Confirmation of the Consensus that Glycinergic Postsynaptic Inhibition is Responsible for the Atonia of REM Sleep

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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BROOKS AND PEEVER CONCLUDED THAT NEITHER GLYCINE NOR GABA, BUT RATHER AN UNKNOWN "BIOCHEMICAL SUBSTRATE," IS RESPONSIBLE FOR preventing trigeminal motoneurons from discharging during the tonic periods of REM sleep. Nevertheless, based on data from intracellular studies, Brooks and Peever stated that it is commonly accepted that "glycinergic inhibition of somatic motoneurons is responsible for loss of postural muscle tone in REM sleep."[1] The reasons why Brooks and Peever failed to confirm the results of intracellular studies are discussed as are the critical flaws in their experimental design and methodology that prohibited them from obtaining physiologically relevant data.

The preceding and other aspects of this research are addressed below within the context of the various sections of the Brooks and Peever paper. The intracellularly derived data that are referred to regarding glycinergic postsynaptic inhibition of motoneurons during REM sleep and related information were originally presented in publications listed among the references to this paper.[2-23]

INTRODUCTION

Brooks and Peever introduce the reader to their paper with the following statement: "There is considerable controversy concerning the neuronal mechanisms generating muscle atonia in REM sleep." However, no references are provided to substantiate their claim that a "considerable controversy" exists. In contrast, as recently as this year, Allan Hobson, in a major address to The Italo-American Brain Stem Alliance given at the Accademia Pontaniana in Napoli (January 18, 2008), discussed "the brilliant analysis of REM sleep motor inhibition undertaken by Ottavio Pompeiano, Moruzzi's second in command at Pisa, and Adrian Morrison, a visiting veterinarian from Pennsylvania over thirty years ago." Hobson further stated that, "Together they showed that the inhibition of muscle tone, seen in REM sleep, was produced by descending inhibitory influences from the brain stem to the anterior horn cells of the spinal cord," and concluded that, "Michael Chase using intracellular techniques confirmed Pompeiano's theories regarding inhibition of spinal motorneurones…"

Brooks and Peever continue by noting that, "although numerous studies have shown that the role of glycinergic inhibition of motoneurons is responsible for the loss of postural muscle tone in REM sleep," it is still only an "hypothesis"; further, they state that it is based upon the observation that "lumbar and trigeminal motoneurons are hyperpolarized by large amplitude IPSPs that are reduced, but not eliminated, by antagonism of glycine receptors."[16,19] First, in the entirety of the literature, there is not a single report that has questioned the validity of the results from intracellular studies that demonstrate unequivocally that postsynaptic inhibition of motoneurons, mediated by unique glycinergic IPSPs, fully accounts for the atonia of the somatic musculature that occurs throughout REM sleep. Thus, glycinergic postsynaptic inhibition resulting in atonia during REM sleep is not simply an "hypothesis." Second, their statement that the large amplitude IPSPs are "reduced, but not eliminated by antagonism of glycine receptors" misrepresents the published data and opens the door to the possibility that other control mechanisms are present. In point of fact, the studies that Brooks and Peever referenced demonstrate that the large amplitude REM-specific IPSPs can be completely eliminated by antagonism of glycine receptors;[19] they are not simply "reduced," as claimed by Brooks and Peever. Moreover, IPSPs and hyperpolarization are only two of the many membrane potential changes that confirm the exclusive role of glycinergic postsynaptic inhibition in producing atonia during REM sleep (Table 1).

