ENDOCRINE CELL EXCITABILITY OPENS THE WAY TO NOVEL PHARMACOLOGICAL INTERVENTION: EXAMPLE OF THE ANTERIOR PITUITARY CELL

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For a long time, endocrine cell investigators were biochemists rather than electricians. Credit is due to them for having developed the concept of receptors and second messengers, which was later to profit neurobiologists. However, in a reciprocal fashion, the notion of cell excitability, originally described by the neurobiologists as a property exclusive to neurons and muscles, is now being extended to endocrine tissue.

During the past decade the neurons have gradually lost their exclusive privilege of electrophysiological properties; numerous endocrine cells have been shown to have comparable membrane characteristics such as excitability, and voltage-sensitive calcium channels. These findings were in line with the concept of the APUD system developed by Pearse (Pearse, 1983), which is more or less superimposable on Fujita's paraneuron (Fujita et al., 1984) as based on embryological, morphological and functional data. Among endocrine cells which respond to stimuli with action potentials, we may cite chromaffin cells (Biales et al., 1976), pancreatic cells (Matthews and Sakamoto, 1975a) and finally adenohypophyseal cells (Dufy et al., 1980).

Concerning the latter, our work has principally been carried out on somatotroph and lactotroph cells which respectively secrete growth hormone (GH) and prolactin (PRL). A major difference between these cells and neurons is that the membrane regions from which the secretory product is liberated, and the regions receptive to incoming stimuli are undissociated on the cell membrane. There are no membrane prolongations, and no synaptic terminals. Such a cell is thus perfectly adapted to the study of stimulus-secretion coupling.

As in the case of the neuron, liberation is strictly dependent on the level of intracellular calcium $[Ca^{2+}]_i$, i.e., an increase in $[Ca^{2+}]_i$ leads to an increase in hormone release, and vice versa.

Besides well-known intracellular mechanisms that have been shown to increase or to decrease $[Ca^{2+}]_i$ by directly acting on cytosolic calcium pools such as those in the endoplasmic reticulum and calciosomes, there exists another possibility involving extracellular calcium. The concentration of extracellular calcium is approximately $2 \times 10^4$ times greater.

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than that in the cytosol (2 mM vs. 0.1 μM), and in addition to the calcium/sodium exchange and/or the ATP-dependent calcium pump, a preferential way for calcium entry into the cell could be via specific channels located in the cytoplasmic membrane. During the last decade, considerable data have accumulated indicating the importance of membrane ionic permeability in the mechanism of stimulus-secretion coupling (Dufy et al., 1982). Several groups have shown that both tumoral and normal pituitary cells are excitable, i.e., they are able to display action potentials, the majority of them being calcium dependent (review in Israel and Vincent, 1990). Moreover, the presence of sodium and potassium channels, by elevating or decreasing the resting membrane potential, can give rise to regenerative properties and control the opening of calcium channels. One can therefore postulate that membrane electrical properties could be implicated in hormone release processes via modulation of the intracellular calcium level.

Another interesting point of comparison was found with the discovery that somatotroph and lactotroph cells show a number of receptors for different types of neurotransmitters in common with cells of the central nervous system i.e., for dopamine (DA), somatostatin (SRIF), thyreotropin (TRH), angiotensin II (A II), GABA and endorphins. The transduction mechanisms and second messengers brought into play by these factors are also the same for the two cell types, i.e., G proteins, phospholipids and nucleotides. It is therefore clear that these endocrine cells are an excellent model for the pharmacological study of transduction mechanisms.

As in the case of the nervous system, anterior pituitary cells show a certain degree of plasticity which gives rise to modifications in their pharmacological properties according to the physiological environment, or following steroid hormone treatment, in vitro as well as in vivo.

Finally, certain technical advantages to these cells are worth emphasizing. Somatotrophs and lactotrophs can be obtained as almost pure populations for in vitro cell culture. Their morphological characteristics make them ideal for patch-clamp studies, with the possibility of working on individual pre-identified cells. It is now evident that these cells constitute an unique model for a pharmacological approach to the study of ionic channels.

MODELS

Normal vs. Tumor
The first attempt to record the electrical activity from anterior pituitary cells in vivo was performed about 20 years ago by York and colleagues (York et al., 1971). In 1975, Kidokoro first reported results obtained from rat tumor cells, i.e., GH3 cells, which secrete both prolactin and growth hormone (Kidokoro, 1975). These cells were shown to exhibit action potentials and their spontaneous activity was enhanced by thyrotropin-releasing hormone (TRH). Several groups confirmed these findings and showed that TRH acted through a biphasic response, i.e., a hyperpolarization followed by a slight depolarization that could