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## Editorial

# Mysteries of pedunculopontine nucleus physiology: Towards a deeper understanding of arousal and neuropsychiatric disorders <sup>☆</sup>



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This issue of *Sleep Science* contains two excellent review articles by Garcia-Rill and his colleagues examining the role of reticular activating system, especially the pedunculopontine (PPT) nucleus, in the pathophysiology of insomnia, schizophrenia, and other neuropsychiatric disorders [1,2]. The PPT nucleus is one of the major aggregations of cholinergic neurons in the mammalian brainstem capable of synthesizing acetylcholine, but also other neurotransmitters and peptides [3]. In addition, PPT cholinergic cells also synthesize a gaseous neuromodulator, nitric oxide. Interestingly, cells in the PPT are involved in regulation of both wakefulness and REM sleep [3,4].

About 10 years ago, the Garcia-Rill lab reported for the first time the presence of electrical coupling through gap junctions of some cells in each of three major elements of the arousal system, including the PPT [5]. This discovery helped explain how gap junction blockers like halothane and propofol can put us to sleep so rapidly. A year later, his lab resolved a 20-year mystery, the mechanism of action of the stimulant modafinil used in the treatment of narcolepsy. Modafinil was found to increase electrical coupling and coherence of cell activity in the same centers found to manifest electrical coupling, increasing arousal [6]. All of these breakthroughs

are addressed in review articles from Garcia-Rill lab appearing in this issue of *Sleep Science* [1,2]. However, these major contributions are only the tip of the iceberg.

About 5 years ago, Garcia-Rill first reported the presence of gamma band activity in these arousal-related centers, suggesting that this system generates its own high frequency activity [7]. They went on to show that this activity was mediated by intrinsic membrane oscillations due to the presence of high threshold voltage-dependent N- and P/Q-type calcium channels [8]. This year, they found that a protein over expressed in schizophrenia and bipolar disorder blocks the manifestation of gamma band activity in the PPT [9]. They also showed that one of the mechanisms by which lithium has a therapeutic effect is because it blocks the over expressing protein to allow the maintenance of gamma band activity, which is reduced in these disorders. So much for the 60-year mystery of the action of lithium. These findings are described in his *Sleep Science* review on schizophrenia and bipolar disorder, which are characterized by serious sleep-wake disturbances.

Also this year, the Garcia-Rill group reported the presence in the PPT of different populations of cells with only N-type, only P/Q-type, or both N- and P/Q-type calcium channels [10].

<sup>☆</sup>Peer review under responsibility of Brazilian Association of Sleep.

These populations may correspond to *in vivo* studies showing “REM-on”, “Wake-on” and “Wake/REM-on” cells, respectively, resolving a 30-year mystery [3,4]. This segregation suggests that waking and REM sleep are controlled by two separate intracellular pathways, which we investigated for many years [11–13]. This discovery implies that the gamma band activity observed during waking is different from that seen during REM sleep. In his Sleep Science review on insomnia [2], Garcia-Rill proposes a novel mechanism for this disorder (excessive waking due to increased expression or activity in the CaMKII-P/Q-type channel system). This imaginative proposal provides excellent new therapeutic targets for this difficult to treat condition.

In addition, Garcia-Rill provides preliminary data for the mechanism behind the developmental decrease in REM sleep (decreased expression of N-type calcium channels mediating REM sleep across development), resolving a 50-year mystery. They also suggest a mechanism behind the basic rest-activity cycle (BRAC) (alternation of CaMKII-P/Q-type channel waking-like gamma band activity with cAMP/PK-N-type channel REM sleep-like gamma band activity). I would not bet against this theory in resolving this 75-year mystery.

A new book entitled, “Waking and the Reticular Activating System” outlines his work over 40 years on locomotion, arousal, and waking, and is peppered with innovative ideas, solutions, and suggestions [14]. In fact, one reason Garcia-Rill became interested in the PPT was due to his studies in the 1980s and 1990s on the mesencephalic locomotor region [15]. This work led to a series of discoveries related to spinal cord injury, including investigations reducing hyper-reflexia after spinal cord injury using passive exercise, and the descending pathways mediating changes in postural muscle tone and locomotion [16]. This work emphasized the fact that the PPT not only triggers cortical arousal through its ascending projections through the intralaminar thalamus, but also activates descending postural and locomotion pathways in charge of fight-or-flight responses. These efforts led to the suggestion that stimulation of the PPT could be used for the treatment of the postural and walking deficits in Parkinsonism. It took 20 years, but the PPT is now a region implanted in Parkinson’s patients to perform deep brain stimulation, with impressive clinical outcomes [17].

Another area of study by this lab involves the midlatency auditory evoked P50 potential. The Garcia-Rill lab was the first to describe decreased habituation of the P50 potential in posttraumatic stress disorder [18], one of the few markers for the disorder that has withstood the test of time. They also were the first to show decreased habituation of the P50 potential in depression [19], Parkinson’s disease [20], and Huntington’s disease [21]. They were the first to identify the rodent equivalent of the P50 potential, the P13 potential [22]. These waveforms are present during waking and REM sleep (they are sleep state-dependent), are blocked by scopolamine (they are cholinergic), and habituate rapidly (reticular in physiology), indicative of their origin in the PPT. That is, the P50 potential is a marker for PPT output in the human, an unexplored but potentially productive research area.

As if this were not enough, Garcia-Rill has co-authored several law reviews. These articles address the contributions of modern neuroscience to the formulation and application of

the law. His law reviews run the gamut from scientific evidence to violence and future dangerousness, to intent and culpability. In keeping with new responsibilities as a modern neuroscientist, Garcia-Rill makes sure that his readers in the legal profession are exposed to the latest concepts derived in our field.

The fact is that the Sleep Science reviews reveal only some of the enormous range of this lab. Few individuals have contributed so many advances to the sleep field. These are not merely incremental advances but represent paradigm shifts characterized by imagination and intelligence. We sleep researchers have been introduced to the wonderful, puzzling, and inescapable world of gamma band activity by this group. These revelations have produced some of the most astounding advances in the sleep-wake field. I for one can hardly wait for the next mystery to be solved.

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## 1. Conclusion

Garcia-Rill has opened the door to gamma band activity in the ascending reticular activating system (ARAS), with ever increasing implications. Their proposal that this system is involved in the process of preconscious awareness has major ramifications for volition and free will, as well as consciousness. We are all familiar with the profound sleep disturbances caused by dysregulation of this region, but the significance of these changes has much wider implications for neurological and psychiatric disorders. The door has been opened by this lab and we should not only salute their accomplishments, but join them in their search for the answers to the mysteries of the ARAS.

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