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# Brainstem regulation of slow-wave-sleep

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## Abstract

Recent work has helped reconcile puzzling results from brainstem transection studies first performed over 60 years ago, which suggested the existence of a sleep-promoting system in the medullary brainstem. It was specifically shown that GABAergic neurons located in the medullary brainstem parafacial zone ($PZ^{GABA}$) are not only necessary for normal slow-wave-sleep (SWS) but that their selective activation is sufficient to induce SWS in behaving animals. In this review we discuss early experimental findings that inspired the hypothesis that the caudal brainstem contained SWS-promoting circuitry. We then describe the discovery of the SWS-promoting $PZ^{GABA}$ and discuss future experimental priorities.

## Introduction

Sufficient quality and quantity of sleep is the *sine qua non* for optimal physiologic, neurocognitive and psychologic function. Yet, the ‘how’ and ‘why’ of sleep remain among the most enduring mysteries in the neurosciences. To the former, there exist several conceptual models for how the brain achieves sleep, spanning humoral [1], local network [2], distributed network [3] and circuit-based theories [4,5]. And while these models provide varying levels of explanatory power for “whole brain sleep”, we will emphasize in this review the circuit-based model, as this model assumes that delimited nodes of sub-cortical neurons differentially and specifically contribute to the initiation and maintenance of slow-wave-sleep and its electroencephalographic (EEG) correlate.

The circuit and synaptic bases by which sub-cortical cell populations regulate behavioral and EEG SWS is complex and remains incompletely understood. Previous lesion, transection and stimulation work has suggested not only redundancy in sleep-promoting circuitry but also, and rather remarkably, that the forebrain and brainstem can independently regulate

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sleep. For instance, early postnatal midbrain transections in kittens revealed the ability of the forebrain and brainstem to drive, albeit often in temporal dissociation, electrocortical and behavioral rhythms, respectively, of sleep [6].

With respect to the forebrain “sleep system”, the preoptic area (POA) plays an important, if indispensable, role in the initiation and maintenance of SWS [7,8]. Within the POA region both the ventrolateral (VLPO) and median preoptic (MnPO) nuclei contain high-density clusters of sleep-active neurons [4,9,10]. These sleep-active VLPO and MnPO neurons are largely GABAergic [11,12] and project to, and hence presumably inhibit, multiple arousal-regulatory centers. Considerable convergent evidence has, in fact, identified a particularly important role for VLPO neurons in the sleep process, including: 1) VLPO neurons show a dramatic increase in firing during SWS [13-15]; 2) cell-body specific lesions of the VLPO produce a sustained and dramatic decrease (~40-50%) in SWS in rodents [16,17]; and 3) chemo- and opto-genetic activation of VLPO neurons produces sleep (C.B.Saper, perscomm).

As indicated, transection studies - reaching back over 60 years - as well as more recent human imaging studies [18] have inferred the existence of a brainstem “sleep system” but, until recently, a brainstem “homolog” of the POA or VLPO remained elusive. This rather conspicuous temporal gap in identifying and characterizing brainstem sleep-promoting circuitry was likely a consequence of several issues. First, there is history: the seminal clinico-anatomic studies by von Economo established that relatively discrete inflammatory lesions within the anterior hypothalamus/POA could produce a chronic state of insomnia [19], setting the stage for decades of focused experimental work on the anterior hypothalamus/POA. Second, experimental approaches that proved fruitful in the forebrain, such as excitotoxic lesions, did not prove as successful in the brainstem, often, instead, resulting in subject death. Third, there is extensive interdigidation of excitatory(glutamate) and inhibitory (GABA) neurons in the cellular brainstem, rendering the interpretation of nonselective experimental ablation, stimulation or inhibition experiments challenging. Fourth, the rodent brainstemis located deep in the skull, below the cerebellum and is therefore far less accessible than the forebrain. Taken together, it is perhaps not surprising that until the recent advent of molecular–genetic tools [20,21], which enabled selective and reversible interrogation of cell populations, a considerable void existed in the literature regarding brainstem sleep systems. In this review, we will describe the seminal historical work that first inspired the hypothesis of a brainstem sleep system, and then move to more recent findings that have identified specific cells and pathways by which the brainstem may control SWS and, finally, we will discuss current knowledge gaps and thoughts on future experimental directions.

