In the adult, IGF-I is a pleiotropic signal involved in numerous processes to maintain adequate brain cell functions, while the role of insulin is better known in relation to the control of food consumption and glucose metabolism. The potential involvement of IGF-I in brain diseases associated with neuronal death is strongly supported by its neuroprotective role. Further, the unexplained high incidence of glucose metabolism dysregulation in brain diseases makes also insulin a strong candidate in neuro-pathological research. Because mounting evidence suggests a complementary role of insulin and IGF-I in the brain, unveiling the cellular and molecular pathways involved in brain insulin/IGF-I actions is helping to establish potentially new therapeutic targets and its exploitation may lead to new treatments for a wide array of brain diseases.

2. INTRODUCTION

Insulin-like peptides are found already in multicellular eukaryotes (1), and possibly originated separate entities (insulin and insulin-like growth factors) before the vertebrate-invertebrate divergence around 600 million years ago (2), although this is still not entirely clear (3). Thus, relatively modern organisms such as the fruit fly (~250 million years of existence) still have a single mixed type of insulin-like peptides (4). The known physiological role of these hormones is very well conserved and they act as neuroactive messengers in very primitive organisms with a simple nerve organization such as the nematode *C. elegans* (5). These factors are secreted by specialized sets of neurons within the proto-nervous system of this worm to control body functions such as the coordination of energy balance with food intake. These actions have been found to be important determinants of longevity in worms and probably other more complex organisms (6). Although similar functions are known to take place within the brain of more evolved organisms such as flies (7), the fact that in mammals the major organs involved in the production of these peptides are the liver and the pancreas might contribute to neglect the study of the actions of insulin and IGFs in the brain. Moreover, the brain produces very little IGF-I and negligible amounts, if any, of insulin, and, as a whole, systemic hormones were considered to be unable to cross the blood-brain-barriers. However, a central action of insulin in controlling glucose disposal is firmly established (8), explicitly highlighting a neuroactive effect for at least

Hippocampal field activity

Neocortical field activity
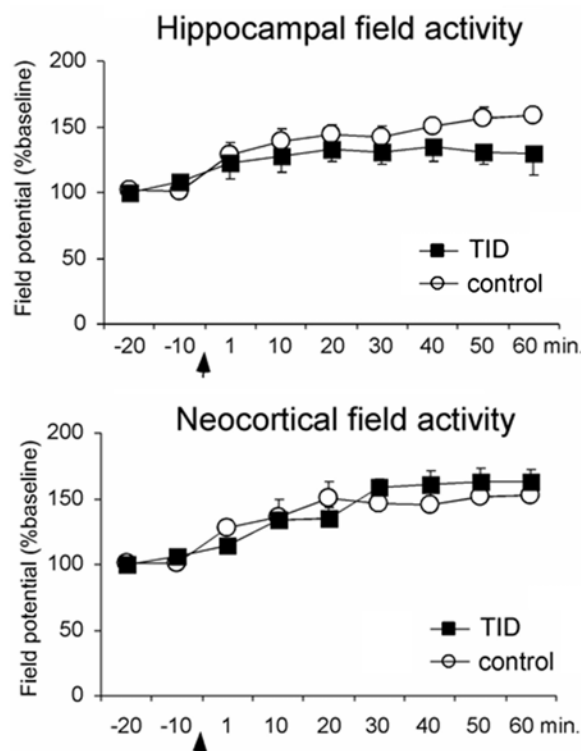
Figure 1. Synaptic plasticity is unaltered in telencephalic IGF-I deficient (TID) mutant mice. Long-term potentiation (LTP) in hippocampus and cortex was elicited by tetanic stimulation in anesthesized TID and control littermates (controls). Plots of the populational EPSP slope before and after tetanic stimulation of the perforant path (upper graph) or contralateral neocortical (lower graph) side shows LTP of the EPSP in both groups of mice. Horizontal lines indicate mean baseline values, which were taken as 100%. Arrow indicates tetanus (three pulse trains of 100 µA).

circulating insulin. In the present article we will discuss those aspects of the biology of insulin and IGF-I in the brain that are less characterized and even controversial, referring the reader to recent reviews discussing better established brain actions of these hormones (9, 10).

