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Review Article

Bidirectional interactions between the baroreceptor reflex and arousal: an update

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ABSTRACT

Studies involving genetic engineering on animal models and mathematical analysis of cardiovascular signals on humans are shedding new light on the interactions between the arterial baroreceptor reflex (baroreflex) and arousal. Baroreceptor stimulation, if very mild or performed under anaesthesia, may inhibit cortical arousal. However, substantial increases or decreases in baroreflex activation cause arousal in animal models and human subjects in physiological conditions. On the other hand, cardiovascular changes during autonomic arousals and between the states of wakefulness and sleep involve changes in the baroreflex set point and balance with central autonomic commands. Neural connectivity and functional data suggest that the nucleus of the solitary tract, adrenergic C1 neurons of the medulla, and the parabrachial nucleus of the pons mediate the bidirectional interactions between the baroreflex and arousal. These interactions may constitute a positive feedback loop that facilitates sharp and coordinated brain state and autonomic transitions upon arousal: upon arousal, central autonomic commands may increase blood pressure, thereby loading baroreceptors and further increasing arousal. Anomalies of this feedback loop may play a role in the pathophysiology of disease conditions associated with cardiovascular and sleep–wake cycle alterations. These conditions include: obstructive sleep apnoea syndrome, with its association with excessive daytime sleepiness and baroreflex impairment; and insomnia, with its association with autonomic hyperarousal and hypertension. When faced with disorders associated with cardiovascular and sleep–wake cycle alterations, clinical reasoning should entertain the possibility that both conditions are strongly influenced by anomalies of baroreflex function.

1. Introduction

Changes in arterial blood pressure (ABP) are sensed by stretch receptors (the baroreceptors) in the wall of the carotid sinuses and aortic arch, leading to changes in the activity of the central neural circuits that control the heart and blood vessels. The resultant changes in cardiac output and vascular resistance tend to buffer the ABP changes that have triggered the baroreceptor reflex (baroreflex) response. Claims that the baroreflex modifies arousal date back to more than 80 years ago [1]. The seminal paper on humans by Smyth and colleagues came 40 years later, with a claim that sleep increases cardiac baroreflex sensitivity (BRS) (ie, the change in heart rate (HR) per unit change in ABP) [2]. These early findings have been replicated with variable success, expanded, and even partially forgotten, so that the interactions between the baroreflex and arousal have remained a topic of debate. This brief review aims to provide a critical update on these interactions and to highlight their potential clinical implications.

The first section addresses the definition of arousal and the concept of a hierarchical continuum in the arousal response from signs of subcortical activation, including autonomic activity, to brain cortical events under more powerful arousing stimuli. The second and third sections review the functional relationships between arousal and the baroreflex, arguing that these interactions are bidirectional in two significant respects: the baroreflex may either inhibit or stimulate cortical arousal, depending on conditions and stimulus intensity, and the baroreflex is itself modulated by arousal and sleep. The next two sections address the neuroanatomical

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structures that underlie the interactions between arousal and the baroreflex, highlighting the tight reciprocal connections between the brain regions involved in baroreflex control and in arousal modulation. The last section reviews the clinical implications of the concepts developed in the previous sections.