## Historical studies

The first experimental evidence to suggest that the brainstem might participate in sleep control came from work by Batini who showed that transection of the brainstem just rostral to the origin of the trigeminal roots (i.e., the “pretrigeminal” preparation) produced chronic EEG activation [22]. Batini subsequently showed that the chronic EEG desynchrony/ behavioral insomnia in the pretrigeminal preparation was not dependent upon sensory inflow

from the auditory or visual systems [23]. And, in fact, findings by others showed that a genuine state of alertness was present, e.g., vertical object tracking, pupillary response to visual stimulus, in the pretrigeminal cats during EEG desynchronization [24-26]. Batini's findings were therefore in stark contrast to that seen following slightly more rostral (~2-3mm) transections of the brainstem, i.e., Bremer's *cerveauisolé* preparation, which produced chronic EEG deactivation [27,28]. Hence Batini's findings had important implications, namely that an EEG-synchronizing/sleep-promoting influence might arise from the caudal brainstem and that this sleep-promoting influence was not dependent upon sensory inflow. Conversely, these findings also suggested that tonic sensory inflow, which was preserved in Bremer's *cerveauisolé* preparation, was insufficient to support EEG activation/behavioral wake. Similar results to that of Batini were obtained by Belucchi who showed using bulbar cooling in the *encephalaeisolae*cat* that cooling of the medullary floor of the 4$^{th}$ ventricle during slow wave sleep produced EEG and behavioral arousal [29,30]. Taken together, these experimental findings were consonant with Batini's prescient surmise that “a synchronizing, or possibly sleep-inducing, influence exerted by some structure in the caudal brain stem can be tentatively envisaged”.

Building upon Batini's observation in the pretrigeminal preparation stimulation and lesion studies in the early 1960s provided evidence that a “deactivating influence” might be localized within the region of the solitary tract [31-33]. For example, Magnes and colleagues showed that low rate electrical stimulation of the cat solitary tract could induce EEG synchrony, and that this synchrony was not simply due to stimulation parameters used [31]. It was similarly shown that electrical or chemical stimulation of the nucleus of the solitary tract (NTS) could produce a cortical slow-wave-sleep like state [34,35]. Importantly, however, these stimulation studies were performed in anesthetized rats and the evoked synchronized cortical EEG showed a dominant 5 Hz band whereas the typical SWS frequency band is 0.5-4 Hz. In some contrast, a recent study in freely moving cats demonstrated that electrical stimulation of the NTS enhanced cortical EEG theta and beta, but not delta, band power and increased wakefulness [36]. Given however that the NTS is a long nucleus extending most of the dorsal part of the medulla oblongata, and relays inputs from the cranial nerve V (trigeminal), VII (facial) and IX (glossopharyngeal), at different rostro-caudal levels, one might expect the cortical effect of NTS stimulation to be highly dependent upon the actual region of NTS activated. It certainly remains possible that the NTS may contain sleep-promoting cells, and it is our hope that this intriguing possibility will be explored going forward.

## Recent studies

Approximately 5 years ago, our group set out to uncover the location and identity of brainstem neurons that might contribute to the regulation of SWS. In doing so, we reasoned that any SWS-promoting brainstem neurons would likely project to and inhibit neurons of the parabrachial nucleus (PB), a cell population that we had previously identified as making an especially important contribution to the maintenance of behavioral and EEG arousal [37].

*the bulbar cooling model was preferred for brainstem-based studies because it helped avoid the contaminating effects of autonomic and respiratory changes, which are typically evoked by stimulation of the medulla.