3. INSULIN AND IGF-I IN THE BRAIN: SOURCES AND PATHWAYS

When studying the central actions of insulin and IGF-I one has first to consider that while the developing brain produces readily detectable amounts of these hormones, particularly IGF-I, this is not at all the case in the adult, where very low and anatomically restricted IGF-I mRNA is detected, and the expression of insulin is questionable (11-15). However, receptors for these hormones are distributed all along the neural axis (16-20), and both insulin and IGF-I have been shown to cross the blood-brain barriers (BBB) through receptor-specific processes (21-23). Collectively, all these observations lead to the conclusion that peripheral insulin/IGF-I modulate central neurons. While this is implicitly assumed for insulin regulation of hypothalamic nuclei involved in energy regulation (24) a central role of blood-borne IGF-I is not

yet widely recognized. Because brain endothelium and scattered neuronal subpopulations together with reactive microglia produce IGF-I (25-29), the functional distinction between peripheral and central IGF-I, if any, is at present difficult to establish. The fact that forebrain-specific deletion of IGF-I elicits only minor detectable brain changes (Figure 1 and Table 1) together with the strong brain phenotype of serum IGF-I deficient mice (30) strengthens a role of peripheral IGF-I on brain function but does not help clarify the meaning of brain IGF-I.

This mismatch between ample insulin/IGF-I receptor distribution throughout the brain and low or negligible local production of these peptides invokes the existence of a peripheral source of insulin/IGF-I providing support for a functional significance of regulated transport of circulating insulin/IGF-I into the brain across the BBB (31). Areas devoid of a BBB such as the basal hypothalamus, where insulin- and IGF-I-sensitive neurons involved in energy and hormonal regulatory loops are located, can be directly accessed by blood-borne insulin/IGF-I, but most brain areas are inaccessible to circulating proteins (32). While passage of insulin/IGF-I across the BBB has started to be characterized (33-38), the intra/extracellular pathways used by these hormones to reach its cellular targets once they are in the brain are not clear. Assuming that most neurons will be close to a capillary, interstitial fluid diffusion of insulin/IGF-I away from the perivascular space may suffice. However, the presence of IGF-I receptors in glial end-feet covering brain endothelial cells (39), together with the ability of astroglia to transport intracellularly this peptide (40) suggests that blood-borne and/or endothelial IGF-I may reach its neuronal targets through a transcytotic process involving astroglia. The fact that IGF-I is transcytosed across the epithelial layer at the BBB of the choroid plexus (see below) reinforces this possibility. Whether insulin is transported via a similar pathway cannot be determined yet since the anatomical arrangement of insulin receptors at the BBB has not been described.

A parallel or even alternative transport pathway for systemic insulin/IGF-I into the brain is across the choroid plexus BBB (22, 33, 35, 41) since both peptides are found in CSF (42, 43). The presence of abundant IGF transport proteins (IGFBPs) in the cerebrospinal fluid (CSF), particularly IGFBP-2 (44) supports a carrier-mediated process whereby IGF-I can access relatively distant targets deep within the brain (45). Again, the fact that IGFBPs cannot bind to insulin makes more difficult to explain how CSF insulin can reach its cellular targets. Nevertheless, many growth factors/hormones devoid of a known carrier system and directly delivered into the CSF affect neuronal function, indicating that the CSF is a functional pathway for humoral signals.

Although the evidence for an important external source of brain insulin/IGF-I is gaining momentum, analysis of the mechanisms involved in entrance of peripheral insulin/IGF-I through brain vessels and the choroid plexus is at its infancy. The fact that these peptides may enter the brain through two distinct routes, if finally

Insulin-like factors in brain

Table 1. Behavioral evaluation of TID mice

	Motor coordination[1]	Visual discrimination[2]	Marginal/center preference[3]	Sensorimotor integration[4]	Spatial task learning[5]
Control	240 ± 10	3,2 ± 0,4	60 / 40 ± 8.5 %	41.0 ± 15	31 ± 5
TID	240 ± 31	2,9 ± 0,2	*50 / 50 ± 4.4 %	47.1 ± 13	42.0 ± 10

