What Causes Muscle Atonia in REM?

Commentary on Brooks PL and Peever JH. Glycinergic and $GABA_A$-mediated inhibition of somatic motoneurons does not mediate rapid eye movement sleep motor atonia. J Neurosci 2008;28:3535-45.

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THE IMPORTANT AND PROVOCATIVE PAPER BY BROOKS AND PEEVER[1] DESCRIBES EXPERIMENTS IN INSTRUMENTED FREELY BEHAVING ADULT RATS THAT addresses the question of whether inhibitory synaptic transmission is responsible for muscle atonia seen in REM sleep. The importance of augmented inhibitory (glycinergic and perhaps to a lesser extent GABAergic) synaptic inputs to motoneurons (MNs) as the key factor causing the atonia of REM has been an underlying principle of sleep physiology.[2] Brooks and Peever[1] used local drug application via microdialysis into the trigeminal motor pool to demonstrate that glycine- and $GABA_A$-receptor mediated inhibition is not the primary cause of REM atonia. This study builds upon and extends to non-respiratory MNs the earlier work of Richard Horner's group,[3,4] which used the same experimental approach applied to the hypoglossal motor pool. In that work, Morrison et al.[3] concluded that glycine and $GABA_A$-receptor mediated inhibition only makes "a small contribution to the marked suppression of genioglossus activity…in periods of natural REM sleep."

A key novel result in the study of Brooks and Peever[1] are the data presented where strychnine (to block glycine-receptors), bicuculline (to block $GABA_A$-receptors) and AMPA (to excite glutamatergic AMPA receptors) were all co-applied to the trigeminal motor pool during different behavioral states. One would have thought that this "cocktail" would have been an extremely potent excitatory "cocktail" and resulted in pronounced activation of trigeminal (masseter) MNs even during the atonia of REM. Contrary to expectations Brooks and Peever[1] found that the atonia of REM continued all the while masseter MNs were exposed to AMPA and inhibitory synaptic transmission was blocked. Specifically, while applying this excitatory "cocktail," they found profound excitation in both the awake state (on average, over a 1500% increase in masseter muscle EMG activity), and in the NREM (on average, over a 950% increase in masseter muscle EMG activity), but the data showed that during tonic REM no significant EMG increase was observed.

What are the possible reasons for this intriguing result? Clearly the effects in waking and NREM are what were expected, but why didn't activity in the masseter EMG increase in the presence of the excitatory "cocktail" during the atonia of REM? What might this result tell us about the mechanism(s) for the generation of REM atonia? Clearly in REM something happened to the masseter MNs that prevented them from being activated by this "cocktail" of agents. A couple of possibilities come to mind.

First, during REM the MNs could be actively inhibited by non-glycine- and non-$GABA_A$-receptor mediated pathways. This inhibition needs to be so profound that it blocks the effects of direct AMPA activation of the MNs. It is possible that such a profound inhibition increases motoneuronal input conductance to the extent that there is a significant shunting inhibition. Thus activation of AMPA receptors and the resulting AMPA-induced inward current is insufficient to depolarize the membrane potential MNs above spike threshold. Therefore in REM AMPA-receptor mediated MN excitation is no longer effective as it was during the awake and NREM states. Previous work by Soja et al.[5] and others has demonstrated that in REM there is an increase in lumbar MN input conductance. It would have been of interest to know how the input conductance of masseter MNs changed across the different behavioral states (waking versus NREM versus REM) with and without the dialysis of the "cocktail" of agents. This type of measurement (intracellular recordings), while difficult in freely behaving animals, has been accomplished in other studies including in spinal MNs during REM.[2,5]

Second, the results of Brooks and Peever[1] suggest an important role of another state-dependent neurotransmitter system that is markedly altered when comparing waking from NREM from REM. Important state-dependent inputs to motoneurons include inputs derived from serotonergic, adrenergic and cholinergic systems. In regard to the latter system, our laboratory[6] showed that activation of muscarinic presynaptic receptors (likely M2 receptors) significantly depresses excitatory synaptic transmission to HMs. Thus based on this mechanism, and the observation that cholinergic neurons that project to motor nuclei are most active in wakefulness and REM sleep, it is possible that an important contributory mechanism for REM atonia is a disfacilitation that arises presynaptically via activation of muscarinic receptors on glutamatergic excitatory inputs. On the other hand, application of AMPA by Brooks and Peever[1] should have directly activated AMPA receptors on masseter MNs, and this should have resulted in depolarization and enhanced MN activity in REM. Alternatively and not exclusively there maybe some form of postsynaptic cholinergic inhibition caused by the local release of acetylcholine in REM.

Pharmacological experiments such as those described by Brooks and Peever[1] invariably raise issues regarding specificity

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of the agents that are employed. For example, it is well-known that in addition to bicuculline's antagonism of $GABA_A$-receptors, bicuculline directly reduces the after hyperpolarization that follows an action potential. This has been observed in many cell types including MNs[7] and hippocampal neurons.[8] Additionally, we have previously shown in hypoglossal MNs studied in brainstem slices, that at a concentration of 10 μM strychnine can block not only the glycine-receptor-mediated responses but almost all $GABA_A$-receptor-mediated responses.[9] At 10 μM, bicuculline blocks about one-fourth of the glycine receptor-mediated responses. Brooks and Peever[1] applied both strychnine and bicuculline at a concentration of 100 μM.

While in science we often hunt for a single "holy grail" or mechanism that explains an important observation. I think what will turn out to be correct is that a multitude of mechanisms each contribute to the muscle atonia of REM. We may even find enhanced inhibitory synaptic transmission, as proposed by Chase and his colleages[2] and involving activation of glycine- and maybe $GABA_A$-receptors plays some type of role, and the relative importance of this mechanism may depend on the species studied (rodent versus feline versus human) and the experimental conditions. Disfacilitation, by a reduction in excitatory glutamatergic inputs that is due to activation of presynaptic muscarinic receptors on glutamatergic synaptic terminals,[6] may also be important. Disfacilitation due to reductions in state-dependent drives, such as serotonergic and noradrenergic drives during REM, may also contribute to the atonia. Clearly what is needed is an open view of a number of simultaneous possibilities that can cause atonia and not a single "holy grail."

DISCLOSURE STATEMENT

Dr. Berger has indicated no financial conflicts of interest.

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