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## Depression of Spinal Sensory Transmission During REM Sleep: Dopaminergic Involvement and Insights Into Restless Legs Syndrome. Focus on “State-Dependent Changes in Glutamate, Glycine, GABA, and Dopamine Levels in Cat Lumbar Spinal Cord”

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Rapid-eye-movement (REM) sleep is also called paradoxical sleep because brain electroencephalographic (EEG) activity is similar to wakefulness. Aside from the obvious, one distinction between wakefulness and paradoxical sleep is the central suppression of both somatosensory and motor activity. The mechanisms that control these state-dependent changes appear to involve bulbospinal systems, while the contribution of diencephalospinal dopaminergic projections are not known. A recent article by Taepavarapruk et al. employed *in vivo* microdialysis and high-performance liquid chromatography (HPLC) analysis techniques to provide the first evidence of spinal cord amino acid transmitter and dopamine release related to these descending systems during naturally occurring sleep/wake cycles.

The authors measured release in the vicinity of two ascending tracts, the dorsal spinocerebellar tract (DSCT; Clarke's column) and the spinoreticular tract. Both tracts receive multiconvergent sensory input from numerous sensory qualities. The DSCT is a major relay point for the processing of spinal proprioceptive sensory information (Bosco and Poppele 2001) while the spinoreticular tract (SRT) also encodes nociceptive stimuli (Willis and Coggeshall 1991). Naturally occurring release profiles were also compared with that seen during stimulation of the nucleus reticularis gigantocellularis (NRGc), an area known to inhibit both motoneurons and activity in the aforementioned ascending tracts. The authors tested whether changes in transmitter release during REM sleep are associated with the known reduction of sensory inflow to higher brain centers via the DSCT and SRT.

When compared with wakefulness, whether during REM sleep or following NRGc stimulation, glutamate and glycine levels *increased* identically (48 or 69%, respectively) supporting release by common mechanisms. The neural pathways involved in this process therefore likely include reticulospinal and local interneuronal systems. In comparison, GABA levels increased only modestly during REM sleep and not at all following NRGc stimulation.

More intriguingly, the authors also showed that dopamine levels significantly *decreased* during REM sleep when compared with wakefulness. Spinal dopamine is derived from the A11 dopaminergic nucleus of the dorsoposterior hypothalamus (Skagerberg et al. 1982). Because Clarke's column contains the fewest dopamine (DA) fibers of all spinal cord regions (Holstege et al. 1996) changes in measured DA may be more

associated with modulatory actions on other nearby spinal cord functional systems. Regardless, the observation of a depression in DA release during REM sleep suggests that hypothalamic dopaminergic drive is inhibited at a time when sensory (and motor) activity is preferentially depressed, providing the first glimpse into A11 function during natural behavior. While the link between reduced DA and depression of spinal cord activity is uncertain, one possibility is that lower DA concentrations are preferentially inhibitory. For example, spinal reflexes are depressed by lower doses of DA and higher DA doses may facilitate reflex activity (Clemens and Hochman 2004). All dopamine receptor subtypes appear diffusely distributed in the spinal cord (Zhu et al. 2007), so a conceivable explanation is that lower DA levels preferentially activate higher-affinity G<sub>i</sub>-coupled D<sub>2</sub>-like (D<sub>2,3,4</sub>) receptors to depress activity while higher DA levels also activate lower-affinity G<sub>s</sub>-coupled D<sub>1</sub>-like (D<sub>1,5</sub>) receptors to facilitate sensorimotor responsiveness.

Overall, this paper provides a major advance in our understanding of how transmitter release profiles change in the vicinity of spinal sensory relay centers during the natural sleep-wake cycle. The two principle findings on amino acid transmitters and DA afford a broader understanding of spinal state-dependent transmitter release dynamics. The results for DA are also relevant to elucidating the potential mechanisms that underlie sensorimotor disturbances such as Restless Legs Syndrome (RLS). RLS is a disorder involving abnormal limb sensations that peak at night, worsen at rest, and are reduced during movement. Hypothalamic A11 dopaminergic neurons are strongly implicated in RLS, as treatments involve D<sub>2</sub>-like receptor agonists, and these neurons reside in a region that exhibits diurnal rhythmicity, a notable feature of the RLS phenotype.

RLS does not appear to be associated with REM sleep but instead an inability to fall asleep because of sensory dysesthesias. Still the decreased DA associated with REM sleep provides insight into the effect of dopaminergic drive on spinal cord excitability. One proposed hypothesis is that RLS involves loss of A11-derived spinal DA (Clemens et al. 2006; Qu et al. 2007). Given the results of Taepavarapruk et al., it seems possible instead that an increased DA drive could aberrantly facilitate nighttime sensorimotor activities in RLS. This would be consistent with the emergence of periodic limb movements and increased reflex excitability in sleep (Bara-Jimenez et al. 2000; Trenkwalder et al. 1999) and the need for D<sub>2</sub>-like agonists for symptomatic relief. Future work by these investigators will undoubtedly be vital to further unraveling the modulatory role of dopamine in spinal cord sensory function.

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