Human longevity : crosstalk between the brain and periphery

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CHAPTER 12

KEY FINDINGS GENERAL DISCUSSION AND FUTURE PERSPECTIVES REFLECTIONS

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In this thesis, we examined three interacting systems that have been identified as contributing to a slower pace of ageing, namely the glucose/ insulin metabolism (part I), thyroid (HPT) axis (part II), and the autonomic nervous system (part III). In this chapter, the key findings of the studies will be discussed, and the results put into the context of scientific literature. Finally, directions for future practice and research will be discussed.

KEY FINDINGS

In this thesis, we found that familial longevity is associated with more pronounced relation of insulin parameters with microstructural brain parameters, and by higher TSH secretion, in the absence of differences in metabolism. In addition, familial longevity was not associated with differences in heart rate and its variability as a proxy for the autonomic nervous system. Using specialized MRI techniques (MTI), we showed that subtle changes in microstructural brain parenchymal homogeneity in relation to insulin can be detected, even in brain tissue that appears normal on conventional MR imaging sequences. From our studies, peripheral insulin action seemed to be a stronger indicator of micro- structural (perhaps early) brain integrity than glucose in normo-glycemic older adults. Furthermore, we found that intranasal application of insulin improved brain perfusion in parietal grey matter, occipital gray matter and in the thalamus. Our results strengthen the growing body of evidence that the brain plays a key role in glucose regulation.

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

In literature, IGF-1/glucose/Insulin signaling (IIS), the hypothalamic/pituitary/thyroid (HPT) axis and the autonomic nervous system have been identified as part of the key modifiers of the rate of ageing. Elasticity, robustness and precision of these processes, as co- ordinated by the brain are proposed to be critical to a slower pace of ageing. Conversely, dysregulation in one or more of these systems would accelerate the pace of ageing.

Glucose/ insulin and longevity

With the global population ageing, there has been an astonishing increase in the prevalence of obesity [1], metabolic syndrome [2], type 2 diabetes [3] and neurodegenerative diseases [4]. Insulin resistance is a shared feature in these diverse pathologies [5-9]. Besides regulating peripheral glucose homeostasis, insulin is an important neuromodulator that contributes to neurobiological and other processes [10, 11].

From the magnetization transfer imaging studies, we showed that peripheral insulin action seemed to be a stronger indicator (than glucose) of micro- structural (perhaps early) brain integrity in older adults without diabetes. Higher insulin parameters were associated with measures of decreased myelin and axonal integrity, and these associations were more pronounced in offspring and "younger" older adults in whom glucose-regulatory compensatory mechanisms are probably more intact. Theoretically, the inverse association between peripheral parameters of glucose metabolism and microstructural brain parenchymal homogeneity can be due to either loss of brain integrity as a consequence of defects in glucose regulation, or explained by defects in glucose metabolism being a consequence of deficits in brain integrity.

Due to paucity of experimental studies in humans on the effects of insulin in the brain, the exact mechanism through which insulin relates to brain function remains unclear. To possibly account for our findings, we therefore propose two candidate mechanisms, which we would refer to as 'ageing brain effect' and 'ageing insulin effect'.

The first candidate mechanism is the 'ageing brain effect' (figure 1A). It is becoming clearer that the brain plays an important role in the regulation of peripheral glucose and insulin action [6]. Age related brain changes (reduced integrity of myelin and axons, and shrinkage of large neurons) are accompanied by reduction in brain volumes and function. Brain control of glucose levels may also be affected, for which the body may compensate by higher peripheral insulin secretion by the pancreas. Thus, age induced reduction in brain integrity is proposed to be the trigger for increased peripheral insulin resistance.

The second candidate mechanism is the 'ageing insulin effect' (figure 1B), in which reduced brain integrity is proposed to occur as a consequence of peripheral insulin resistance. Here, due to ageing, peripheral tissues such as muscles and adipose tissues become less sensitive to insulin, leading to increase in circulating glucose levels [12]. To compensate for this, more insulin is secreted peripherally to maintain tight glucose control [13]. Thus, the brain may become overstimulated or insulin resistant as a consequence of chronically

elevated peripheral insulin levels, both of which could result in reduced brain integrity [5, 14]. Both candidate mechanisms ultimately result in peripheral hyper-insulinaemia. To protect the brain from overstimulation of neuronal insulin signalling by chronic hyper-insulinaemia, brain insulin receptors may be down regulated, resulting in central insulin resistance. The inferred inverse relation between peripheral and CSF insulin levels in humans supports this hypothesis [15, 16]. Central insulin resistance may also have adverse consequences, as insulin signalling pathways are important for regulation of neuronal growth and differentiation and insulin has neuro-protective roles against neuronal apoptosis induced by oxidative stress [17]. Thus, deficits in central insulin action may further aggravate decreased brain integrity.

