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Review

The anterior pituitary gap junctions: potential targets for toxicants

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ABSTRACT

The anterior pituitary regulates endocrine organs and physiological activities in the body. Environmental pollutants and drugs deleterious to the endocrine system may affect anterior pituitary activity through direct action on anterior pituitary cells. Within the gland, endocrine and folliculostellate cells are organized into and function as individual tridimensional networks, each network regulating its activity by coordinating the connected cells' responses to physiological or pathological cues. The gap junctions connecting endocrine cells and/or folliculostellate cells allow transmission of information among cells that is necessary for adequate network function. Toxicants may affect gap junctions as well as the physiology of the anterior pituitary. However, whether toxicants effects on anterior pituitary hormone secretion involve gap junctions is unknown. The folliculostellate cell gap junctions are sensitive to hormones, cytokines and growth factors. These cells may be an interesting experimental model for evaluating whether toxicants target anterior pituitary gap junctions.

1. The anterior pituitary

The mammalian hypophysis or pituitary gland is located in the "sella turcic" of the sphenoid bone. The gland is composed of two parts each of distinct embryological origin: the neurohypophysis and the adenohypophysis. The neurohypophysis originates from the floor of the developing diencephalon whereas the adenohypophysis develops from an evagination of the roof of the oral epithelium, the Rathke's pouch. The proximal wall of the Rathke's pouch is in contact with the neural lobe of the pituitary and gives rise to the "*pars intermedia*". The lateral lobes of the Rathke's pouch wrap around the pituitary stalk where they form the "*pars tuberalis*". The distal wall of the Rathke's pouch gives rise the anterior lobe of the adenohypophysis, the "*pars distalis*".

The *pars distalis* or anterior pituitary is composed of several differentiated cells. The isolation and purification of anterior pituitary hormones allowed for the identification of different endocrine cells, each secreting at least one hormone: lactotropes secrete prolactin (Prl), gonadotropes secrete the gonadotropins, luteinizing hormone (LH) and folliculo-stimulating hormone (FSH), thyrotropes secrete thyroid-stimulating hormone (TSH), somatotropes secrete growth hormone (GH) and corticotropes secrete the adrenocorticotropic hormone (ACTH). In addition, agranular, non-endocrine, stellate-shaped cells, so-called folliculostellate (FS) cells are contained in the parenchyma of the anterior pituitary gland [1]. The FS cells secrete cytokines and factors controlling anterior pituitary endocrine activities [2–4].

By secreting several hormones, the anterior pituitary controls development, growth, metabolism, reproduction, lactation, and stress and immune responses. The regulation of anterior pituitary hormone release is a complex process that requires the integration of multiple levels of control. Hypothalamic stimulating and inhibiting factors released by neurosecretory neurons at the level of the median eminence of the hypothalamus reach the anterior pituitary through the hypophyseal portal veins. The hormones released by end-target organs and tissues reach the anterior pituitary gland through the systemic circulation and contribute to regulate anterior pituitary secretion. In addition, each hypothalamic-pituitary-organ axis influences the remaining axes and helps the anterior pituitary to adapt to physiological conditions of the moment [5,6]. Within the anterior pituitary itself, cells regulate hormone secretion in "paracrine", "juxtacrine" or "autocrine" manners [7–13].

The role of cell-to-cell interactions in coordinating the cells' behaviour to ensure an appropriate anterior pituitary hormone response is receiving increasing attention. Anterior pituitary cells interact with neighbouring cells through junctional complexes. As their name implies, the complexed are composed of different types of intercellular junctions namely: tight junctions, adhering junctions, desmosomes and gap junctions (Fig. 1A). Annular junctional complexes are extensive. The fact that they are frequently encountered in anterior pituitary cells is suggestive of a rapid turnover of the many different types of junctions (Fig. 1A and A'). The endocrine cells are joined to FS cells by different types of intercellular junctions (Fig. 1B). Tight junctions, adherens junctions, desmosomes (Fig. 1A, B and E) and gap junctions (Fig. 1B, C and D, and [14,15]) join neighbouring FS cells. Endoplasmic reticulum cisternae typically accompany the junctions (Fig. 1D). The presence of