[1] Motor coordination was measured as time (sec) spent in the rota-rod in the last trial (n=7 per group). Duration of the test was 240 sec., [2] Visual discrimination was determined by number of errors before correct performance (n=7). [3] Activity test (marginal versus centre zones preference; number of beam cuts) in the actimeter (n=7; data are percentage of time spent in each area). [4] Sensorimotor integration was evaluated using the cued version of the water maze (sec to reach the visible platform; n=7). [5] Learning of a spatial memory test. Escape latency in the 7th trial of a one-day water maze task (sec) (n=7). *P<0.05 vs control by Student´s t-test.Controls are littermates. All animals were 2-4 months old.
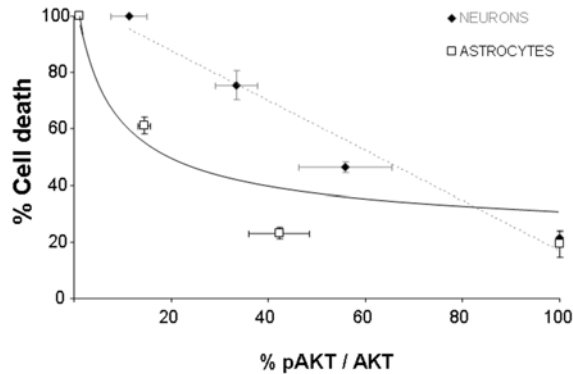
Figure 2. Differential sensitivity towards the pro-survival actions of IGF-I in neurons and astroglia. Cell death in relation to activity of AKT (assessed as ratio of phospho-AKT/total AKT) is shown. This kinase is the key mediator of the pro-survival actions of IGF-I. Purified neuronal or astroglial cultures were submitted to varying doses of IGF-I or the AKT inhibitor LY294002 to achieve differing degrees of AKT activation: 100% activity was obtained with 100 nM IGF-I while 100% inhibition was obtained with LY294002. While neurons were very sensitive to the loss of AKT activity, astroglia were more resistant to the lack of AKT activation, showing cell death only after large decreases in AKT activity. These results suggests that neurons are exquisitely dependent on IGF-I input for survival.

established, is intriguing. In this regard, new evidence from our group indicates that entrance of IGF-I through brain endothelium is a regulated process, whereas entrance across the choroid plexus epithelium appears constitutive. The latter is supported by the observed constant IGF-I CSF levels in humans (46). Further work along these lines is warranted.

4. HOUSE-KEEPING VS BRAIN-SPECIFIC ACTIONS OF INSULIN/IGF-I

Both insulin and IGF-I have a broad range of target tissues; indeed, one may say that all tissues in the body are insulin/IGF-I dependent. As a general rule, insulin regulates glucose and fatty acid disposal and IGF-I cell growth and survival on target tissues. In the brain, the nutrient disposal role of insulin appears less evident, as glucose metabolism in neurons is relatively insulin insensitive (47, 48), but insulin is still participating in energy balance in the brain by controlling food intake and

peripheral glucose production (24). Growth-promoting actions of IGF-I are necessarily less conspicuous in the adult brain due to the limited growth capacity of this organ, but its pro-survival actions may still be essential. The fact that neurons, as compared to glia, are more sensitive to the survival-promoting actions of IGF-I (Figure 2) may underlie the greater resilience of glia to insults.

Intriguingly, the intracellular pathways recruited for the maintenance of these basic cellular needs are apparently shared by insulin and IGF-I, and involve the canonical PI3K/Akt/Foxo route (49, 50). Because insulin-sensitive neurons participating in the control of energy expenditure are concentrated in the hypothalamus while IGF-I-sensitive neurons are widely distributed throughout the brain, one may assume that cell-specific actions for these hormones are achieved through cell-specific expression of the respective specific receptor. However, it is quite probable that many neurons (as many cells elsewhere in the body) simultaneously express both insulin and IGF-I receptors, making it difficult to outline a mechanism to explain the distinct actions of insulin and IGF-I on neurons. In this regard, although pro-survival actions of insulin have been reported for neurons, these effects have been always found in developing cells (51). Similarly, while a role of IGF-I on neuronal glucose handling has also been shown (52), this action is reminiscent of the classical regulatory role played by insulin on peripheral target cells in relation to glucose transporters, having no known association to the insulin-mediated central control of body energy expenditure.

