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PERSPECTIVES

Ion channel activity drives ion channel expression

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During embryonic development, excitable cells acquire a repertoire of ion channels that finely tune their electrical properties. Although the mechanisms by which an excitable cell selects its complement of ion channels are poorly defined, cell-autonomous as well as non-autonomous programmes of differentiation have been implicated. These issues have frequently been studied in non-mammalian vertebrates and chordates. These systems offer the advantage that developing embryonic cells are identifiable at early stages of their differentiation, often prior to morphological differentiation. Moreover, embryonic cells can be studied electrophysiologically enabling assessment of emergent excitable membrane properties.

The channels that an excitable cell selects are in a position to regulate transient elevations of intracellular calcium, an important intracellular messenger. Further, depending on the total repertoire of channels present at a particular developmental stage, electrical activity and subsequent calcium entry may occur spontaneously.

Such early periods of activity influence several aspects of subsequent cellular differentiation (Spitzer *et al.* 1994) including ion channel expression, as shown by Dallman *et al.* (1998) in this issue of *The Journal of Physiology*.

In neurons, activity-dependent modulation of cellular properties is prevalent during embryonic development. Do non-neuronal excitable cells also display spontaneous activity during embryonic development? Developing muscle cells of *Xenopus laevis* demonstrate an early period of spontaneously occurring calcium transients (Ferrari *et al.* 1996). Calcium transients were imaged using fluorescent calcium indicator dyes, a relatively non-invasive method which potentially reports the natural frequency of transients. In this issue Dallman *et al.* 1998 address this question using the ascidian embryo which has the advantage that cells of the muscle lineage are easily identified due to a unique orange pigmentation. The developmentally regulated expression of an ensemble of ion currents in ascidian muscle predicts a restricted period of spontaneous activity (Greaves *et al.* 1996). This prediction was confirmed previously by recording action potentials using perforated-

patch whole cell techniques (Greaves *et al.* 1996) and recently by Dallman *et al.* (1998) using cell-attached recording to register action potentials. While calcium transients were not directly imaged, the activity measured most likely leads to intracellular calcium transients since action potentials of ascidian muscle cells are calcium dependent. This contrasts with the source of calcium for transients in developing *Xenopus* muscle cells, which rely solely upon internal stores (Ferrari *et al.* 1996).

Spontaneous and temporally restricted calcium transients, then, are not unique to developing neurons and may be a general feature of development of excitable cells. Do they provide differentiation cues in muscle as they do in neurons? Again, the answer appears to be yes. In *Xenopus* muscle, suppression of transients for an ~4 h period prevents normal morphological and cytoskeletal differentiation; however, development of the acetylcholine-induced response and an inwardly rectifying potassium current is unaffected (Ferrari *et al.* 1996). In ascidian muscle cells, three voltage-dependent ion currents (calcium current, I_{Ca} ; inwardly rectifying potassium current, $I_{K(IR)}$; and calcium-dependent potassium current, $I_{K(Ca)}$) undergo developmental regulation and their normal expression requires new RNA synthesis (Greaves *et al.* 1996; Dallman *et al.* 1998). However, as reported in this issue of *The Journal of Physiology*, block of spontaneous activity for 6 h prevents subsequent maturation of only one of the three currents, $I_{K(Ca)}$ (Dallman *et al.* 1998), even though general synthesis of RNA is permitted.

By regulating expression of $I_{K(Ca)}$, activity allows for its own negative feedback regulation. Since excessive activity can lead to cellular toxicity and death, it is strategic for activity to recruit its own limiting mechanisms. In the proposed negative feedback loop, the regulated variable is activity and the sensor detects intracellular calcium concentration. What is unusual about this negative feedback loop is that the identity of the sensor is developmentally regulated. At early stages, the sensor detects calcium elevations brought about by spontaneous activity and somehow feeds into biochemical cascades that upregulate functional expression of $I_{K(Ca)}$. In contrast, at later stages, the sensor is the calcium regulatory portion of the K_{Ca} channel itself. Increased K_{Ca} channel activity can thus terminate and consequently restrict periods of spontaneous activity to specific developmental windows. Dallman *et al.* (1998) demonstrate that expression of $I_{K(Ca)}$ can be selectively prevented by suppressing spontaneous activity during a limited period of development. Under these conditions, one would expect that

the period of spontaneous activity would be extended and not restricted to a particular developmental window.

How does activity lead to functional up-regulation of $I_{K(Ca)}$? A first step in answering this question is to identify the relevant $I_{K(Ca)}$. Three general classes of K_{Ca} channels (BK, IK and SK) exist and are distinguishable on the basis of single channel conductance, pharmacological profiles and molecular identities. Expression of genes encoding the BK type *Slo*, are subject to dynamic regulation at many levels. In developing amphibian and chick neurons, the calcium sensitivity of $I_{K(Ca)}$ is developmentally regulated (Blair & Dionne, 1985; Subramony *et al.* 1997). Activation of the hypothalamic-pituitary-adrenal axis in rats modifies the pattern of *Slo* splice variants present in adrenal chromaffin cells (Xie & McCobb, 1998); stressful treatments promote expression of variants that would increase repetitive firing and secretion of adrenaline (epinephrine). The proven ability to combine functional and molecular analyses in ascidians (Okamura *et al.* 1994) indicates that studies of development of their electrical excitability can lead to identification of molecules that play a key role and underscores the undiminished power of these systems.

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