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Activity-independent intracellular signaling contributes to rate variability among neurons in the globus pallidus

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Synchrony among neurons is seen throughout the mammalian CNS, in particular within networks of GABAergic neurons. The globus pallidus (GP) consists of GABAergic neurons that project to neurons throughout the basal ganglia in addition to each other via local axon collaterals. The GP does not display synchronous rhythms and there are no clear correlations between neurons in healthy mammals. In contrast, strong correlations among GP neurons emerge in Parkinson's disease patients and MPTP treated primates. Why GP neurons show no correlations in healthy animals is not known. GP neurons are autonomous pacemakers and are thought to discharge at a constant frequency. Theoretical work shows that the degree of synchrony in interconnected networks depends on the amount of heterogeneity in firing rate.

We have observed in cell-attached recordings of GP neurons, in slices, that their firing rates are not stationary, but instead visit a range of rates over a period of one hour in a non-stereotypical fashion. The fluctuations in rate are stable for periods of minutes, can vary as much as 30 Hz, and appear to be unaffected by blocking synaptic inputs. HCN channels are a critical component of the GP neuron's pacemaking mechanism, and their availability is positively correlated with the firing rate of GP neurons. Paired recordings revealed that these fluctuations in rate were neuron-independent. We hypothesized that these slow non-stereotypical fluctuations in firing rate could be attributed to regulation of HCN channels by cAMP. cAMP alters HCN availability by shifting the channel's activation curve to depolarized potentials. Consistent with this, up-regulation of cAMP levels by bath application of 50 μM Forskolin increased the firing rate of GP neurons from 12.7 ± 1.3 to 20.5 ± 1.5 Hz. After the Forskolin induced increase in firing rate stabilized, there was a marked decrease in the amount of variability in interspike intervals (ISIs) observed over a one hour period of recording in the cell-attached configuration. In control conditions the average coefficient of variation of ISIs (CV), measured over one hour, was 0.43 ± 0.22 and was 0.09 ± 0.02 after exposure to Forskolin. Thus, fluctuations in cAMP can create heterogeneity in firing rate among GP neurons by altering the availability of the voltage-gated ion channels necessary to drive pacemaking. By this mechanism, activity independent intracellular signaling could potentially contribute to the absence of synchrony in the GP.

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