METHODS

One of the principal methodological problems in this study was the inappropriate use of the microdialysis technique, which, as employed by Brooks and Peever to explore the state-dependent control of motoneuron activity, was incapable of yielding either meaningful or interpretable data. This technique would have been appropriate if the trigeminal motor pool were a) an isolated nucleus, b) comprised solely of alpha motoneurons, c) controlled exclusively by projections from distant sites, and d) functioned solely to modulate the level of discharge of motoneurons in a state-dependent fashion. Unfortunately, the trigeminal motor nucleus consists of a variety of cells including alpha motoneurons, gamma motoneurons, excitatory interneurons, and inhibitory interneurons, as well as projection fibers from nearby and distant sites. All of the preceding cells and

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projection fibers were exposed to the substances that Brooks and Peever dialyzed in addition to cells and fibers in the immediately adjacent supratrigeminal nucleus, juxtatrigeminal area, intratrigeminal area, and the parvocellular reticular formation which interact with each other and with trigeminal alpha and gamma motoneurons, principally in the service of promoting waking functions involving the masseter musculature. Thus, thousands of glycinergic, GABAergic and glutamatergic synapses (that are not responsible for the state-dependent control of trigeminal motoneurons, as well as those that are) were simultaneously and indiscriminately activated/inhibited by the dialyzed substances. This problem was exacerbated due to the fact that Brooks and Peever delivered drugs continuously for periods of two to four hours, and the tips of the probes that they used were located, as they state, not only in the motor pool, but sometimes in adjacent sites as well.

Thus, when Brooks and Peever dialyzed neurotransmitters and their antagonists, in addition to affecting the relatively few receptors on trigeminal alpha motoneurons that are innervated by state-dependent projections from distant sites, complex, artificial patterns of synaptic actions and interactions were initiated, simultaneously, between all of the preceding neuronal groups and projection fibers. For example, when Brooks and Peever dialyzed the glycine antagonist, strychnine, glycinergic receptors on alpha motoneurons were antagonized, which resulted in an increase in motoneuron excitability. However, since inhibitory interneurons (which also contain glycinergic receptors) suppress the discharge of other inhibitory interneurons within the trigeminal motor nucleus, strychnine also decreased the excitability of alpha motoneurons. In addition, when glycinergic receptors on all cells in the sphere of influence of the dialyzed substances, including receptors on neurons in adjacent nuclei, were antagonized, complex nonphysiological patterns of synaptic effects which resulted in changes in EMG activity that Brooks and Peever used to document the effects of various neurotransmitters and antagonists. By recording intracellularly from identified alpha motoneurons and ejecting substances juxtacellularly, one is able to completely eliminate the confounding effects of the multitude of neuronal actions and interactions that occurred when Brooks and Peever dialyzed substances, for an extended period of time, into the trigeminal motor nucleus and adjacent sites.

RESULTS

The results of Brooks and Peever confirmed data from numerous intracellular studies showing that glycinergically mediated postsynaptic inhibition is responsible for atonia during the phasic periods of REM sleep. However, they did not confirm the results from the same intracellular studies demonstrating that glycinergic inhibition also occurs during the tonic periods of REM sleep, even though both sets of intracellular data were obtained during the course of experiments in individual animals, throughout alternating tonic and phasic periods of REM sleep, which were separated in time by only a few seconds. Brooks and Peever did not attempt to explain either the discrepancy or the similarity between the results of their studies and those generated by intracellular experiments. I suggest that because the dialysis methodology used by Brooks and Peever induced abnormal synaptic patterns of activity, it was simply a coincidence that some of their results were similar to those obtained when recording intracellularly, while other results were dissimilar. Because an enormous number of neurons that are not involved in the state-dependent control of motor activity were affected by the dialyzed substances, it is literally impossible to conclude that the Brooks and Peever data confirmed, or did not confirm, the conclusions of intracellular studies, wherein the responses to substances were confined to receptors on alpha motoneurons. In addition, due to the fact that there was only a single end point (EMG activity) in Brooks and Peever's study, it is not surprising that they generated inexplicable data; in contrast, intracellular studies have examined not only EMG activity, but they also documented correlated variations in synaptic processes (IPSPs and EPSPs), membrane polarization, input resistance, conductance, time constant, etc. in identified trigeminal and lumbar motoneurons.