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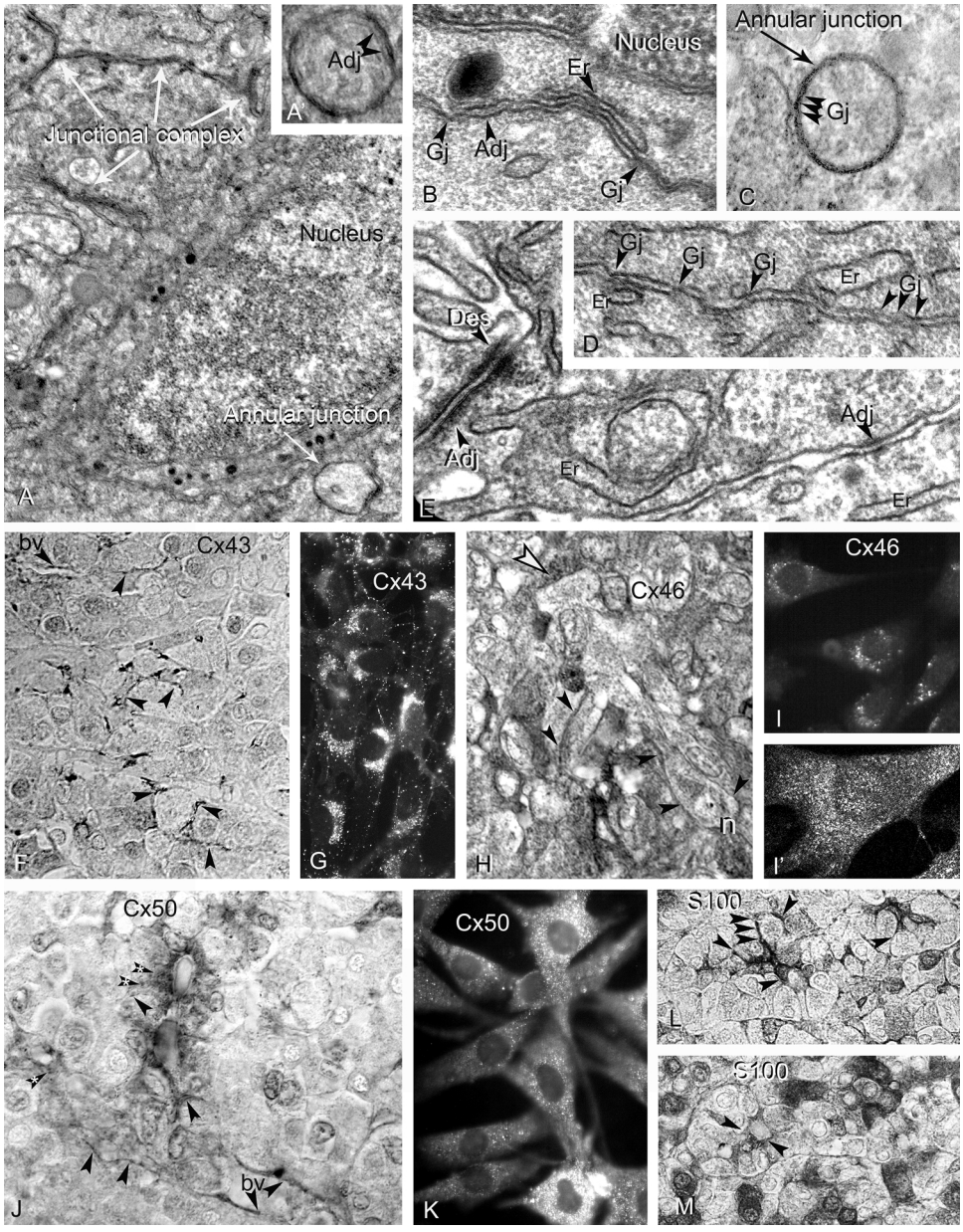

