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PERSPECTIVES

Potassium channels shape and brake primary sensory neurone excitability

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Categorizing sensory neurones into groups has been an old game already played by classic neuroscientists who tried to classify sensory ganglion neurones according to cell body size, diameter, circumvolutions of the axon and presence or absence of a myelin sheath (Ramón y Cajal, 1899).

With the advent of electrophysiological techniques, functional differences among sensory neurones of somatic and visceral ganglia were also recognized, first in conduction velocity of their peripheral axons (Iggo, 1960) and later on passive and active membrane properties of the soma (Gallego & Eyzaguirre, 1978). A correlation between certain soma membrane properties and the transduction characteristics of receptor terminals of sensory ganglion neurones was first noticed by Belmonte & Gallego (1983) in chemoreceptor and mechanoreceptor petrosal ganglion neurones innervating, respectively, carotid body and sinus. Chemoreceptor neurones exhibited a wide somatic action potential (AP) with a hump in the falling phase and a long afterhyperpolarization (AHP) while APs produced by mechanosensory baroreceptor neurones were fast, without hump and with a short AHP. Likewise, neurones of the dorsal root ganglion exhibited different soma membrane properties depending on the sensory receptive properties of their peripheral endings (Koerber *et al.* 1988). Studies in trigeminal ganglion (TG) neurones confirmed that their functional properties correlate with distinct electrophysiological phenotypes. Thus, stretch-activated neurones had brief APs and a strongly adapting firing response, while neurones activated by the pungent compound capsaicin (i.e. putative nociceptors) had broad AP and a more sustained firing (Viana *et al.* 2002). A distinct electrophysiological phenotype was also evident for trigeminal cold thermoreceptors (Viana *et al.* 2002). These, and a myriad of other papers, have suggested a functional relationship between electrical properties of the soma and the transduction characteristics of their receptive terminals.

In this issue of *The Journal of Physiology*, Catacuzzeno and colleagues (Catacuzzeno *et al.* 2008) provide additional insight into the ionic mechanisms underlying electrophysiological differences between mouse TG neurones. They identify three distinct firing patterns among TG neurones which correlate with the biophysical and pharmacological signatures of different low-threshold K^+ currents. One population, labelled MF, fired repetitively during depolarizing pulses. This firing pattern was the most frequent ($> 50\%$) and was typical of small-diameter neurones with a long-duration action potential (AP). Furthermore, most of these neurones were activated by capsaicin suggesting a nociceptive function. Low-threshold K^+ currents in MF neurones were small and slowly activating and were not explored in detail. A second population ($\sim$25%), DMF neurones, fired repetitively but with a marked delay in the start of the response. They showed a large fast transient current with pharmacological characteristics consistent with those of Kv1.4 channels. DMF neurones were also small and had a less prominent hump in the AP but they were insensitive to capsaicin. The functional phenotype of these neurones is unknown. A third population ($\sim$25%) was labelled SS for firing a single, brief AP during long depolarizing pulses. Most characteristic was the expression of a sustained, fast activating K^+ current. Inhibition of this current with dendrotoxin I (DTX-I), a blocker of several Kv1 type channels, transformed the firing phenotype. The large size of these neurones, their infrequent response to capsaicin, and their firing are consistent with a mechanosensitive role.

Further pharmacological studies, combined with the characterization of transgenic mice and the use of siRNA techniques are needed to pinpoint the exact molecular nature of these potassium currents. These studies are far from simple, especially since native functional channels may consist of heteromeric combinations of different subunits. It is also surprising the apparent interspecies variation: for example, most small rat DRG neurones express a prominent DTX-sensitive current (Gruss *et al.* 2006), a result at odds with the study by Cataccuzeno *et al.* in the mouse. Furthermore, the three classes of neurones distinguished on the basis of their macroscopic K^+ currents innervate a much larger functional variety of peripheral sensory endings. Therefore, differences in K^+ channel expression may only contribute broadly to determine the encoding properties of primary sensory neurones.

In summary, we learned in this carefully performed study that the firing of specific sensory neurones is critically regulated by distinct K^+ currents. Could the response to natural stimuli also be influenced by regulated expression of K^+ channels? This of course needs to be tested at sensory nerve terminals, the site of transduction for external stimuli. Along this line, recording from neuromas, the expanded sensory ending produced after a peripheral nerve injury, Roza *et al.* (2006) showed that low doses of the K^+ channel blocker 4-AP produced a dramatic enhancement of excitability to thermal pulses of mechanosensitive endings.

The potential clinical implications of these findings are important. Indeed, they suggest that specific modulators of potassium channels could stabilize the membrane potential of selective populations of sensory receptors, opening new approaches for the rational treatment of conditions ranging from painful neuropathies to migraine.

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