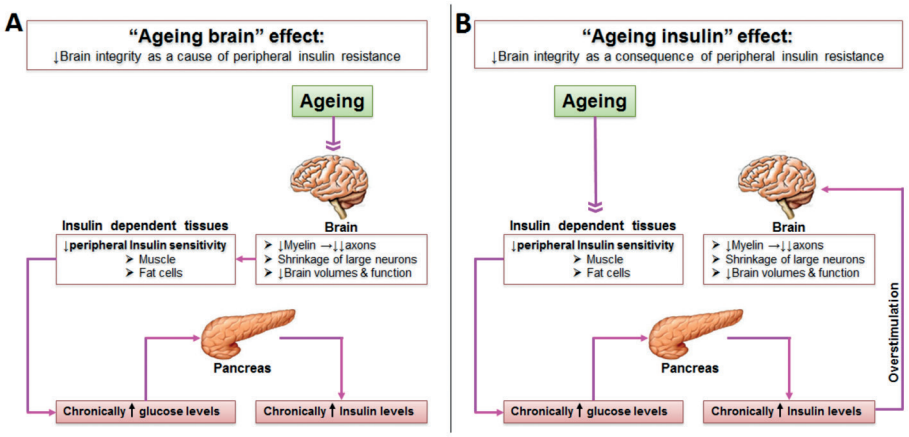

FIGURE 12.1 | Schematic diagrams showing the possible trajectories for the effect of ageing on the relationship between insulin and the brain.

Panel 1A shows the 'ageing brain' effect, in which peripheral insulin resistance occurs due to ageing- induced diminished brain function, which is then compensated for by increased insulin production. The second candidate mechanism is the 'ageing insulin' effect (panel 2B), in which ageing- induced decrease in insulin sensitivity in peripheral tissues stimulates the pancreas to secrete more insulin. The subsequent continued brain stimulation by chronically elevated insulin levels eventually lead to decreased brain integrity.

Previous studies have shown that selective administration of insulin to the brain can have beneficial effects on brain (cognition, memory) and peripheral (weight control, food intake and palatability, body fat) function [18-23]. However, the mechanisms through which insulin does this remains unclear. We showed that intranasal insulin led to increased

perfusion in the parietal and occipital grey matter regions, and in the thalamus of older adults. However, the functional and clinical implications of this increased perfusion remain unclear. Future studies can be aimed at deciphering this, and establish the link (if any) between increased perfusion and the previously known and other beneficial effects of intranasal insulin. The data from our intranasal insulin study and previous studies show that insulin can be safely delivered to the brain through the intranasal route, without affecting circulating glucose and insulin levels. Further studies are also required whereby insulin is targeted at the brain of persons with metabolic disturbances, such as type 2 DM, to investigate whether intranasal insulin can rescue some of their existing metabolic disturbances.

Thyroid axis and longevity

Thyroid hormones (TH) influence a wide range of peripheral and brain-related functions including cognition and regulation of energy homeostasis. Like the glucose/ insulin axis, the hypothalamic-pituitary-thyroid (HPT) axis plays a critical role in the maintenance of energy homeostasis (intake and expenditure) by acting on metabolic tissues. TH levels tend to decline during ageing, and higher thyroid stimulating hormone (TSH) levels have been associated with longevity in humans. In our study, we looked at the mechanism underlying the link between TSH/TH and longevity. Although serum levels of TSH were higher in offspring from long-lived families at every 10- minute time point during 24 hours, TH did not differ between the groups. We also assessed energy metabolism in relation with familial longevity in humans, since metabolism has been associated with longevity in different animal models and plays a central role in different ageing theories. Familial longevity was not associated with differences in energy metabolism. Experimental studies are needed to explore how higher TSH levels are related with familial longevity.

Besides TH having marked influences over brain structure and function, their hyper- and hypo- secretion adversely affect neuronal production and survival, dendritic arborisation and other neuroplastic events, and neurotransmitter supply, all of which are reflected in disruptions of cognitive performance and mood and emotional states as well as circadian rhythms and sleep. Since subclinical hypothyroidism (SCH), considered as early thyroid failure, might also influence brain structure and function, we reviewed existing literature on the relation between SCH and cognition in older adults. No evidence was found to support the association between SCH and cognition. The review however showed that

epidemiological studies on SCH have used different TSH cut- off values. There is therefore a need for standardisation of reference ranges in all ages, and for age- appropriate reference ranges when evaluating thyroid dysfunction in the elderly.

