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The survival of a mammalian species relies on the ability of its individuals to promptly, efficiently and reproducibly transmit homeostatic signals to the hypothalamic neuronal population that releases gonadotropin-releasing hormone (GnRH) and controls fertility. This requires the intervention of neuronal networks that make continual adjustments to brain function in response to moment-to-moment changes in physiological inputs throughout life (1-6). Intriguingly, a report in this issue of *Endocrinology* (7) reveals that in complement to these transsynaptic regulatory mechanisms, GnRH neurons themselves may have direct access to peripheral information via the extension of dendrites outside the blood-brain barrier (BBB).

In rodents, the cell bodies of GnRH neurons are diffusely distributed throughout the basal forebrain and are particularly abundant in the preoptic hypothalamic region at the level of the organum vasculosum of the lamina terminalis (OVLT). They exhibit a simple bipolar morphology with one or two very long dendritic processes that can extend up to 1 mm (8, 9). GnRH is released from neuroendocrine terminals in the median eminence at the base of the hypothalamus into the pituitary portal circulation, and stimulates the synthesis and release of the gonadotropins luteinizing hormone (LH) and follicle stimulating hormone (FSH), which in turn act on the ovaries and testes to regulate the secretion of sex steroids and the production of eggs and sperm. In addition to sending abundant axonal projections to the median eminence, GnRH neurons also extend fibers towards the OVLT (10, 11), a discrete

periventricular area with highly permeable, fenestrated endothelial cells that, as in the median eminence (12, 13), form a brain-periphery interface outside the BBB (12) - features that are characteristic of the circumventricular organs. However, in contrast to the median eminence, in which the primary direction of communication is from neural tissue (neuroendocrine terminals) to the circulation, it is thought that the primary functional consequence of the absence of a BBB in the OVLT is that this allows circulating factors that do not normally cross the barrier to gain direct access to neurons within the central nervous system (14).

The presence of GnRH fibers in the OVLT has been known since the first description of the neuroanatomical distribution of GnRH neurons in the mammalian brain by Barry and colleagues in 1973 (10). The finding by Broadwell and Brightman in 1976 (15) using intravenously injected horseradish peroxidase (HRP) as a tracer, that the OVLT is a neurohemal region with permeable blood vessels, together with studies by the Kordon laboratory in 1977 (16) demonstrating that microdissected OVLT explants release GnRH *in vitro* as efficiently as median eminence explants, has led to the longstanding concept that the OVLT contains GnRH neurosecretory axons.

The current study by Herde *et al*. (7), however, elegantly shows that the GnRH processes in the OVLT are mainly dendritic rather than axonal in nature, and that they may play an important role in the regulation of the GnRH system. Using a combination of neuroanatomical and electrophysiological approaches, the authors (7) convincingly demonstrate that about 70% of the GnRH neurons located in the vicinity of the OVLT (> 20% of the total population of GnRH neurons in the rostral preoptic region) extend dendrites into this structure. Using the same HRP method as that employed by Broadwell and Brightman (15), they show that most of these dendrites lie outside the BBB and that they respond electrophysiologically to locally applied transmitters, including peptides that are unlikely to cross the BBB, such as kisspeptin. In addition, using c-Fos as a marker of neuronal activation, the authors demonstrate that the majority of GnRH neurons with dendrites in the OVLT are activated at the time of the GnRH/LH surge, and thus conclude that these GnRH neurons, identified more

than two decades ago as probably contributing to the GnRH/LH surge (17, 18), are exposed to blood-borne molecules through their dendrites. This work thus identifies a new mechanism for the modulation of GnRH neurons that considerably extends the range of factors that they can directly sense and integrate for the control of fertility. These findings also raise the exciting possibility that these GnRH neurons, which have direct access to plasma vs. brain levels of hormones, glucose or other metabolic substrates, act as metabolic sensing neurons (19) that could be used by the neuroendocrine brain to match fertility levels to the homeostatic status of the individual (20). In line with this idea, recent studies have demonstrated that GnRH neurons in brain slices are capable of directly sensing glucose in a concentration-dependent manner and that this glucosensing is modulated by gonadal steroids (21, 22).

The study by Herde *et al.* (7) showing that subsets of GnRH neurons have direct access to the periphery greatly improves our understanding of how abrupt changes in the plasma level of molecules can acutely modulate pulsatile GnRH/LH secretion (23, 24), thus establishing a direct and permanent link between metabolism and fertility (20). From a practical point of view, the realization that the GnRH system directly senses molecules in the periphery opens up avenues for future research and the development of new therapeutic tools for infertility.

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