Although we can associate the PI3K/Akt/Foxo pathway with house-keeping actions of insulin/IGF-I on neurons, this canonical route, together with other less characterized (involving PKC or PKA for example), are also participating in brain-specific effects of these hormones. Paramount among these are the rapid modulatory actions of insulin/IGF-I on neuronal plasticity. This latter term refers to the functional repertoire supporting the wide range of adaptive responses displayed by neurons. In a previous review we provided a detailed account of the processes related to synaptic plasticity that are modulated by the IGFs (53). Additional information gathered in recent years confirms and extends the role of insulin/IGF-I on functional plasticity. Both peptides modulate diverse membrane channels, many neurotransmitter receptors and are even able to modulate neurotransmitter release (Table 2). All these constitute critical aspects of neuronal excitability and therefore, of its integrative capacities. In addition, insulin and IGF-I

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Table 2. Fast actions of insulin/IGF-I on parameters related to neuronal plasticity

Parameter	IGF-I	Insulin	Reference
Neurotransmitter release	Acetylcholine ↑↓		96-98
	GABA↓	GABA↑	99, 100
Membrane channels	Ca^{++}↑		101, 102
	K$^+$↑↓	K$^+$↑↓	70, 103, 104
	Cl$^-$↑		105
Neurotransmitter receptors	Kainate↑		106
	AMPA↓	AMPA↑↓	54, 55, 107, 108
		NMDA↑	109
	Glycine↑		110
	Vanilloid TRPV1↑	Vanilloid TRPV1↑	111
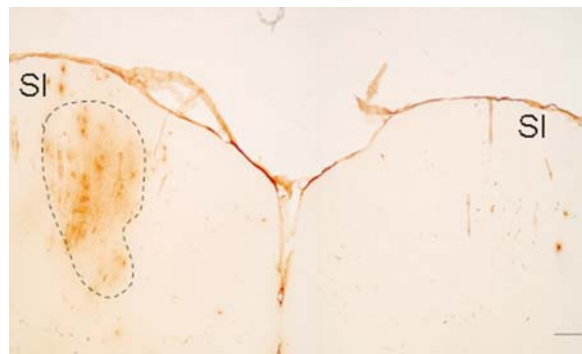
Figure 3. Regulated entrance of blood-borne IGF-I into the brain. Digoxigenin-labelled IGF-I accumulates in the left rat primary somatosensory (SI) cortex (circled area) after unilateral sciatic nerve stimulation. Note diffuse digoxigenin immunostaining surrounding the vessels only in the stimulated side probably reflecting diffusion of labelled IGF-I into the brain parenchyma. Immunostaining with anti-IGF-I antibodies show co-localization of signal (not shown). At later times, labelled IGF-I is found within neurons (not shown). Photo-montage to illustrate both sides. Bar is 400 μm.

modulate long-term depression and potentiation, the two hallmark mechanism of synaptic plasticity (54-56). These processes, together with long-term trophic actions of insulin/IGF-I likely underlie the influence of these hormones on cognition. Indeed, deficient brain insulin signalling is reported in demented patients (57-59), and clinical trials with insulin-sensitizing agents show promising results (60). Not coincidentally, disturbed IGF-I signalling may also underlie cognitive loss in dementia (61) and even in normal brain aging (62), and again, pre-clinical trials with IGF-I in Alzheimer´s dementia models are promising (63).

5. COOPERATIVITY OF INSULIN AND IGF-I IN THE BRAIN: COGNITION AND THE BRAIN RESERVE HYPOTHESIS

The latter observations point to an intriguing, as yet poorly analyzed aspect of insulin/IGF-I actions; namely, their possible complementary effects, which may help understand the existence of parallel cell sensitivity towards both hormones. Sensitivity to insulin is directly related to IGF-I levels (64), and low insulin sensitivity associates always with low IGF-I sensitivity and viceversa, as seen in aging or type 2 diabetes (65, 66). As already commented elsewhere, cooperative actions between both may also contribute to appropriate brain amyloid β handling (61, 67), healthy aging (62), or cognitive status (68).