Fig. 1. A-E: Electron micrographs of thin sections of intercellular junctions in the mink anterior pituitary. **A**: An extensive junctional complex exhibiting roughly aligned cell junctions of different types joining non endocrine cells is identified at the top of the figure. An annular junctional complex made up of cell junctions of different types occupies the bottom right in Fig. 1A. In Fig. 1A' the annular junctional complexes contains mainly adhering junctions (Adj). **B**: Two minute gap junctions are identified Gj, the one on the left of the figure is accompanied by a small adhering junction (Adj). The membrane segment involved in the intercellular contact is sided by short cisternae of endoplasmic reticulum (Er). **C**: In Figure C, the annular junctional complex shown contains principally gap junctions (Gj). **D**: Short cisternae of endoplasmic reticulum (Er) are in close proximity with the adjoined cell membranes engaged in cell junctions. The anterior pituitary cells are joined by numerous albeit typically minute gap junctions (Gj). A: 38,000X; A': 72,000; B: 70,000X; C: 63,000X; D: 70,000X; E: 72,000 × . **F**: Cx3-positive gap junctions (arrowheads) are plentiful in male mink FS cells during the breeding season. In addition, Cx43 labeling is found in the blood vessels (bv). **G**: TtT/GF cells exhibit intense Cx43 labelling at the cell membrane and in the perinuclear area. **H**: Cx46 labeling is found not only at the cell membrane involved in the intercellular contacts (arrowheads) but also within the cell (large arrowhead). In addition, a minute punctate Cx46 labeling is seen in the vicinity of the nucleus (n) and within the nucleolus of FS cells in this male mink anterior pituitary harvested during the breading season. **I**: Cx46 localizes to the perinuclear region in TtT/GF cells. **I'**: Confocal microscopy showing Cx46-immunoreactivity in the cell nucleus. J: The arrowheads covered by an asterisk point to minute Cx50-positive granules within the cell body of a FS cell occupying the center of a follicle (arrowheads) in a male mink anterior pituitary during the breeding season while the remaining arrowheads point to Cx50 labeling of the cell membrane. In addition, Cx50 labels the blood vessels (bv). **K**: However, Cx50 labeling is mostly cytoplasmic in resting TtT/F cells. **L**: The lactating female mink FS cells of the anterior pituitary typically send extensive thin cytoplasmic projections that are S100-positive (arrowheads) rendering their cell bodies and projections readily visible within the follicle during the period of high Prl secretion. **M**: By contrast, the non-lactating female mink pituitary FS cells are smaller and their S100-positive cytoplasmic projections are somewhat shorter. F: 280X; G: 530; H: 490X; I: 670; I': 1350; J: 620X; L-M: 260 × .

gap junctions among anterior pituitary cells indicates that they are highly communicating cells. Recycled gap junctions are found in annular junctions (Fig. 1C).

FS cells and endocrine cells of the same lineage establish homotypic contacts among themselves that allow them to form individual cellular tridimensional networks within the pituitary parenchyma [16,17]. Recent investigations begin to identify not only the cell junctions involved in the organization of these networks but, in addition, their essential functional contribution to the network [18–24]. Moreover, hypothalamic and peripheral hormones and physiological stimuli influence the network shape and activity [25–29]. In this manner, gap junctions involved in the establishing of the network are potential targets for environmental toxins with hormone-like activities.

2. Toxicant effects on anterior pituitary function

The fine tuning of anterior pituitary hormone secretion ensures optimal and appropriate responses of the gland to physiological needs and environmental challenges. Environmental pollutants and drugs that compromise this delicate hormonal equilibrium may result in various pathologies such as infertility, obesity and cancer [30–32]. This notwithstanding, the research focussed on the effect of toxicants and drugs on end-target organs like the gonads and the adrenal cortex. To date reports on the effect of metals and xenobiotics, particularly the "endocrine-disrupting chemicals" on the anterior pituitary are scarce. These studies show that toxicants affect anterior hormone levels in humans and rodents, the extent depending on factors like, age, sex, dose and time of exposure [24,33–41]. When interfering with anterior pituitary hormone secretion, toxicants may act directly on pituitary cells or they may have secondary and tertiary effects when interfering with