COMMENTARY ON: **Tanycytes: a rich morphological history to underpin future molecular and physiological investigations. Esteban Rodriguez, Montserrat Guerra, Bruno Peruzzo, Juan Luis Blazquez, *J Neuroendocrinol* 2019; 31(3). Doi: 10.1111/jne.12690.**

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Tanycytes are specialized ependymo-glial cells found in circumventricular organs, which are highly vascularized midline structures lacking a complete blood-brain barrier (BBB). Tanycytes resemble embryonic radial glia cells. Their cell bodies line the ventricular floor, and their basal processes extend into the brain parenchyma and interact with fenestrated vasculature via endfeet, thereby coming into direct contact with the peripheral circulation[1]. Over the last decade, tanycytes have become increasingly recognized as gatekeepers of the neuroendocrine system. Tanycytes are involved in the regulation of the BBB in the circumventricular organs; and tanycyte-neuron and tanycyte-endothelial cell interactions play a key role in the control of neuroendocrine functions, including reproduction and energy metabolism[2-4]. Furthermore, a subpopulation of tanycytes displays neural stem cell potential *in-vitro* and *in-vivo*[5,6]. Most of the studies investigating the diverse functions of tanycytes have been focused on the median eminence (ME) and adjacent arcuate nucleus, where tanycytes are classified into four subtypes based on the location of their cell body and endfeet: α1, α2, β1, and β2. In this review, Rodriguez and colleagues provide a comprehensive overview of the communication between the cerebrospinal fluid and peripheral circulation, with a specific focus on the ultrastructural characterization of different subpopulations of tanycytes. The review also provides a morphological and functional comparison between tanycytes and a closely-related glia subtype, pituicytes. In addition to the detailed ultrastructural classifications, Rodriguez and colleagues summarize recent findings on the role of tanycytes as regulators of neuroendocrine hormones secretion and neural progenitor cells.

The first evidence suggesting a functional role for tanycytes in the neuroendocrine system came from an ultrastructural study by Prevot and colleagues in 1999, who found that tanycytes undergo structural remodeling during estrous cycle, and proposed that ME tanycytes play a role in the regulation of gonadotrophin releasing hormone (GnRH) release[7]. This groundbreaking study, as well as follow up work by the Prevot group, demonstrated that during diestrus, when gonadotropin output is low, GnRH secretory nerve terminals are ensheathed by tanycyte processes, preventing GnRH from reaching the portal vessels. On the day of proestrus, following the preovulatory GnRH/luteinizing hormone surge, tanycyte endfeet retract from the endothelium, unsheathing GnRH nerve terminals and allowing their contact with the portal vasculature. In addition to proposing the concept that tanycytes regulate GnRH release, these studies also provided a detailed characterization of the structural plasticity mediated by the orchestrated interplay between tanycytes, endothelial cells, and neurons, as well as underlying molecular signaling pathways[4,7,8]. Similar to the regulation of GnRH secretion, increasing evidence suggests that tanycytes are involved in the control of thyrotropin-releasing hormone (TRH) secretion[9-11]. A recent elegant study by the Schwaninger group has demonstrated that tanycytes control the hormonal output of the hypothalamic-pituitary-thyroid axis by regulating the release of TRH into the pituitary portal blood system via calcium-mediated remodeling of tanycytic endfeet[12].

Notably, Rodriguez et al. highlight unique ultrastructural features present in tanycytes, related to their function as an interface between the central nervous system and peripheral blood

circulation, focusing on tanycyte exclusive machinery for endocytosis and transcytosis. These observations are particulary important, as recent findings demonstrate that tanycytes can transport blood-borne BBB-impermeable substances, such as leptin and grehlin, from the peripheral circulation into the cerebrospinal fluid[13,14].

Rodriguez et al. discuss an interesting association and present an anatomical and functional comparison between tanycytes and pituicytes. Pituicytes are glial cells located at the posterior pituitary and play an important role in neurohypophyseal hormone release[15]. Similar to tanycytes, pituicytes can undergo dynamic morphological changes to modulate hormonal release by allowing direct contact between nerve terminals and the vasculature. In addition, pituicytes can also modulate hormonal release from adjacent terminals via local release of taurine[16]. The authors highlight that both pituicytes and tanycytes display specialized structures, where axons directly contact pituicyte/tanycyte processes, called synaptoid contacts[17]. The function of synaptoid contacts is unknown, however, since they are specifically formed between axons and the basal processes of pituicytes and tanycytes, these structures may facilitate pituicyte-neuron and tanycyte-neuron interactions. Studies describing the presence of synaptoid contacts between neurons and tanycytes are very limited[17], however synaptoid contacts between hormone-releasing neurons and pituicytes were found during periods of low hormone release. Moreover, there is a massive increase in the number of synaptoid contacts as well as increased pituicyte proliferation in response to increasing demand in hormonal release (e.g. following 72 hours dehydration)[15,18].

In conclusion, this comprehensive and timely review by Rodriguez et al. summarizes an extensive body of ultrastructural data describing tanycytes, highlighting their role in hormonal release, and progenitor potential. By analyzing the similarities with pituicytes, the authors indicate the potential importance of synaptoid contacts between tanycytes and axons, raising a fascinating idea that tanycytes can be directly regulated by neuronal inputs. The characterization of these structures, as well as deciphering their functional role, represent one of the most captivating questions to be addressed in the future.

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