be caused by concave geometrical formations that transiently trap diffusing particles. In rat granular layer, large and abundant synaptic glomeruli formed by concave processes of astrocytes that ensheathe complex synapses may function as the traps. To test this hypothesis, we employed Integrative Optical Imaging method to measure diffusion of small dextran molecules (*MW* 3000) in the granular layer of isolated turtle cerebellum where complex synapses are present but have no or very limited astrocytic ensheathment. In turtle granular layer, the anomalous diffusion model quantified $d_w = 2.6$, which is significantly less than $d_w = 5.0$ observed in rat granular layer but similar to d_w extracted from normal diffusion in a free medium (2.1) and in other brain regions (e.g., 2.3 in rat neocortex). Thus the extracellular diffusion was normal in the granular layer of turtle cerebellum that lacks trap-like astrocytic ensheathment of synaptic glomeruli. In conclusion, diffusion measurements in turtle support our hypothesis that astrocytic processes ensheathing synaptic glomeruli cause anomalous extracellular diffusion. Our approach is potentially useful for quantification of astrocytic ensheathment in the living brain under normal and pathological conditions. Our result also has implications for the interstitial transport of molecules and drugs in brain regions containing synaptic glomeruli. Supported by NIH(NS047557).

718-Pos

A Model of Spike-Timing-Dependent Plasticity

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It has been shown that postsynaptic calcium dynamics plays an important role in spike timing-dependent plasticity (STDP), a process in which changes in synaptic strength are determined by the relative timing of pre- and postsynaptic activity. It has been suggested STDP involves a postsynaptic chemical network with stable states corresponding to long term potentiation (LTP) and long term depression (LTD). It is believed that the switching of this network between these states is driven by the postsynaptic Ca2+ concentration, but the manner in which the Ca2+ dynamics causes the switching to depend on the relative timing of pre- and postsynaptic activity remains unclear. We describe a model of STDP that combines the chemical network model of Pi and Lisman (2008), with a model of Ca2+ dynamics that builds on the work of Shouval and coworkers (2002). Following Shouval and coworkers, we assume that a portion of the influx of postsynaptic Ca2+ is controlled by NMDA receptors that allow an inward Ca2+ current in response to both glutamate binding and a back propagating action potential (BPAP). To this we add a contribution from voltage dependent calcium channels (VDCCs). We show that this model is able to reproduce the observed time dependence of STDP when a single presynaptic pulse is either followed or preceded by a single BPAP. The behavior of the model with triplet pulse protocols, e.g., two presynaptic pulses separated by a BPAP, or two BPAPs separated by a presynaptic pulse, and the incorporation of more sophisticated models of AMPA trafficking are also described.

Pi, H. J. and Lisman, J. E. (2008) J. Neurosci 28: 13132-13138.
Shouval, H. Z., Bear, M. F., and Cooper, L. N. (2002) Proc. Natl. Acad. Sci. USA 99: 10831-10836.

719-Pos

Plasticity of Chloride Homeostasis can Cause Bistability and a Switch in Neuronal Spiking Pattern

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Plasticity of $GABA_A$/glycine synapses can be mediated by changes in intracellular chloride concentration ($[Cl^-]_i$). While chloride influx through ligand-gated channels alters $[Cl^-]_i$, the extent and time scale of those changes depend on transmembrane cation-chloride cotransporters (CCC). Because changes in the chloride reversal potential influence the membrane potential which in turn affects chloride currents, we show that there is a positive feedback loop between intracellular chloride accumulation, excitation and firing. To investigate further how this positive feedback loop modifies the firing dynamics of the cell, we extended the Morris-Lecar model with an extra dimension to account for changes in $[Cl^-]_i$. The model exhibits a novel form of chloride-related bistability and associated hysteresis which can switch the neuron from type I to type II firing. A 2D reduction of the model allowed us to identify regions in parameter space for which this change in firing type occurs. Chloride-related bistability is most likely to occur when CCC activity is reduced. This phenomenon can dramatically prolong changes in $[Cl^-]_i$ caused by an otherwise brief trigger. We quantified how chloride-mediated $GABA_A$ synaptic plasticity allows the spiking pattern to carry information about past inhibitory activity. This is achieved by computing the mutual information between spiking and past inhibitory activity for various time windows. While high levels of CCC activity limits $[Cl^-]_i$ mediated ionic plasticity, reduced CCC activity decreases the mutual information between inhibitory input and spiking output. Given this trade off, there is an optimal level of CCC activity for which mutual information is maximal given different input distributions and different time windows. These results show that beyond membrane currents taken into account in conventional cable modeling, chloride dynamics and electroneutral transport activities critically determine the computational properties of neurons.

