PTHrP regulates cerebral blood flow and is neuroprotective

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In 1925, Collip and Clark (the same Collip who had extracted insulin from the pancreas several years earlier) infused crude parathyroid extracts into dogs and observed a decrease in systemic blood pressure (5). Thus began an interest in the putative regulation of excitable cells by parathyroid hormone (PTH) that persisted for over 60 years (4). We now know that parathyroid hormone-related protein (PTHrP) is the natural ligand that mediates such effects and also that this regulation is local not systemic (4).

PTHrP was discovered in the late 1980s as the tumor product that is responsible for most instances of the syndrome of humoral hypercalcemia of malignancy (2, 12). As the (perhaps unfortunate) terminology implies, the PTH and PTHrP genes are related, and the NH2-terminal products of these two genes are highly homologous. Yet the functions of these two peptides are remarkably different: PTH is a classical systemic peptide hormone, whereas PTHrP is widely expressed in both fetal and adult tissues and normally functions entirely in an autocrine/paracrine fashion. In 1991, the PTH receptor was cloned and found to be expressed in PTH target cells and in lower abundance in the many tissues that also express the PTHrP gene, often in a classical “hand-in-glove” fashion that bespeaks autocrine/paracrine function (9, 11). Indeed, it is now clear that this receptor serves the NH2-terminal sequences of both PTH and PTHrP (and is therefore referred to as the type 1 PTH/PTHrP receptor or PTH-1R) and that the specificity of PTH and PTHrP signaling is entirely the result of the temporospatial and quantitative patterns of expression of the two ligand and the receptor genes (4, 9, 11, 15).

One well-established function of PTHrP is as a developmental regulatory molecule. PTHrP gene-manipulated mice display chondrodysplastic and ectodermal dysplastic phenotypes (10, 14, 17), and rare human syndromes have been identified that phenocopy these findings. These phenotypes reflect PTHrP regulation of endochondrial bone formation, mammary epithelial development, and tooth eruption as well as the morphogenesis of other structures.

Another emerging theme in PTHrP biology is the increasing assumption by PTHrP of functions that were previously attributed to PTH. The PTHrP gene seems to be expressed in every smooth muscle cell in the organism and to be capable of relaxing contiguous smooth muscle cells. For example, in so-called accommodative smooth muscle structures, such as the stomach, uterus, and bladder, the PTHrP gene is induced by mechanical stretch, and it is this stretch-induced PTHrP-driven relaxation that allows these structures to accommodate gradual filling (4, 16). Vascular smooth muscle cells also express both PTHrP and the PTH-1R, and PTHrP has been shown to regulate vasodilatation and flow in a number of arterial beds; the gist of these studies is that PTHrP seems to act as a local modulator of smooth muscle tone in specific vascular beds rather than as a systemic regulator (4, 13). The PTHrP and the PTH-1R genes are also expressed in endothelial cells and may affect endothelial cell function and/or that of subjacent smooth muscle cells (8). In fact, several recent studies provide convincing evidence that PTHrP can have potent antiangiogenic effects in vitro and in vivo (1, 6); these effects appear to be mediated by some combination of endothelial and smooth muscle actions.

Enter into this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology data from the Funk and Ritter laboratories (7) indicating that PTHrP may regulate central nervous system arterial flow and thereby serve a neuroprotective function. The key findings here are three: 1) that ischemia increases PTHrP in the endothelium of cerebral microvessels, 2) that PTHrP(1–34) superfluously dilates and markedly increases flow in pial vessels (seen as surrogates for the underlying cerebral vessels), and 3) that PTHrP(1–34) treatment limits the size of infarction in the rat middle cerebral artery occlusion model. Taken together, these findings constitute a well-constructed and novel package regarding PTHrP function in the cerebral vasculature. It was also reported recently that PTHrP is expressed in some neurons as a function of depolarization-driven L-channel Ca2+ influx and that the PTHrP so produced can feed back to dampen L-channel Ca2+ flow, protecting against Ca2+-associated neurotoxicity (3). It is possible that PTHrP of vascular origin could also enter into this neuroprotective pathway.

The findings reported by Funk et al. (7) will likely stimulate additional interest in the physiological and pathophysiological roles of PTHrP in the central nervous system. For example, in light of the data concerning PTHrP effects on the pial microcirculation, it would be of interest to investigate the putative role that PTHrP might play in other central vascular pathologies such as migraine, which is associated with pial arterial vasodilatation and an increase in vascular permeability.

The PTHrP story thus far has been a prototypical example of science being informed by a clinical syndrome, in this case by the discovery of a biologically
versatile molecule in a bad neighborhood. It will be of considerable interest to see if work in the next decade completes the circle that leads back to the clinic.

REFERENCES