This latter aspect is only recently becoming recognized. The combined actions of insulin and IGF-I on key cellular processes such as neuronal excitability or energy balance would be sufficient to explain an essential role of these hormones in cognition. But the significance of insulin/IGF-I on cognitive processes appears to be due to mechanisms beyond merely basic cellular processes and more directly related to this higher brain function. For instance, infusion of insulin under a glucose clamp to human volunteers rapidly influences cognitive performance (69), which eliminates glucose as a possible mediator of insulin effects, and suggests acute direct actions of this hormone at an unknown site. Furthermore, rapid site-specific accumulation of IGF-I after brain stimulation (Figure 3) may be related to an expansion of the respective neuronal receptive fields seen after IGF-I uptake by neurons. (70). This process is strikingly reminiscent of the plastic changes taking place during cognitive operations (71, 72). The fact that cognitive status is inversely related to serum IGF-I levels in aged human subjects (73) and that aging is associated to lower sensitivity to insulin/IGF-I (74) prompted us to examine the underlying processes. A first finding is that circulating IGF-I influences cognitive status in mice by modulating excitatory/inhibitory transmission (Trejo *et al.*, submitted), an observation that warrants a similar analysis in human samples obtained from healthy and cognitive impaired old subjects because it may provide a mechanistic explanation of age-associated cognitive deterioration and therefore a potential therapeutic intervention.

We anticipate that detailed knowledge of the molecular and cellular pathways involved in the cognitive effects of insulin/IGF-I, undoubtedly requiring further studies, will provide a biological framework for the "cognitive/brain reserve" concept (75). The tacit assumption of this concept is that the brain increases its functional resources in direct proportion to its activity (76). Studies using "enriched-housing" conditions in laboratory animals strongly support this idea. Enhanced neuronal activity as a result of increased sensory, motor and cognitive stimulation produces profound effects on brain physiology and anatomy (77). This activity-functional

performance link can easily accommodate the existence of complementary actions of insulin and IGF-I in the brain. Brain activity increases uptake of IGF-I from the periphery (Figure 3) which may trigger many of the functional/biochemical effects described in "enriched" animals, such as increased BDNF levels (78), and significantly, may also increased overall insulin sensitivity as intraventricular administration of IGF-I reduces serum insulin levels (79). The latter process will improve neuronal energy balance and therefore neuronal function will be enhanced. While this proposal needs experimental validation, we suggest that two mechanisms should be explored in detail to determine a possible biological basis for the cognitive reserve concept: 1) mechanisms involved in activity-dependent entrance of serum IGF-I into the brain; and 2) physiological and intracellular pathways underlying insulin-sensitizing effects of IGF-I in neurons.

6. RESISTANCE TO INSULIN/IGF-I: A UNIVERSAL PATHOGENIC MECHANISM IN BRAIN DISEASE

The clinical impact of insulin/IGF-I actions on brain is potentially far-reaching. As discussed in detailed elsewhere (80), the pleiotropic actions of IGF-I, and to a lesser extent of insulin in the brain, may lead to conclude that any homeostatic disturbance in brain tissue will eventually affect the activity of these hormones. Indeed, we recently postulated that loss of input of IGF-I, eventually leading to similar decreases in insulin input, are inevitably associated to neurodegeneration (61, 81). Because we favor IGF-I as the primary player in neuroprotective networks (as compared to insulin, which in this reductionist view will be downstream of IGF-I), we have focused on the processes leading to IGF-I resistance in brain cells. Building on the wealth of knowledge on mechanisms of insulin resistance, such as inflammation or cell stress (82), an interference of the inflammatory mediator tumor necrosis factor-alpha (TNF-alpha) on IGF-I signalling onto neurons (83) and choroid plexus epithelial cells (36) was first documented. To these former observations followed that excitotoxic levels of glutamate also disturb IGF-I input to neurons (84). Based on the competitive action of amyloid peptides with the insulin receptor (85), that shares similar ligand affinities with the IGF-I receptor, we recently proposed that resistance to IGF-I should be present in Alzheimer´s amyloidosis (61). A similar situation may be envisaged in conditions where aberrant protein accumulation will lead to endoplasmic reticulum (ER) stress (86), a known trigger of insulin resistance (87). Because excess cell protein load underlying the "unfolded protein response" (UPR) and subsequent ER stress is associated to a wide variety of neurodegenerative diseases (86), we predict that UPR diseases will be associated to IGF-I resistance. Another pathogenic process commonly invoked in neurodegeneration is oxidative stress, that not only produces insulin resistance in other tissues (88), but also has been proposed to interfere with IGF-I signalling on neurons. Analysis of the pathways involved in this latter case indicate that reactive oxygen species (ROS) override IGF-IR/Akt-mediated Foxo inactivation and at the same time directly activate Foxo through Jun-kinase, which sets in motion a cell death cascade (unpublished observations).

