

NEURONAL COLD SENSITIVITY: A COMPUTATIONAL STUDY ABOUT DISCREPANCIES BETWEEN SPONTANEOUSLY ACTIVE RECEPTORS AND TRANSIENTLY DISCHARGING SOMATA.

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ABSTRACT

Neuronal cold sensitivity has recently attracted particular attention with several reports and comments on cold and menthol sensitive ion channels and membrane receptors [7,8,9]. However, all of these studies were performed at the somata of isolated and cultured cell bodies from trigeminal and dorsal root ganglia although the physiological sites of temperature encoding are the sensory nerve terminals in the skin. The reason is that these are very tiny and sparsely distributed nerve endings [5] which, so far, prevented any direct recordings of membrane potentials and ion currents.

Information about cold transduction, previous to the above mentioned studies on neurons somata, could only be obtained with extracellular action potential recordings from the afferent fibres. Based on such impulse recordings, cold receptors could clearly be classified according to the following criteria [5]: a) spontaneous activity at constant temperatures over a broad temperature range (between about 5°C and 35°C), b) transient frequency increase on fast cooling and transient inhibition of the firing rate on fast warming, c) no responses to moderate mechanical stimuli.

Further impulse patterns analysis indicated that stimulus encoding in cold receptors – as well as in other temperature sensitive receptors - is based on the modulation of membrane potential oscillations with contribution of noise [1,2] which, more recently, could successfully be simulated with a Hodgkin-Huxley-type computer model [3,4]. Physiological plausible temperature scaling of the time constant of ion current activation revealed to be sufficient – with minor changes of the maximum conductances - to account for the static temperature dependencies. However, there was no experimentally justified

idea about the nature of the membrane processes which generate the specific dynamic responses of cold receptors. This was one of the last unsolved problems of peripheral sensory receptors.

Hence, above mentioned recordings of cold sensitive ion currents are considered an essential step forward towards a better understanding of the ionic mechanisms of cold transduction with comments like “Cold emerging from the fog” [7]. However, the same authors also say that “much remains to be clarified”. One of the reasons is that the cold receptors somata obviously lack major features of the cold sensitive nerve endings. The most obvious difference is that the somata fire action potentials only transiently during fast cooling but do not show spontaneous discharges at constant temperatures - the first point of the criteria for cold receptors. Such discrepancies raise the question whether the results from the somata can really shed light on transduction mechanisms at the sensory terminals. As the discrepancies undoubtedly exist, we have to deal with the more specific question whether the lack of spontaneous activity is caused by qualitative differences of cold sensitive membrane mechanisms or by rather unspecific, quantitative differences between receptors and somata.

It is near at hand first of all to consider the morphological differences between cell bodies and peripheral nerve ending, i.e. the differences in size. The somata are, for sure, manifolds bigger than the terminals which means that they should have a much higher membrane capacitance than the tiny nerve terminals. Also the leakage conductance should be much higher while the expression of specific ion channels might not increase to the same extent. Hence, the idea is that the lack of spontaneous activity in the soma is due to a lower density of cold sensitive ion channels.

This cannot be tested experimentally for the same reasons that prevent intracellular recordings from the nerve terminal: no access. However, we can make use of the above mentioned computer model [3,4] in which we have additionally included a transient cold current I_{cold} to account for the dynamic responses. I_{cold} depends on the slope of the temperature change ($1\mu\text{A}/\text{cm}^2 \cdot \text{s}$ per $^{\circ}\text{C}/\text{s}$) and relaxates to zero at a time constant of 4 s. Fig. 1A shows an impulse recording from a peripheral cold sensitive afferent and Fig. 1B the corresponding computer simulation which mimics the experimental impulse sequences fairly well. I_{cold} introduces a transient high frequency discharge with subsequent adaptation to static activity including burst discharges (impulse groups) riding on subthreshold oscillations.

Next, we tested whether spontaneous activity is eliminated when the size of our model neuron is increased and the ion channel density is reduced. As exact information about the absolute values of membrane properties and the size of the peripheral terminals is not available, we linearly increased the membrane capacitance and leakage conductance and kept all other model parameters constant (Fig. 1C). Indeed, spike activity disappeared already at an approximately 60% increase of these values. At an about 100% increase also subthreshold oscillations were almost eliminated. A stable membrane potential with only random fluctuations remained.

Now we had to make the second test to see whether under these conditions dynamical responses on a cold stimulus still can be induced. Indeed, the cold stimulus also induced a transient discharge in the model soma which is lacking spontaneous activity (Fig. 1D). The response is very similar to the recent electrophysiological recordings from isolated somata as, for example, shown in Viana et al., Figs. 2 and 3 [9]. Even transient occurrences of

slow-wave oscillations can be seen. Hence, the “cold receptor model” has been converted into a “soma model” with modifications of only passive membrane properties.

