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LETTER TO THE EDITOR

An alternative mechanism for slow pacemaking

We have read with great interest the recent review by Bean on pacemaking of mammalian neurons (Bean, 2024). The author's hypothesis is that a persistent Na^+ current is responsible for many types of slow pacemaking and that other currents such as I_h and perhaps $Ca_v1.3$ serve as adjuvants to the pacemaking.

However, we believe that another hypothesis should be considered. Indeed, Bean's group made the instrumental observation that the current needed for pacemaking is extremely small, ∼−1 to −5 pA in midbrain dopaminergic (DA) neurons and in suprachiasmatic neurons (Jackson & Bean, 2004; Khaliq & Bean, 2008). As the author writes in his review "Thus the net ionic current driving the spontaneous firing is not much bigger than the size of the current through a single ion channel." This raises a problem: knowing the extreme regularity of pacemaking in these cells, and therefore the need for a very steady inward current, it is actually difficult to envision that this could be obtained with few channels, given the stochasticity of channel opening. An alternative possibility would be that several macroscopic (both inward and outward) currents sum up, with a net (very) small inward current. In the case of DA neurons, this is also difficult to envision given the known heterogeneity in the amplitude of various currents in neurons within this area. In addition, computational work suggests that it is quite difficult to obtain a robust slow pacemaking by using only a combination of voltage-dependent conductances (Drion et al., 2015).

Could there be an alternative/complementary hypothesis? We believe so. For example, in his paper on persistent Na^+ current in histaminergic neurons, Bean wrote: "An unexpected feature of the interspike sodium current recorded using spontaneous action potential waveforms is the presence of current immediately after spikes at voltages as negative as -70 mV. No measurable persistent current (elicited by slow ramps) is evident at voltages this negative, even with equivalent signal averaging. The origin of the postspike sodium current during pacemaking is unclear" (Taddese & Bean, 2002). In our opinion, because of the problem raised above, numerous pores with a very small conductance (fS instead of pS) would be much more suitable to generate a very small and stable inward current. What could these pores be? The study of various pathological channel mutations has shown that when a positively charged amino acid in S4 is mutated to a neutral one, a continuous leak can be observed in various voltage-dependent channels (e.g. Sokolov et al., 2007). This is called a 'gating pore current.' Moreover, such currents can be blocked pharmacologically. One such blocker is 1-(2,4-xylyl)guanidinium (XG) (Sokolov et al., 2010). We set out to test the effect of XG on DA neurons and found that it completely blocks pacemaking of DA neurons without affecting their main currents and, importantly, without inducing any change in the mean membrane potential or in the cell conductance (Jehasse et al., 2021). Additionally, in collaboration with another group, we recently found that XG also blocks the pacemaking of another type of regular slow pacemakers, still with no effect on the main currents expressed by these cells. At this point, we have not yet identified the molecular target(s) of XG. Nor can we be sure that a gating pore current is involved. However, we believe that these pieces of evidence suggest that atypical low conductance pores could be the actual generators of slow pacemaking in several cell types.

On the other hand, we completely agree with Bean when he states that we should reverse the question 'what currents drive neuronal pacemaking?' to 'why don't all neurons fire spontaneously?'. It may indeed be that pacemaking is the 'default' mode in mammalian neurons and is prevented by strong expression of K2P or Kir channels in 'silent' neurons. Experiments are in progress to test these possibilities.

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Additional information

Competing interests

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Author contributions

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Supporting information

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