bacterial homologs of cys-loop receptor family of ion channels has provided atomic-level detail of these proteins and led to several proposed mechanisms of receptor gating. We used structures of two related bacterial channels to construct homology models of the chick alpha7 nicotinic receptor in putative closed and open states [1,2]. Profiles 3D and PROCHECK were used as an initial means to validate these models. We then compared our models with those constructed from multiple structural templates, such as bacterial ACh-Binding Proteins and the *Torpedo* AChR. While the closed and open alpha7 models share a great degree of global similarity to these related structures, we observed conformational variability in the agonist-binding site(s) that would appear to preclude binding of cholinergic agonists and antagonists. This observation is not unexpected, as neither of the bacterial homologs are acetylcholine-activated. We next asked if the models could be used to predict experimental data and perhaps lead to the development of testable hypotheses for gating. We compared rates of MTS modification of introduced cysteines [3] to *in silico* measurements of side chain solvent accessibility, local electrostatic potential, and pH. Our comparisons suggest that homology models such as these are likely to require an iterative process of refinement based upon experimental data before they can be used for molecular dynamics and predictive approaches.

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1.22

Heterogenity in release probability and depression dynamics at a nicotinic CNS connection

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The axo-axonic contact(s) between the Mauthner (M-) axon and cranial relay neuron (CRN) of the goldfish are readily accessible *in vivo* and provide a unique opportunity to study fast cholinergic synaptic transmission in the central nervous system (CNS). Using variance-mean analysis we have demonstrated that steady state frequency-dependent depression at CRN connections mediated by α7 nicotinic acetylcholine receptors (nAChRs) is largely due to a decreased release probability, *p*, under stationary conditions. Development of depression for α7 nAChR mediated CRNs under non-stationary conditions is shown here to also be due to a decrease in release probability, as explored with MPFA and corroborated with covariance analysis. The variance-mean data are well fit by a modified parabolic function and no correlation is observed between successive EPSP amplitudes (EPSPn + 1 vs EPSPn). Interestingly, latency increases with depression, which we attribute to the refractory state of the release machinery and not to a change in conduction velocity. The composite variance-mean data from M-axon/CRN connections mediated by α7/α3β2* or α7/α3β4* nAChRs often are not well fit by a single modified parabolic function, but are best approximated by two parabolic functions that represent different values of *p*, quantal size, *q*, and vesicles ready for release, *n*. These fits of composite variance-mean data are corroborated by determining the variance-mean data for each component, α7 and α3β*, separately. This is achieved by stripping the α7 component from the composite EPSP to yield the α3β* either with antagonists or by subtracting the α7 component, approximated from curve fitting and latency analysis. The resulting α3β* component data enables variance-mean, covariance and latency analysis. Based on non-stationary as well as steady state depression data we conclude that contacts mediated by different nAChRs, namely α7 and α3β2* or α3β4*, exhibit a wide range of release probability. Composite variance-mean data well fit by one modified parabola reflect M-axon/CRN connections mediated by α7 nAChR and by α3β* contacts that have similar release probabilities. However, composite variance-mean data better fit by two modified parabolas reflect contributions from α7 and α3β* contacts that exhibit release probabilities quite different from one another.

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Section 2. Cognition/cognitive deficits

2.1

Nicotinic receptor activation increases glutamatergic transmission and plasticity in the rat cerebellum

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Neuromodulatory systems of the brain have been suggested to profoundly impact on neurotransmission and long-term synaptic plasticity, the cellular correlate for learning and memory. The cerebellum, involved in procedural memory, receives abundant cholinergic innervation and shows a dense nicotinic acetylcholine receptor (nAChRs) expression. However, the functional effects of nAChRs in the cerebellum are still largely unknown. To address this issue we have performed voltage-clamp recordings in whole-cell configuration in the granular layer of acute slices obtained from the cerebellar vermis of P18-P22 rats. A 100-sec application of nicotine (1 μM) significantly enhanced glutamatergic EPSCs. The effect was transient, suggesting that nAChR were progressively desensitizing. As nAChRs are often located in the presynaptic terminals where they modulate other neurotransmitter release we have therefore investigated whether a similar mechanism could operate in the cerebellum. EPSCs mediated by AMPA receptors were elicited in pairs with an interpulse interval of 20 ms. Nicotine exposure readily caused a reduction of the pair pulse ratio (PPR). Moreover, a high calcium buffer concentration in the intracellular solution was still accompanied by a significant PPR decrease during nicotine application supporting its presynaptic origin. EPSCs mediated by NMDA receptors were not influenced by nicotine. Interestingly, when a high calcium buffer concentration was added to the intracellular solution, the effect of nicotine was restored and NMDA EPSCs increased. Therefore, nicotine could act both pre- and postsynaptically. The enhancement of neurotransmission caused by nicotine suggested that nicotine could also enhance the induction of LTP. We therefore tested whether a single 100 ms/100 Hz burst, which determines a long-term depression of EPSC peak could turn into LTP induction in the presence of nicotine. Exposure to 1 μM nicotine led the development of LTP of the EPSCs following the 100 ms/100 Hz burst. To explore