Table 1—Comparison of Membrane Properties of Motoneurons During Postsynaptic Inhibition, REM Sleep, and Disfacilitation (Due to the Withdrawal of EPSPs) (for Details see Chandler.[6] and Soja[24])

Membrane Property	Postsynaptic Inhibition	REM Sleep	Disfacilitation
REM-specific IPSPs	Yes	Yes	No
Decreased input resistance	Yes	Yes	No
Increased membrane conductance	Yes	Yes	No
Decreased time constant	Yes	Yes	No
Decreased antidromic spike peak potential	Yes	Yes	No
Increased spike IS-SD delay	Yes	Yes	No

These intracellular data have shown that during the tonic as well as the phasic periods of REM sleep, there is an actively generated decrease in motoneuron input resistance and time constant, and an increase in conductance as well as specific changes in spike and EPSP/IPSP potentials. Table 1 presents a coherent set of cellular changes that are present only during REM sleep in conjunction with actively generated postsynaptic inhibition; they do not occur as a result of disfacilitation (Table 1).

Some of the most dramatic data sets demonstrating that glycinergic postsynaptic inhibition is solely responsible for the suppression of motoneuron excitability during REM sleep emanate from the studies of Soja et al.[24] and Chase et al.[19] They demonstrated that when glycine is antagonized by strychnine, there is no significant difference in any of the membrane properties (level of polarization, input resistance, conductance, EPSP and spike activity, IPSPs, etc.) between NREM sleep and REM sleep. There is no significant "leftover" reduction of motoneuron excitability that could be accounted for by a process of disfacilitation or by the actions of other inhibitory neurotransmitters or neuromodulators. Therefore, glycinergic postsynaptic inhibition was shown to completely account for the entirety of the suppression of motoneuron excitability during REM sleep.

The source of the preceding suppression of motoneuron excitability has been demonstrated to be due to the actions of unique large amplitude IPSPs that only occur during REM

sleep. Not only do these IPSPs exhibit REM-sleep specific distinguishing patterns of activity, but their amplitudes, rise-times, rates-of-rise, and half-widths are also unique and differentiate them from all other IPSPs. They can be completely blocked by strychnine; neither picrotoxin nor bicuculline has any effect on these IPSPs. Therefore, there is no doubt (as many studies have confirmed) that atonia is due to the fact, not hypothesis, that motoneurons are "actively" and powerfully inhibited by glycinergic postsynaptic inhibitory processes during the tonic periods of REM sleep, and that these same processes are not only present, but also enhanced during the phasic REM periods of sleep.

DISCUSSION

First Discussion Topic: *"A tonic glycinergic and GABAergic drive at the trigeminal motor pool suppresses masseter motor tone in waking."* Brooks and Peever state that, "We confirm the presence of an endogenous glycinergic and GABAergic tone that contributes to levels of trigeminal motoneuron excitability and masseter muscle activity during waking." According to Brooks and Peever, their findings confirmed that, "Intracellular studies demonstrate that trigeminal motoneurons are hyperpolarized by IPSPs in waking cats."[1] This is a factually inaccurate statement. Evidence of hyperpolarization by IPSPs during wakefulness was not included in the referenced chapter or in the primary literature, nor was any role described for either glycine or GABA in such nonexistent processes. In fact, opposite data were presented; namely, that trigeminal motoneurons are tonically depolarized, not hyperpolarized, during active wakefulness and that there is no significant change in the level of polarization between quiet wakefulness and NREM sleep. Clearly, the membrane potential of motoneurons is depolarized during wakefulness compared with NREM sleep, not hyperpolarized, as stated by Brooks and Peever.

