Editorial

The Anterior Pituitary Gland - Co-Ordinating an Alphabet of Peptides

The pituitary has been described as the Master Gland, even as we progress through the contemporary era of comprehensive proteomic arrays [1, 2]. The label is a reflection of the range of the gland's influences. The variety of contributions that the anterior pituitary gland makes to so many of the clearly observable events as well as covert metabolic processes in the body (e.g. stress, reproduction, growth) is a result of many pathways within the multi-cell tissue. The anterior pituitary is covered by a fibrous capsule, and the parenchyma is composed substantially of epithelial secretory cells arranged in cords or follicles. A network of fenestrated capillaries provides a system that enables transport of secretions to other distant tissues. The gland was until recent times summarised as having five endocrine cell types [3], which were later called corticotrophs, gonadotrophs, lactotrophs, somatotrophs and thyrotrophs, and additionally some apparently non-endocrine cells were identified, including folliculo-stellate cells. This model of the pituitary was a useful staging post for the investigative process. Biology is well fertilised with temporary hypotheses that enable questions to be formulated and prevailing views examined. There is sometimes danger that a plausible guess becomes sanctified as dogma. One can wonder if for a short time such occurred with this tidy model of the adenophypohysis, and in the mid 20th century some evidence for paracrine interactions were ignored by some researchers.

Nevertheless these ideas aroused considerable excitement, and were supported by much more detailed evidence than the earlier suggestions, proposed by Galen in the second century AD, that the pituitary was a receptacle for mucus that had drained from the brain through the pituitary stalk and filtered to the nasopharynx. In fact the speculatively inaccurate interpretation led to the gland being named from the Latin word for mucus, 'pituita', and the adjective 'pituitous' meaning mucoid was derived.

The adenohypophysis is a network of cells, which must co-ordinate their secretions so that the pituitary is able to respond with appropriate activity in particular circumstances. Further, pituitary cells are themselves dependent for their own differentiation and growth on a large group of compounds which are derived from the pituitary, such as nitric oxide, endothelin, and insulin-like growth factor. The hormones traditionally associated with the anterior pituitary gland were characterised, and the regulation for their secretion was proposed, by Geoffrey Harris, as being dependent on the capillaries connecting it to the hypothalamus. Then the releasing factors were discovered. In 1977 Roger Guilleman and Andrew Schally were awarded the Nobel Prize for their discoveries concerning the peptide hormone production of the brain. Interactions between these hypothalamic factors and intrapituitary compounds is an important component in regulating pituitary endocrine function (e.g. the GnRH- activin-follistatin module reviewed here [4]).

It was suggested that one type of endocrine cell was associated with one hormone (except gonadotrophs that were characterised as having two). This apparently sturdy scaffold, that was resting on careful experimental observations, nevertheless began to shudder as new observations became accepted but did not fit easily with the scheme. Co-localisation of hormones was detected in some cells e.g. prolactin with growth hormone (indeed the somatolactotroph is the subject of one of the reviews in this issue [5]), growth hormone or prolactin with gonadotrophins, and TSHβ with adrenocorticotrophic hormone and with growth hormone. Further, when cell populations that had been rich or depleted in a particular cell type were recombined, the results demonstrated that different types of cells interact to elicit a secreted product; thus a cell type was noted to not act in isolation from other types [6]. The relationship of the releasing factors from the hypothalamus had enticing clinical implications but at the same time became less certain [7]. In addition it seems that the folliculo-stellate cells act as an important communication system transmitting messages to the diverse cells within the pituitary (reviewed here [8]).

Subsequently, compounds that are potentially involved in these inter-cell paracrine processes have been identified [9]. Compounds were not confined to those secreted from the endocrine cells, and the non-endocrine cells such as folliculo-stellate cells have also been identified as a source of regulating peptides. Substances, such as activin [10], bradykinin [11, 12], cytokines [13], ... metalloproteinases [14], neurotensin [15], oxytocin [16, 17], ... urocortin [18], VEGF [19], neuropeptide W [20] ... and many, many more were found in the gland. Many compounds, as is well-recognised now, are not found exclusively in one tissue. An example is leptin, which first gained attention as a nutrition-related peptide, but is reviewed in this issue as a part-regulator of the ovulatory cycle [21]. On the other hand some petpides are recently identified and may be functional particularly in the hypothalamo-pituitary axis. One group of them, RFamide peptides, and the observations around them is reviewed here [22]. It would be possible (while admitting to a certain imprecision for some of the letters) to find pituitary compounds to start with every letter of the alphabet. The concept of paracrinicity and the importance of the microenvironment eventually took hold with regard to the pituitary [6, 23]. The role of the extracellular matrix (ECM) also became recognised (reviewed in this issue [24]). However direct evidence for paracrine action is yet to be obtained for some of the peptides that are potential mediators of inter-cell communication.

