Principles of Neuroscience example essay 1

XXXX

Bloodgood et al[1] showed that stimulation of spines using glutamate uncaging resulted in ~5 fold higher VGCC mediated *$\Delta[Ca]_{spine}$* compared to that evoked by similar stimulation (adjusted so somatic uEPSP amplitudes were the same under both protocols) on dendrites (figs. 1, 2). Their interpretation of this result, that R_N is sufficiently large to produce a physiologically important drop in voltage from spine head to dendritic shaft, is problematic since both putative negative controls for the experiment gave positive results. Because the authors used *$\Delta[Ca]_{spine}$* as an indirect indicator of membrane potential, their conclusion depends critically on *$\Delta[Ca]_{spine}$* being mediated exclusively by voltage gated Ca^{2+} influx, and not by other glutamate sensitive Ca^{2+} sources. One way to show that *$\Delta[Ca]_{spine}$* represents purely voltage gated Ca^{2+} entry under their conditions is to block VGCCs and show that Ca^{2+} transients are reduced to zero. However, after adding VGCC blockers, a sizable *$\Delta[Ca]_{spine}$* was still observed, and *$\Delta[Ca]_{spine}$* evoked by spine stimulation remained larger than that evoked by dendritic stimulation (fig. 2b). The authors explain this finding by suggesting that some VGCCs resistant to the VGCC blockers may be present. While this is possible, an equally valid interpretation is that mGluRs (which mediate voltage-independent Ca^{2+} release from internal stores) or NMDARs (whose Ca^{2+} conductance is only partially voltage dependent) were incompletely blocked, and thus that the *$\Delta[Ca]_{spine}$* observed in the presence of VGCC blockers represented Ca^{2+} entry from voltage-independent sources. Therefore, although their results were suggestive, the authors were not able to prove that *$\Delta[Ca]_{spine}$* is a reliable indicator of membrane potential using this approach, since even in the presence of VGCCs a positive result was obtained.

[1] Bloodgood et al. PLoS Biology. 2009. 1-10.

As the authors point out, if somatic uEPSPs are equal in amplitude, then the membrane potential at the base of the spine during stimulation should be the same regardless of stimulus location. Thus, if calcium transients reliably report membrane potential (i.e., if they are mediated exclusively by VGCCs), $\Delta[Ca]_{den}$ should be equal for both stimulus locations. (Actually, $\Delta[Ca]_{den}$ evoked by spine stimulation should be slightly larger than that evoked by dendritic stimulation, since Ca^{2+} from the large $\Delta[Ca]_{spine}$ following spine stimulation should diffuse into the dendrite.) Unexpectedly, when the authors examined $\Delta[Ca]_{den}$ under their conditions, they found that $\Delta[Ca]_{den}$ was ~4 fold larger when the dendrite was stimulated compared to when the spine was stimulated (figs. 1g and 2a, b; text, p. 4; note that this result is similar in magnitude to the ~5 fold increase in $\Delta[Ca]_{spine}$ that the authors report as their positive result). Again, a simple explanation for this finding is that mGluRs or NMDARs were not completely blocked, and thus calcium transients may represent local glutamate concentrations, rather than membrane potential.

Clearly, the authors' results are complicated both by the non-specific effects of glutamate and by the presence of voltage-independent sources of Ca^{2+}. A better experiment would have taken advantage of more specific methods for measuring membrane depolarization. For instance, the authors could have measured membrane potential more directly using voltage sensitive dyes instead of Ca^{2+} indicators, thus avoiding the complications introduced by voltage independent sources of Ca^{2+}.