Second Discussion Topic: *"Somatic motoneurons are inhibited by a tonic glycinergic and GABAergic drive during NREM sleep."* Brooks and Peever continue by stating that, "Inhibitory tone is maximal during NREM sleep…" However, when recording directly from trigeminal motoneurons, there is no significant difference in the level of the membrane potential or motoneuron activity during NREM sleep compared to quiet wakefulness. In addition, the data presented by Brooks and Peever contradict their own conclusions. In the figures in their paper in which records of the tonic activity of the masseter muscle is shown (Figures 2, 5, 6, 7, and 8), there is no observable difference between NREM sleep and REM sleep. Thus, inhibitory tone is neither maximal during NREM sleep, nor is there pervasive inhibitory tone during this state, as claimed by Brooks and Peever. In contrast, data derived from intracellular studies clearly demonstrate that "inhibitory tone" is only maximal during REM sleep, as reflected by the phase, "the atonia of REM sleep."

Third Discussion Topic: *"A phasic inhibitory drive functions to oppose muscle twitches during REM sleep."* The first sentence of this section is as follows: "We demonstrate that the functional glycinergic and $GABA_A$-mediated drive present at the trigeminal nucleus in waking and NREM sleep is immediately switched off and converted to a phasic glycinergic drive during REM sleep." As discussed above, there are no data demonstrating "that a functional glycinergic and $GABA_A$-mediated drive is present at the trigeminal nucleus in waking and NREM sleep," as claimed by Brooks and Peever. In addition, it is not clear what is meant by the word "functional," which is not defined, nor is their any discussion of the mechanisms that could possibly "switch off" glycinergic and GABAergic inhibitory drives, skip tonic REM sleep, and then "convert" one part of a tonic (glycinergic) inhibitory drive to a phasic one during the rapid eye movement periods of REM sleep. As we and others have reported, glycinergic inhibitory drives that are due to REM-specific IPSPs predominate during the phasic and tonic periods of REM sleep; Brooks and Peever do not refute or discuss these data.

Fourth Discussion Topic: *"Glycinergic and $GABA_A$-mediated inhibition of somatic motoneurons is not responsible for mediating REM sleep atonia."* Brooks and Peever begin by reiterating their belief that glycinergic inhibition of motoneurons is the "prevailing hypothesis." They continue by claiming that, "Chase and Morales (2005) established this hypothesis because they found that lumbar and trigeminal motoneurons are hyperpolarized by the REM-specific large amplitude IPSPs that are reduced (but not eliminated) by antagonism of glycine receptors."[1,16,19] We did not "establish" an "hypothesis"; we obtained results that have been confirmed in multiple studies by different investigators. More importantly, the preceding statement is not only inaccurate but is also misleading because it implies that because these IPSPs are not eliminated by strychnine, some other mechanism must play a role in hyperpolarizing the membrane potential. First, hyperpolarization is only one of a multitude of indices of the presence of glycinergic inhibition during REM sleep. Second, Chase et al.[19] found that the REM-specific IPSPs are completely eliminated; they are not simply "reduced," as Brooks and Peever states, by "antagonism of glycine receptors." It is true that occasionally a small number of IPSPs remains following the juxtacellular ejection of strychnine; however, these potentials are small-amplitude, short-duration, state-independent IPSPs. In addition, even if a few REM-specific IPSPs that impinge on the distal dendritic tree are not completely blocked in all cells, it is a consequence of geometry and distance, not of the lack of effectiveness of strychnine. The critical point is that all IPSPs are able to be completely eliminated by strychnine. Perhaps the most persuasive data are those that reveal that there is no statistical difference during REM sleep and NREM sleep in all of the REM-related changes in membrane properties when strychnine is administered, whether or not a few IPSPs remain! If any other mechanism or process were involved in producing atonia during REM sleep, then when strychnine was applied, there would be statistically different membrane potential values (e.g., input resistance, conductance; see Table 1) during NREM and REM sleep, but there are not.

