PERSPECTIVE

Adipose-brain crosstalk: do adipokines have a role in neuroprotection?

Accumulating evidence from epidemiological and experimental studies indicate that obesity, and its related metabolic consequences of insulin resistance and type 2 diabetes, are associated with accelerated cognitive decline (Yates et al., 2012). The etiology of neurodegeneration in obesity is undoubtedly complex, with vascular, metabolic, inflammatory, and structural changes all likely to play a role (Yates et al., 2012). The discovery of leptin in 1994 and the subsequent advancement in our understanding that adipose tissue is an endocrine organ that can communicate with the brain to regulate appetite (Zhang et al., 1994) brings about the intriguing possibility that adipose-brain crosstalk can regulate aspects of neuronal physiology and pathology (Aguilar-Valles et al., 2015). Indeed neurons have been shown to express receptors for various adipokines, indicating that factors released from adipose tissue have the potential to communicate directly with the brain. Research in this area is relatively new, and while epidemiological data points towards the negative consequences of adipose-brain crosstalk (Whitmer et al., 2005), some intriguing new studies highlight that the secretory profile of adipose tissue might be involved in reduction in neurodegeneration *via* maintenance of neuronal viability (Tezapsidis et al., 2009; Wan et al., 2015).

Obesity is accompanied by inflammation in adipose tissue. Much of this inflammation is driven by infiltration of macrophages and other immune cells, although adipocytes themselves can also secrete pro-inflammatory cytokines (termed "adipokines"). By virtue of its elevated mass, pro-inflammatory secretions from macrophage-infiltrated adipose tissue are believed to contribute to systemic low-grade inflammation, insulin resistance, and vascular dysfunction in obesity (Ouchi et al., 2011). Increased expression of pro-inflammatory cytokines and activation of inflammatory responses are prominent in brain of Alzheimer's disease (AD) and aging-related dementia patients. Rodent models of obesity demonstrate elevated markers of brain inflammation and oxidative stress (Pistell et al., 2010) and a recent study has supported that humans with obesity have elevated markers of brain inflammation in hypothalamus assessed *in vivo* (Thaler et al., 2012). On the other hand, both *in vitro* and *in vivo* studies have reported that adipokines like leptin can mitigate systemic and central nervous system molecular pathologies associated with AD (Greco et al., 2009; Chakrabarti et al. 2015). Taken together, these findings provide speculative support that secretions from adipose tissue may impact brain inflammation and subsequently alter the risk of neurodegeneration in obesity. This also warrants immediate attention to profile the secretome based on the source of adipose tissue (lean vs. obese mouse models or human subjects), which may determine positive or negative adipose-brain cross talk.

Direct experimental evidence for adipose-brain crosstalk *in vivo* presents many technical challenges, particularly in humans. Recently, Wan et al. (2015) performed a series of experiments using an *in vitro* model of adipose-brain crosstalk in attempts to shed light on possible communication between human adipose tissue and neurons. Adipose tissue organ cultures, which retain *in vivo* secretory profile and intercellular communication between adipocytes and immune cells, were prepared from human donors. Adipose tissue organ culture (ATOC) conditioned media, containing the full ensemble of secretory products, was applied to human SH-SY5Y neuronal cells that were left untreated or treated with hydrogen peroxide (H_2O_2) to induce oxidative stress-induced cell death. ATOC conditioned media obtained from lean subjects had no effect on SH-SY5Y cell viability in the untreated condition but when neuronal cells were exposed to H_2O_2 they were almost completely protected from oxidative stress-induced cell death. However, ATOC conditioned media from obese donors lacked this protective effect. Since oxidative stress has been shown to drive neurodegenerative processes in AD and related dementias (Perry et al., 2002), the protective effect of lean ATOC conditioned media on SH-SY5Y neuronal cells suggests that some factor(s) secreted from lean adipose tissue may possess neuroprotective properties. Unfortunately the authors were unable to isolate what factor(s) were involved but they did show that when ATOC conditioned media was heated to denature proteins (10 minutes at 95°C) the neuroprotective effects were lost, implicating the peptide nature of the putative neuronal pro-survival adipokine(s).

These preliminary findings suggest that adipokines can regulate adipose-brain crosstalk and can play a role in neuroprotection or neurodegeneration depending on the adiposity status of the individual. Particularly, the results indicate that lean adipose tissue may secrete certain adipokines that are protective towards neurons whereas in obesity, adipose tissue may lack this protective potential. It appears that proteins or peptides are involved but it remains to be determined which adipokine(s) may possesses these neuroprotective properties.

It must be noted that these findings were obtained in an *ex vivo-in vitro* model system of adipose-brain crosstalk, so the results may not be entirely applicable to the much more complex system *in vivo*, where adipose secretions would interact with multiple different cell types and have to cross the blood-brain barrier prior to eliciting any effect on neurons. It seems clear that adipokines can cross the blood brain barrier, as shown by the classic findings involving leptin and appetite regulation (Zhang et al., 1994). However, the concentrations of adipokines reached in brain areas relevant to AD and dementia (*e.g.*, hippocampus) are currently unclear. Future research confirming the potential benefits of lean adipose tissue secretions on neuronal cell viability is warranted. In this regard, the adipose tissue transplantation model developed by Kahn and colleagues (Tran et al., 2008) would seem to be an ideal model to test this *in vivo*. Much like leptin treatment, lean adipose tissue transplantation into obese mice has been shown to reverse metabolic defects and improve glucose tolerance (Tran et al., 2008); could transplantation of lean

adipose tissue prevent brain inflammation and accelerated cognitive decline in obese animals? In addition, given the key role of glial cells in propagating brain inflammation in neurodegenerative diseases, the impact of adipokines on glial cell function warrants further investigation. An alternative line of research stemming from these findings could also include identifying the putative neuroprotective factor(s) secreted from lean adipose tissue for drug discovery purposes.

In summary, the recent findings of Wan et al. (2015) provide intriguing preliminary evidence that lean adipose tissue may secrete factors that possess neuroprotective properties. Confirmation of these findings *in vivo*, and further exploration into their identity, may enhance our understanding of how adipokines mediate adipose-brain cross-talk and provide new therapeutic targets to help protect neurons from damage.

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