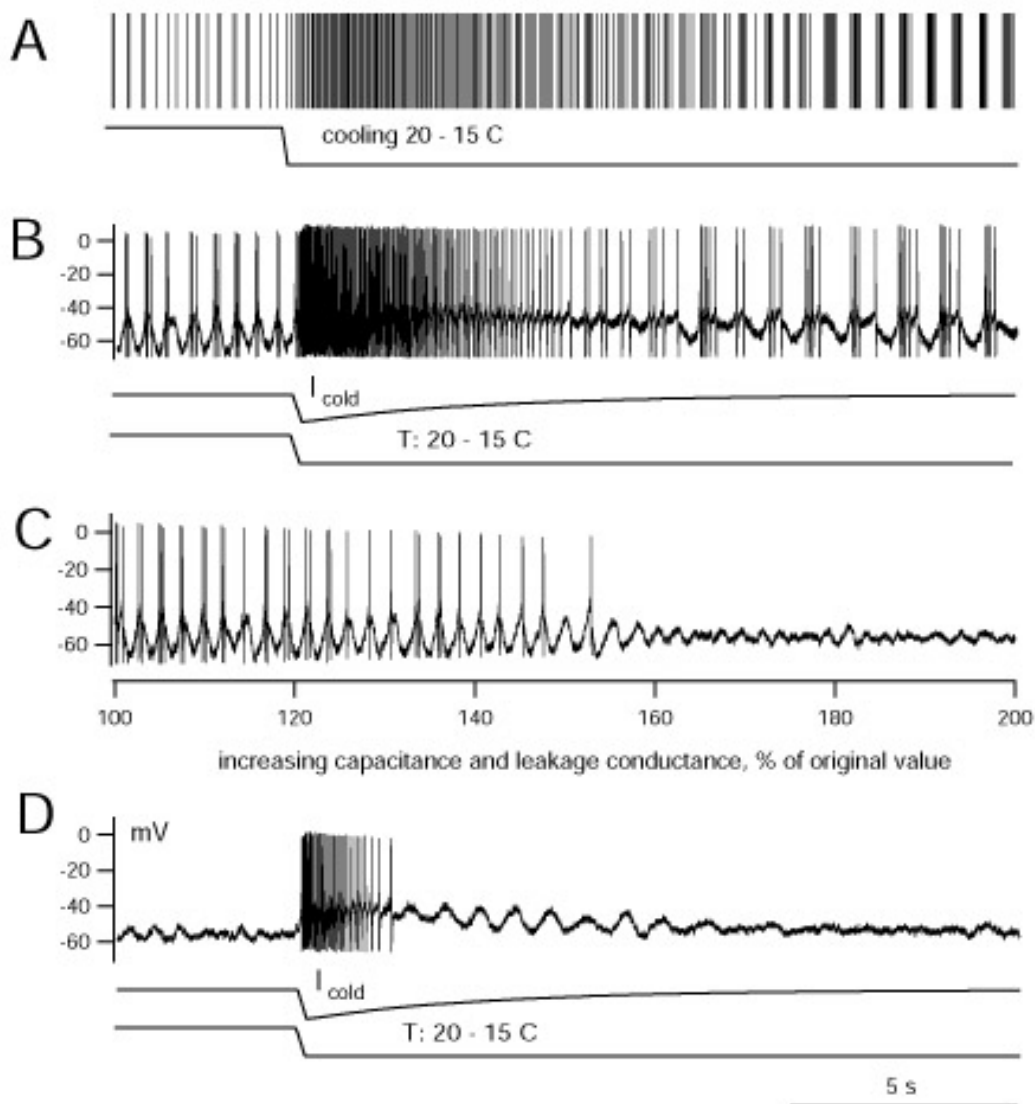
This simulation study, of course, is not a proof but it is a strong argument to justify the use of isolated cell bodies for examination of sensory transduction processes as long as direct access to the nerve terminals is not possible. Additionally, our study might have even broader implications considering that, for example, the ionic mechanisms of nociception can only be examined on the soma - for the same reasons. More generally, these simulations have shown that seemingly minor changes can have drastic effects on the encoding properties which emphasizes the importance of the “operating point” as a very sensitive determinant of nonlinear system’s dynamics which is worth to be examined in more detail. Last but not least, we think that our data convincingly demonstrate that computer modeling studies can be valuable tools for a better understanding of experimental data.

Keywords: cold sensitivity, computer simulation, nonlinear dynamics.

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Figure 1:



- A. Impulse sequence from an extracellular recording of a peripheral cold afferent of the rat skin showing spontaneous activity at constant temperatures and transient frequency increase on fast cooling. Action potentials are plotted as impulses of normalized amplitude.
- B. Computer simulation of the experimentally recorded impulse sequences in A also showing the membrane oscillations.
- C. Voltage traces of the model at a constant temperature of 20 °C in the course of a continuously increasing membrane capacitance and leakage conductance (up to the twofold of their original values).
- D. The model's response to an identical stimulus as in B but with a twofold membrane capacitance and leakage conductance, corresponding to the 200% level in C.