Final Discussion Topic**:** *"What is the root mechanism responsible for REM atonia?"* Brooks and Peever argue that glycinergic inhibition of motoneurons does not occur during the tonic periods of REM sleep because they failed to obtain evidence of its presence. They do not discuss why they believe that their data and that from intracellular studies showing glycinergic inhibition during the phasic periods of REM was correct,

or why they reject data obtained from the same intracellular experiments that demonstrated that glycinergic postsynaptic inhibition is also responsible for motor atonia during the tonic periods of REM sleep.

Nevertheless, Brooks and Peever suggest that an unknown "biochemical substrate" is responsible for the suppression of motoneuron excitability during REM sleep. Leaving aside for the moment the fact that changes in the membrane potential of motoneurons following the application of strychnine exclude this possibility, they then refer to four articles which they state support their alternate suggestion that cholinergic neurons may be responsible for REM atonia.[30-33] Brooks and Peever state that the cells described in these articles 1) project to motoneurons (when they actually innervate thalamic neurons), 2) selectively discharge during REM sleep (when they are actually active during wakefulness and phasic REM), and 3) promote postsynaptic inhibition (when they are really responsible for generating postsynaptic excitation or mediate presynaptic mechanisms).

SUMMARY

An overwhelmingly coherent, integrated body of data developed by independent laboratories, over many decades, using intracellular recording in conjunction with the juxtacellular microiontophoretic ejection of neurotransmitters and antagonists, demonstrates conclusively that postsynaptic inhibition, mediated by glycine, is the critical and sufficient process that completely accounts for the suppression of motoneuron discharge during the tonic and phasic periods of REM sleep. These studies, many of which were conducted in intact, naturally sleeping, adult animals, eliminate potential interpretive complications that arise using reduced, in vitro slice or even intact in vivo preparations; they also provide for levels of resolutions that are not possible with microdialysis. On the other hand, when infusing a cocktail of substances for two to four hours into the trigeminal motor pool and adjacent regions, it is to be expected that uninterpretable and nonphysiological results would be obtained, especially when thousands of receptors on thousands of cells that are exclusively responsible for promoting waking-related functions of trigeminal motoneurons are activated. Because receptors in such a large region were indiscriminately activated by substances that Brooks and Peever dialyzed, it is clearly impossible to conclude that any change in EMG activity was due only to the activation of receptors on alpha motoneurons that are involved in state-dependent processes. In addition, because the results that Brooks and Peever obtained cannot be attributed to any specific class of receptors, synaptic process, or cell type, it is not possible to compare their findings with data obtained from intracellular studies.

The preceding notwithstanding, the technical execution of their experiments was of an extremely high quality. Given this obvious strength of Brooks and Peever, it is unfortunate that they did not utilize a technique that would have allowed them to obtain meaningful data, such as intracellular recording. In point of fact, the generation of a preparation in which it is possible to record intracellularly and eject substances juxtacellularly during naturally occurring states of sleep and wakefulness was developed, over a period of two years, specifically to avoid the problems that are inherent in the microdialysis technique that Brooks and Peever employed.

In conclusion, during wakefulness, numerous receptors on a great many neuronal elements in and in the vicinity of the trigeminal motor nucleus are normally activated in highly regulated sequences depending upon the specific behavior that is being performed, such as vocalization, biting, chewing, swallowing, etc. On the other hand, during REM sleep, only receptors on alpha motoneurons in the trigeminal motor nucleus, which are involved in state-dependent control processes, are excited. These latter receptors have been identified as glycinergic and have been shown to be activated, monosynaptically, by projections from the region of the nucleus reticularis gigantocellularis. Therefore, there is no justification for Brooks and Peever to claim that an unknown "biochemical substrate" is responsible for atonia during REM sleep, nor do they provide any data or reason not to continue to believe in the veracity of their initial statement, reflecting the consensus that "glycinergic inhibition of somatic motoneurons is responsible for loss of postural muscle tone in REM sleep."[1]

DISCLOSURE STATEMENT

Dr. Chase has indicated no financial conflicts of interest.

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