Aberrations of intra-pituitary (i.e paracrine) factors may be underlying features of pituitary pathologies, such as adenomas which can occur in the endocrine cell types. The metabolic errors can take the form of gain or loss of function. Modern clinical understanding of the role of the anterior pituitary was advanced by the success of hypophysectomies for acromegaly performed

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by Herman Schloffer in 1907 and Harvey Cushing in 1909. Increased knowledge has been acquired from diverse areas, and in this issue one review focuses on bony fishes [25].

Further, cell types have been observed to not be scattered randomly through the organ. There is a regionalisation that can be expected to affect specific functional responses. Gonadotrophs are especially in the anterior-ventral portion [26] near the borders of the intermediate and posterior lobes [27]. In mice, gonadotrophs aggregate in the cephalic ventromedial area [28]. Prolactin-containing cells are distributed throughout the gland [29, 30], although two groups of cells were distinguished, one centrally located and one forming a narrow peripheral rim on the gland [31]. In mice, lactotrophs are generally distributed except in the cephalic ventromedial area [28] and in chickens are localized in the cephalic lobe [32]. Lactotrophs exist in close proximity to gonadotrophs in some regions of the gland of rats and also horses [33-35]. Somatotrophs in rats are evenly distributed sagitally and rostrocaudally, but unevenly dorsoventrally [36]; in mice, somatotrophs are generally distributed except in the cephalic ventromedial area [28]; in chickens GH-secreting cells are localized in the caudal lobe [32]. Corticotrophs have mainly an even distribution, frequently in juxtaposition to somatotrophs [26] and are less frequently observed in the antero-ventral region and the area immediately adjacent to the intermediate lobe. In mice, corticotrophs are most commonly located near the ventral surface and in the lateral wings [28]. The scarce thyrotrophs are at the periphery of the gland [26], and in mice almost solely in the ventral region [28]. In an area near the intermediate lobe, GH cells, ACTH cells and TSH cells were not found [26] and the anterior-ventral portion of the gland contains few or no somatotrophs, corticotrophs, prolactin cells and thyrotrophs [26]. The effects of such regionalisation and the potential for paracrine interactions between cell types will affect functioning behaviour. It is suggested, for example, that the cells located in regions of the left lobe release more prolactin than those in right lobe areas, and cells from different regions are differentially responsive to hypothalamic secretagogues [37-39]. In fact in this issue it is noted that the distribution of cytokines, CXCL12 and CXCR4, was not homogeneous throughout the tissue, being undetectable in much of the gland and seen in some occasional zones of high expression [40].

There is a range of compounds and regulatory activities within the pituitary gland [41-43] and this issue reviews several aspects. One of the compounds, IGF-1, is found in different cell types in bony fishes and the integration and coordination of its roles is considered [25]. Many compounds are found in a number of places in the body, and will have diverse roles appropriate to each location. One of these compounds is the fascinating leptin, and its part in linking energy and reproductive function, acting on the expression of more than one pituitary hormone, is discussed in this issue [21]. The importance of the hypothalamus and local pituitary production combining to regulate growth in normal and pathological situations is noted and considered [40]. The effects on several cellular behaviours by a peptide makes understanding the gland a complex task. Examples are activin and follistatin, which may alter endocrine control, pituitary development and tumour growth and are reviewed in this issue [4]. Another paper considers one of the most recently revealed group of potential regulating factors, the RFamide peptides, and discusses evidence for its activity on pituitary cells [22]. Sitting amongst the well-recognised endocrine cells are those cells that are being assigned an increasingly prominent role in pituitary function, the folliculo-stellate cells; these are reviewed in detail, including observations that they exhibit characteristics associated with stem cells [8]. The distance that understanding of the pituitary has moved since the model that was envisaged at the time the releasing factors were discovered is illustrated by the investigation of the mixed-hormone cell, the somatolactotroph, and the involvement of follistatin, a non-traditional protein regulated by one of the first releasing factors identified, TRH [5]. The microenvironment is now well established as an important concept for understanding cell behaviour, and the activities that the extracellular matrix has been identified to exhibit in pituitary cell behaviour is reviewed in another manuscript [24].

This issue of The Open Neuroendocrinology Journal illustrates that while once the pituitary was described by several hormones and simply-defined cell types, the understanding of it is now much more complex. No one currently is tempted to be dogmatic about the detail. In addition this issue notes pituitary characteristics of several species. Understanding the fascinating network that resides in it is the basis of defining events in the pituitary. The associated processes are required to provide the activating and suppressing signals for physiological functioning of this disparate array of cells. Progress has been made; we await further observations that will assist in mapping the linkages that enable the pituitary to exert its profound effects on a wide range of distant organs.

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