Heart rate and its variability in longevity

Heart rate and its variability patterns are believed to change with age, likely due to a change in autonomic control of the central nervous system. Using the validated Equivital (EQ02) lifemonitor, our studies confirmed that heart rate during sleep increased with calendar age. Three heart rate variability parameters (SDNN, NN50 and pNN50) also increased with calendar age, over the 24- hour period, and when analysed during daytime and sleep-time separately. However, such differences were not found when offspring enriched for longevity were compared to controls of similar age. Thus, our findings that heart rate and its variability did not differ between groups would suggest that familial longevity may not be characterized by changes in the autonomic nervous system. This may be in line with previous arguments that HRV studies in older adults could be confounded by increasing erratic rhythms, and so, differences found in previous studies may not be due to longevity [24, 25]. Future studies can be aimed at disentangling this.

REFLECTIONS ON HUMAN LONGEVITY: DOES THE BRAIN (CROSS) TALK WITH THE PERIPHERY?

In model organisms such as *Caenorhabditis elegans* and *Drosophila*, solid evidence has shown that certain brain neurons can mediate environmental influences on ageing, and longevity can be induced by neural manipulation of pathways such as insulin or IGF-1 signaling (IIS) [26-31]. Similar to insulin or IGF-1 signaling, the thyroid axis (HPT), via thyroid hormones (TH) also regulates neural development. The central nervous system is particularly dependent on TH for normal maturation and peripheral and brain function [32, 33]. TH plays a critical role in longevity. In mice, a negative correlation has been demonstrated between thyroid hormones and ageing [33], and a combination of reduced TH and IGF-I signaling results in the long-lived phenotype [32, 33]. In humans, a link has been repeatedly demonstrated

between the thyroid axis and longevity [34-37]. Furthermore, experiments suggest that the brain can rapidly influence insulin sensitivity, in an age- related manner, through the autonomic nervous system (ANS) [38-42]. Thus, these metabolism-controlling signals (IIS, HPT and ANS) are linked via reciprocal controls involving the brain and periphery, and determine an organism's capacity to adapt to changing environments and to ageing.

The hypothalamus is known to have fundamental roles in growth, development, reproduction, metabolism and lifespan. The hypothalamus, via its reciprocal projections to other brain regions and the periphery, is central for the neuroendocrine interaction between the central nervous system and the periphery. Insulin, via the hypothalamus, is considered a link between the adaptive feeding (brain regulated) and changing energy requirements (periphery regulated). Insulin, a signal reflecting energy availability and reserves, provides direct negative feedback to hypothalamic nuclei that control energy and glucose homeostasis, both centrally and peripherally. Likewise, via hypothalamic control, metabolic homeostasis and ageing is integrated by thyroid hormones, possibly via effects of TH on membrane composition, inflammatory responses, stem cell renewal and synchronization of other physiological responses [33].

With the expansion of population ageing, numerous works in literature have focussed on neuro-endocrine features of ageing and longevity. Our studies contribute to existing knowledge of the crosstalk between the brain and periphery. For example, we showed that familial longevity is associated with more pronounced relation of insulin parameters with microstructural brain parameters, and by higher TSH secretion, in the absence of differences in metabolism. Building on our finding of differential TSH secretion with longevity, future studies can be aimed at deciphering the mechanisms underlying the increased TSH secretion with longevity potential. This could be via challenge experiments using recombinant TSH to decipher the thyroidal and extra- thyroidal effects of TSH, its mechanisms of action, and potential therapeutic effects.

Selective administration of insulin to the brain has been previously shown to have diverse central and peripheral effects, including beneficial effects on cognition, memory, weight control, food intake and palatability, body fat, etc. [18-23]. Our studies also show that intranasal insulin increased perfusion in the parietal and occipital brain regions in older adults. Future studies can be aimed at testing the short- and long-term effects of intranasal insulin and the consequent functional and clinical implications, especially in persons with impaired glucose metabolism. Since resetting the hypothalamic programing

has been shown to accelerate or decelerate the ageing process in mice [43], further studies can thus be aimed at deciphering if resetting the hypothalamic programing can be attained in humans, using insulin that is specifically targeted to the hypothalamus. One way to measure such brain effects could be via non- invasive techniques such as measurement of blood oxygen level dependent (BOLD) brain responses, which would allow mapping of brain activities during functional MRI studies.

Indeed, as regards human longevity, the brain cross-talks with the periphery, via (but not limited to) its reciprocal connections with the metabolism-controlling signals (IIS, HPT and ANS). The links between these neuro- endocrine axes can be explored to find new therapeutic measures and strategies for slowing the pace of ageing, thereby facilitate health in old age.

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