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Editorial

Tau-ing and fro-ing: the tanycytic shuttle in neurodegeneration

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ABSTRACT

After more than a century since Alzheimer's disease (AD) was described and decades of research into β-amyloid and Tau proteins, mechanisms underlying pathogenic protein clearance from brain remain poorly understood. Recent research identifies tanycytes—specialized hypothalamic cells lining the third ventricle—as a previously unrecognized clearance system for brain Tau. These cells actively transport Tau from cerebrospinal fluid to blood via pituitary portal circulation but are dramatically fragmented in AD brains. Single-nucleus RNA sequencing reveals altered stress and transport gene expression in AD tanycytes, while functional studies show disrupted tanycytic transport reduces Tau efflux and exacerbates pathology. Beyond protein clearance, tanycytes maintain critical metabolic and neuroendocrine pathways influencing cognition. Their unique blood-brain interface position makes them attractive therapeutic targets. As transcriptomic evidence suggests tanycytes are hotspots for age-related changes, their dysfunction may herald "tanycytopathies" underlying multiple neurodegenerative disorders.

It is now 120 years since Alois Alzheimer first described his eponymous "disease" characterized by progressive cognitive loss, and more than 40 years since the two major proteins thought to underlie its pathogenesis – β-amyloid, which forms amyloid plaques, and Tau, which forms neurofibrillary tangles – were identified. Of the two, Tau, an essential structural component of neurons, is also implicated in several other disorders of brain function, and the detection of pathogenic forms of Tau in the blood now serves as a diagnostic biomarker for Alzheimer's disease (AD). However, despite the growing incidence of AD in countries with aging populations, and well-known susceptibility factors such as menopause or obesity, knowledge gaps in its pathogenesis remain, and treatment options are limited, not to say controversial. Thus, while it is evident that a healthy brain must have mechanisms in place to avoid the accumulation of toxic proteins such as abnormally phosphorylated Tau, the hypotheses put forward so far for its clearance and passage to the peripheral circulation are inadequate or incompatible with what is known of its kinetics. Intriguingly, we have now demonstrated that tanycytes – a little-known population of hypothalamic radial-glia-derived cells lining the third ventricle of the brain and extending long processes through the infundibulum – not only drain Tau from the brain, but are strikingly fragmented in the post mortem brains of patients with AD, highlighting both a new culprit in AD pathogenesis and a potential preventive or therapeutic target.

Tau efflux from the brain once it leaves neurons appears to be a multistep process, comprising, broadly, clearance from the interstitial fluid (ISF) and clearance from the cerebrospinal fluid (CSF). Under normal conditions, concentrations of Tau in the CSF and blood are proportional. Mechanisms such as the astrocyte-mediated glymphatic system are thought to dump proteins from the ISF into the CSF. But the question then arises: how does Tau make its way from the CSF to the peripheral circulation? Until now, the major route postulated has been through the cervical lymph nodes, which are fed by the CSF, but this route is slow, and Tau efflux still occurs in mice lacking a functional dural lymphatic system [1]. However, the brain also possesses a highly specialized population of cells that circumvent the blood-brain barrier, directly linking the CSF to the blood: the tanycytes. Indeed, tanycytes of the median eminence, the mouse equivalent of the infundibulum, are well known for their ability to shuttle metabolic hormones and nutrients from the blood to hypothalamic regulatory circuits that must perceive them in real time [2]. Our recent findings indicate that they also shuttle molecules in reverse, picking up Tau from the CSF and secreting it into the pituitary portal circulation, whence it reaches the peripheral blood more rapidly than through lymphatic drainage [3]. Selectively blocking vesicular transport in tanycytes dramatically reduces the amount of CSF-borne Tau reaching the blood (a phenomenon that mimics the reduced blood-to-CSF Tau ratio we observed in AD patients) and aggravates Tau pathology in the hippocampus, upstream of the hypothalamus, in the THY::Tau22 mouse model of AD and frontotemporal dementia (FTD) [3]. Even more interestingly, our unprecedented single-nucleus RNA sequencing of 31,492 hypothalamic cells, including 3131 tanycytes, from patients with AD and control subjects has revealed that, in addition to their structural degradation, tanycytes in AD show remarkable alterations in the expression of genes involved in cellular stress and vesicular transport [3]. Together, these results suggest that tanycytes constitute a previously unsuspected clearance system for Tau from the brain, and moreover, that tanycytic structural degradation and dysfunctional transcytosis may be elements crucial to the pathophysiology of certain neurological disorders.