Indeed, IGF-I is unable to rescue neurons from ROS-mediated damage. Collectively, these data indicate that the main pathogenic processes involved in brain diseases produce loss of IGF-I input. In other words, development of IGF-I, and subsequently, insulin resistance should be considered a major therapeutic target in treatment of brain diseases. Because insulin sensitizers are already available in the clinic, its use in clinical trials for different neurodegenerative illnesses is within reach. However, as with type 2 diabetes that in many cases eventually requires administration of insulin, the use of IGF-I or small mimetics may be required in specific conditions (extreme resistance, severe concomitant insulin/IGF-I deficiency, long duration of the disease...etc). Synthetic IGF-I is also already available for human use (89), making our proposal fully testable, particularly in those diseases such as Alzheimer´s disease and many inherited neurodegenerative diseases where no effective treatment is still available.

7. CELLULAR AND MOLECULAR PATHWAYS IN INSULIN/IGF-I SIGNALLING IN THE BRAIN

Brain targets of insulin are well delineated in several hypothalamic nuclei (particularly the arcuate nucleus) where specific subsets of neurons are involved in insulin regulation of nutrient homeostasis (24). Many other brain areas respond to insulin, as insulin receptors are found throughout the cerebellum and telencephalon (16, 90), but the precise biological significance of insulin in these areas is undefined. This is probably one of the main challenges remaining in this area of research. Many scattered observations indicate a variety of actions of insulin on neuronal function, including modulation of membrane channel activity, receptor trafficking...etc. On the contrary, brain actions of IGF-I are better described. Probably the dominating notion that the "trophic" actions of insulin in brain were mediated by the IGF-I receptor, based on the repeated observation that the doses of insulin required to elicit a biological effect were always well above the affinity of the insulin receptor, made research focused on IGF-I as the biologically relevant insulin-like peptide in the brain. Increasing evidence of insulin-specific actions at biologically relevant doses of insulin is slowly changing this preliminary view. However, while there is overwhelming evidence of an active, wide-spectrum neuroprotective role for IGF-I, a comprehensive role of insulin outside the hypothalamus is still not described, and whether other type of brain cells are physiological targets of insulin is also unknown (but see (20).

At least based from *in vitro* evidence and the existence of IGF-I receptors, we know that all types of cells in the central nervous system are targeted by IGF-I. These include not only all classes of neurons throughout the brain (including newly formed neurons), but also astroglia, oligodendroglia and microglia, endothelial cells and perycites of brain vessels and epithelial cells of brain ependyma. While for many years canonical signalling through the insulin and IGF-I receptors was considered to include the PI3K/Akt and Ras/MAPK pathways, we now recognized that many other kinases and phosphatases are downstream of these receptors. The signalling network

elicited by IGF-I on nerve cells - and elsewhere, is becoming so complex that at present it is not yet possible to have a clear picture of it. Predictably, once the analysis of insulin on brain cells gains momentum, a similar complexity is envisaged. As is true for any extracellular signal (91), cells respond to IGF-I in a cell-context fashion, making it difficult to adscribe a precise biological effect to a given pathway. The hopefully impending appearance of a comprehensive protein-protein interaction mapping, the "interactome" (92), will be needed to gain insight into these intricate functional networks. However, even with this "blueprint" information, extensive, site-focused research is required if we want to have a physiological understanding of insulin/IGF-I functions on its many potential targets within the brain. In-depth recent advances in the cellular/molecular pathways involved in insulin actions at hypothalamic sites (93-95), the result of years of intense scrutiny, in our view exemplifies the way to proceed.

8. PERSPECTIVE

Increasing evidence indicates that insulin-like peptides are important regulators of brain function but a comprehensive understanding of their physiological role is not yet possible. Driven by the recent recognition of their significance in many brain diseases of devastating proportions we anticipate that the neurobiology of these peptides will soon become a major research arena.

9. ACKNOWLEDGEMENTS

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Abbreviations: BBB: blood-brain-barrier, BDNF: brain-derived neurotrophic factor, CSF: cerebrospinal fluid, ER: endoplasmic reticulum, IGF-I: Insulin-like growth factor I , ROS: reactive oxygen species, TNF: tumor necrosis factor, UPR: unfolded protein response.

Key Words: Insulin, Insulin-Like Growth Factor I, Brain Function, Cognition, Blood-Brain Barrier, Review

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