We initiated our search by retrogradely labeling inputs to the medial PB, and in doing so we uncovered a substantial input from sleep-active neurons in the rostral medulla located lateral and dorsal to the facial nerve, a region we termed the parafacial zone (PZ). Based on this foundational anatomic work, we then showed that (1) cell-specific lesions of the PZ in rats resulted in insomnia, (2) the majority of sleep-active PZ neurons were GABAergic/glycinergic and (3) that targeted genetic disruption of GABAergic/glycinergic transmission from the PZ in mice resulted in large and sustained increases in wakefulness [38]. In other words, our experimental work established that $PZ^{GABA}$ neurons were necessary for normal amounts of SWS. We subsequently showed that genetically targeted activation of $PZ^{GABA}$ neurons was sufficient to rapidly induce SWS, increase SWS amount and produce consolidated and enhanced cortical slow-wave-activity (SWA), the latter being a marker of SWS depth and quality, in behaving mice [39]. We then used optogenetic-based mapping to define, at least in part, the synaptic and circuit basis by which $PZ^{GABA}$ neurons could promote and maintain sleep. We specifically found that $PZ^{GABA}$ neurons monosynaptically innervate and release synaptic GABA onto PB neurons that, in turn, project to and release synaptic glutamate onto cortically-projecting neurons of the wake-promoting magnocellular basal forebrain [37,40], suggesting a circuit substrate through which $PZ^{GABA}$ neurons can rapidly trigger SWS and modulate the cortical EEG. In sum, by means of genetic-based disruption, activation and inhibition we demonstrated both the sufficiency and necessity of brainstem $PZ^{GABA}$ neurons in the regulation of SWS and cortical SWA.

While beyond the scope of this mini-review, a central role for brainstem circuitry in the regulation of rapid-eye-movement (REM) sleep was established over 50 years ago [41]. And similar to the identification and characterization of the SWS-promoting PZ, technical advances have enabled a more refined understanding of the cellular and synaptic basis by which a distributed network of brainstem circuits regulation REM sleep, including the recent identification of GABAergic REM-generator cells in the ventral medulla [42-45].

## Conclusions

Acute and selective activation of $PZ^{GABA}$ neurons rapidly induces SWS cortical EEG SWA in behaving mice. In fact, both the quantity and quality (operationally defined as greater SWA power) of SWS are enhanced, independent of the time of the day, whereas rapid eye movement sleep (REMS) is inhibited. The strong reproducibility and potent sleep-induction, all in a freely behaving framework, suggest a new and unique mouse model of SWS enhancement, which has the very real potential to permit, for the first time, a direct assessment of the role of SWS *per se* in a myriad of neurobiologic processes.

Our understanding of how $PZ^{GABA}$ neurons, and possibly other, as yet unidentified, brainstem sleep-promoting cell populations, regulate SWS and cortical SWA remains rudimentary. Fortunately, the development of new genetic-based tools, some of which played a fundamental role in defining the $PZ^{GABA}$ neurons as a key SWS-promoting brainstem cell population, should enable a rapid and more expansive experimental-based understanding of $PZ^{GABA}$ neurobiology. For example, we are currently seeking to understand how the $PZ^{GABA}$ neurons are regulated by afferent inputs. It is also remains unclear how the PZ can drive, and even enhance, cortical EEG SWA. The firing pattern of $PZ^{GABA}$ neurons across

the sleep-wake cycle also remains to be elucidated. Finally, determining how $PZ^{GABA}$ neurons "fit" within the different models for sleep-wake control, e.g., flip-flop switch, and how $PZ^{GABA}$ neuronal activity may be affected by circadian and homeostatic influences have become high experimental priorities.

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## Highlights

- The mammalian brainstem contains sleep-promoting circuitries
- GABAergic parafacial zone ($PZ^{GABA}$) neurons are sleep-promoting in vivo
- The circuit basis by which $PZ^{GABA}$ neurons induce sleep remains incompletely understood