720-Pos

Integration of Cellular Metabolism and Membrane Excitability in Cerebellar Purkinje Neurons

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Calcium and membrane physiology are crucial to cerebellar Purkinje neuron function. Purkinje cell physiology involves phosphoinositide/calcium signaling and calcium influx through voltage-gated calcium channels, as well as potassium efflux through (i) voltage-gated, and (ii) calcium-activated voltage-gated channels (primarily the BK channel). The interaction between phosphoinositide-induced calcium signaling and calcium-activated/voltage-gated potassium channels have not been explored extensively. We have developed computational models to explore the integration of these mechanisms. We used an electrophysiological model in NEURON to parameterize a compartmental Virtual Cell (VCell) model. We then combined our published calcium metabolism model (created in VCell) with the electrophysiological model. We investigated the influence of IP3R1-mediated calcium release from smooth endoplasmic reticulum close to the plasma membrane on the activity of the BK channel and thus on membrane potential. The model predicts that supralinear IP3R1-mediated calcium release into a submembrane shell can activate BK channels. When coupled with synaptic conductance changes, this activation of the BK channels increases the rate of repolarization (RR) of the spine. As the voltage changes in the spine propagate to the soma, the corresponding RR in the soma is also increased. Simulation of IP3R1 ko abolishes any increase in the RR in both the spine and the soma. Reduced IP3R1 abundance (as found in some cerebellar ataxias; in model, 10% - 50% of the original value), almost completely abolishes any increase in the RR, in both spine and soma. Increasing the sensitivity of IP3R1 to IP3 restores normal IP3R1-mediated calcium, and restores increased activation of the BK channels. The resulting RR of both the spine and the soma are also restored. These results suggest that the BK channel may play a role in integrating signals from cellular metabolism and membrane excitability. (Supported by NIH P41 RR013186)

721-Pos

The Role of Phosphorylation on Mouse Neurofilament Medium Protein (NF-M) Sidearms

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Neurofilaments (NF) are important cytoskeletal filaments that are assembled from three distinct molecular weight proteins - neurofilament light (NF-L), medium (NF-M), and heavy (NF-H). The three proteins are bound to each other laterally forming 10-nm filamentous rods along with sidearm extensions that belong to the C-terminal tails of the proteins. These tails vary in number and sequences of their amino acid residues, and are abundant with charges. Additionally, the sidearm polypeptides attain negative charges through serine phosphorylation of the Lys-Ser-Pro (KSP) repeat motifs that are particularly found in NF-H and NF-M sidearms. NF protrusions mediate the interaction between neighboring filaments, and maintain axonal diameter. However, the role of individual NF proteins and their phosphorylations in regulating interfilament distances, and hence axonal diameter, is not fully understood. A number of studies have implicated NF-M proteins as critical in regulating axonal caliber. However, the conventional viewpoint that NF-M phosphorylation increases axonal caliber has been challenged by recent experimental study that disputes the effect of NF-M phosphorylation in modifying axonal caliber (Garcia et al. J. Neurosci. (2009) 29: 1277-1284). By employing gene replacement technique, the authors deduced that phosphorylation of NF-M KSP repeat is not required for myelin-dependent radial axonal growth. To better understand the effect of NF-M phosphorylation, we investigated the structural organization of mouse NF under phosphorylated and dephosphorylated conditions. We employed the 3D sequence-based coarse-grained model of NF brush (Chang et. al., J. Mol. Biol. (2009) 391:648-660) to perform Monte Carlo simulations of mouse NF by using the sequence and the stoichiometry of mouse NF proteins. Our result shows that the phosphorylation of mouse NF-M does not change the radial extension of NF-M, supporting the notion that NF-M phosphorylation has no effect on axonal diameter of mouse.