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These findings are thought-provoking for several reasons. Firstly, while some hypothalamic nuclei do display amyloid plaques or neurofibrillary tangles, and early clinical manifestations of AD are evocative of hypothalamic dysfunction, the hypothalamus as a whole seems relatively spared by AD pathology [4]. Given the vital role played by its large number of nuclei and neuronal populations in the survival of the individual (energy and water/electrolyte balance, thermoregulation, circadian rhythms and sleep etc.) and the species (reproduction, growth, sexual and parental behaviour), it makes sense for the hypothalamus to be protected for as long as possible from pathogenetic changes. The massive uptake and elimination of Tau by median eminence tanycytes could thus have a two-fold function: draining pathogenic Tau from the immediate vicinity of sensitive hypothalamic circuits, and, accessorily, establishing a concentration gradient in the CSF that reduces its build-up in more distant brain regions. However, we do not yet know whether tanycytic fragmentation and altered vesicular transport are causes or effects of AD pathogenesis. The fact that tanycytes are not degraded in the brain of an FTD patient with tauopathy but show an entirely different type of morphological alteration suggests that at least their fragmentation may be part of the disease process rather than the consequence of an excessive pathological Tau load [3]. Similarly, the fact that tanycytic fragmentation could be observed in all the AD brains we examined, regardless of age or stage, suggests that their dysfunction may be the last straw for a beleaguered brain. Could early indicators of tanycytic distress be potential prognostic or diagnostic biomarkers of AD? Some putative candidates spring to mind: the differentially expressed genes indicative of cellular stress mentioned above [3], whose presence in the blood or CSF might serve as such indicators; tanycytic structural proteins released during their disintegration; resistance to metabolic signals such as leptin or insulin that can no longer access their target circuits; or eventually even changes in tanycytic transcytosis or connectivity visualizable with advances in brain imaging techniques.

Secondly, Tau is not the only pathogenic molecule that must be cleared from the brain. The accumulation of toxic proteins is associated not only with AD and other tauopathies, but synucleinopathies such as Parkinson's disease (α-synuclein), Huntington's disease (huntingtin), prion diseases and others. Certain hypothalamic nuclei or neuronal populations are particularly affected by the aggregation of some of these toxic proteins [4–6], which again raises the same questions as for Tau: could tanycytic efflux mechanisms for these other proteins protect hypothalamic nuclei, in particular those in contact with the CSF; and the corollary, does tanycytic dysfunction during pathogenesis result in the increased vulnerability of these nuclei and neuronal populations, or more distant ones through the alteration of CSF levels via a communicating-vessel mechanism? It is worth noting that the breakdown of tanycytic vesicular transport would also lead to broad metabolic imbalances, since tanycytes shuttle a large array of metabolic signals (glucose, leptin, ghrelin, insulin, fibroblast growth factor 21…) into the brain[2], and most of the disorders above also have a metabolic component, either as a susceptibility factor or as a comorbidity.

Thirdly, tanycytic degradation and dysfunction could participate in the cognitive decline associated with these disorders. Tanycytic processes surround the axons of numerous hypothalamic neuroendocrine neurons such as those producing gonadotropin-releasing hormone (GnRH), thyrotropin-releasing hormone etc., and control their access to pituitary portal capillaries, into which they must release their hormone. Tanycytes also mediate the feedback of these hormonal axes to the brain [2]. GnRH, a "reproductive" hormone, also appears to be important for the maintenance of brain connectivity and cognitive function in both Down syndrome and the Thy::TAU22 mouse model of AD/FTD [7]. The breakdown of tanycytic processes themselves or tanycytic vesicular transport could thus perturb these axes, with repercussions on cognitive performance.

And finally, thanks to their unique position at the interface between the brain and the peripheral circulation, tanycytes could represent novel and accessible targets for drugs that enhance their clearance of pathogenic brain proteins or the entry of peripheral hormones and nutrients, to preserve cognitive function and body-brain metabolic communication for as long as possible. In this context, tanycytes are responsible for transporting GLP-1 receptor agonists (GLP-1RAs), whose efficacy in treating obesity and type 2 diabetes is now well established, and whose beneficial effects in delaying or preventing dementia are beginning to be suspected [8], into the brain [9]. It remains to be determined whether any of these effects are mediated by the preservation or restoration of tanycytic vesicular transport. Interestingly, the breakdown of tanycytic leptin shuttling into the hypothalamus in diet-induced obesity has been shown to be reversed by the activation of ERK, involved in tanycytic exocytosis, by epidermal growth factor (EGF) [10,11]. While EGF cannot be used therapeutically because of its mitogenic effects, it might be worthwhile to ask if similar strategies could reboot tanycytic Tau clearance in the reverse direction in AD.

A recent intriguing transcriptomic study in mice indicates that tanycytes are a veritable hotspot for changes in gene expression in the aging brain [12]. If indeed these enigmatic cells play such a critical role in normal aging, it is to be expected that any slight deregulation of their structure or function would have knock-on effects on wider brain as well as bodily functions.

Are we witnessing the dawn of "tanycytopathies"?

Declaration of generative AI and AI-assisted technologies in the writing process

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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