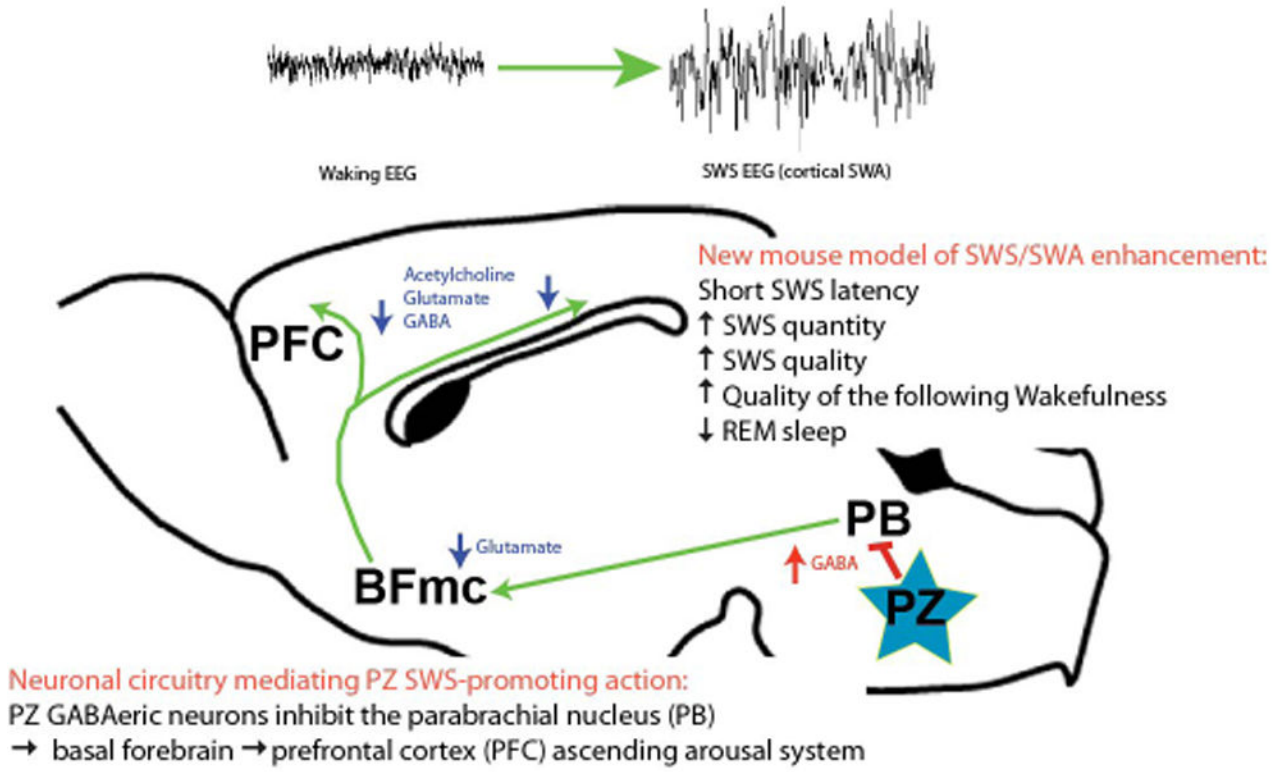


**Figure. The sleep-promoting parafacial Zone (PZ): neuronal circuitry and behavior**

How can *in vivo* activation of $PZ^{GABA}$ neurons potently and rapidly induce SWS and cortical SWA? Optogenetic-based circuit mapping suggests one possible circuit basis for these effects: activation of $PZ^{GABA}$ neurons results in synaptic release of GABA (red arrow) onto BF-projecting PB neurons (green arrow). Inhibition of glutamatergic PB neurons reduces synaptic release of glutamate (blue arrow) onto cortically-projecting BF neurons, in turn reducing cortical levels of wake-enhancing acetylcholine, glutamate and GABA. Hence the net result is a dramatic reduction in ascending arousal influences normally provided by the PB and BF to the cortex. This reduction in arousal inputs is reflected in the cortical EEG as a decrease in the fast frequencies that are characteristic of cortical activation/desynchronization and wakefulness, the appearance of slow waves and delta waves that are characteristic of cortical synchronization and SWS and behavioral sleep. BF: basal forebrain; PB: parabrachial nucleus; PFC: prefrontal cortex; PZ: parafacial zone; SWS: slow-wave-sleep; SWA: slow-wave activity. Modified from [39].