2. Definition of arousal during sleep

The concept of arousal is linked to the state of wakefulness, non-rapid-eye-movement (NREM) sleep, and rapid-eye-movement (REM) sleep, in which it occurs. During wakefulness, the arousal response consists of cerebral, autonomic, and behavioural activation in response to internal and environmental stimuli. During sleep, transient spontaneous events mimicking the response to external stimuli were first described under the name of 'phases d'activation transitoire spontanées' as increases in electroencephalogram (EEG) frequency associated with decreased EEG amplitude; disappearance of permanent (delta and theta waves, < 4 Hz and 4-8 Hz, respectively) and phasic (spindles and K-complexes) sleep EEG activity; concomitant appearance of high-amplitude potentials on the electromyogram; and tachycardia [3]. The term micro-arousal was proposed later to define phasic EEG events not associated with awakenings, which could have either a desynchronised (ie, increased EEG frequency and decreased EEG amplitude) or synchronised (K-complexes and EEG delta bursts) morphology [4]. The advent of sleep medicine in the 1980s called attention to brief arousals during sleep, leading the American Sleep Disorders Association (ASDA) to publish consensus criteria for their scoring [5]. Arousal was defined as 'an abrupt shift in EEG frequency, which may include theta and alpha activity, and/or frequencies >16 Hz but not spindles' of ≥3 s in duration and preceded by ≥10 s of continuous sleep. A concurrent increase in submental electromyogram amplitude was required to score arousals in REM sleep [5]. Nonetheless, the essential feature of the ASDA arousal criteria is EEG desynchronisation, which reflects cortical activation. For this reason, the expressions 'EEG arousal' and 'cortical arousal' have often been used synonymously with the ASDA definition.

Arousals entail distinct autonomic manifestations [6] with a stereotyped sequence of events: HR increases with or even before [7,8] the onset of cortical arousals; ABP rises, reaching a peak; HR returns to or below baseline level; ABP also returns to baseline level [9]. Autonomic arousals may occur without visually discernible cortical arousals [6,10] or with the EEG-synchronisation type of microarousal, such as K-complexes and EEG delta waves [8]. The expression 'subcortical arousal' has also been used to describe events of autonomic activation associated with an EEG pattern different from conventional (cortical) arousal [11] (Fig. 1).

The temporal pattern of autonomic and EEG arousal changes has been studied in association with periodic limb movements during sleep (PLMS). PLMS are stereotyped and repetitive movements of the limbs, mainly the legs, which may be accompanied by signs of arousal. PLMS occur in healthy subjects and more frequently in sleep disorders like restless legs syndrome (RLS), narcolepsy, and obstructive sleep apnoea syndrome (OSAS). While quantitative differences do occur among physiological and different pathological conditions, PLMS are associated with increases in HR and delta EEG activities, which herald the onset of PLMS, followed by a sequence of EEG changes ranging from increases in theta activity to visually discernible cortical arousals [12,13]. PLMS may also occur in the absence of cortical arousal and the two phenomena may be pharmacologically dissociated [14], but PLMS always entail changes in both HR and ABP. These cardiovascular changes are not solely caused by the movement or the cortical activation, despite being potentiated by the co-occurrence of cortical arousals [12–15]. The PLMS-related temporal pattern of autonomic and EEG changes suggests a hierarchy in the arousal response, from autonomic activation, representing the earliest marker of brain arousal, to cortical involvement under more-powerful arousing stimuli [8,13,16]. Furthermore, this temporal pattern suggests a facilitating role of autonomic arousal in gating PLMS, as observed for other physiological and pathological sleep-related motor events [17,18].

Periodic oscillations of EEG activity, systemic and pulmonary arterial pressure, heart rate, and ventilation occur spontaneously during sleep [19] and have been categorised as cyclic alternating pattern (CAP) [20,21]. CAP consists of pseudo-periodic arousal-related intervals shorter than 1 min (A phases) that interrupt the tonic theta/delta activities of NREM sleep (Phase B). In particular, phase A can be classified into three subtypes based on the proportion of high-voltage, slow EEG waves or low-amplitude, fast EEG rhythms. The former and the latter predominate in phases A1 and A3, respectively, with phase A2 in between. A progressive increase in motor and autonomic activation is observed from the A1 to the A3 subtype. Motor events such as PLMS are related to phase A, which may act as a gate to facilitate the occurrence of pathological events [18].

3. The baroreflex may either inhibit or stimulate cortical arousal, depending on conditions and stimulus intensity

In early studies, substantial increases in isolated carotid sinus pressure in a paralysed and vagotomised dog preparation were capable of slowing the EEG down to the delta rhythm, which is characteristic of NREM sleep [22]. This effect was neurally mediated because it persisted when spino-medullary transection (encéphale

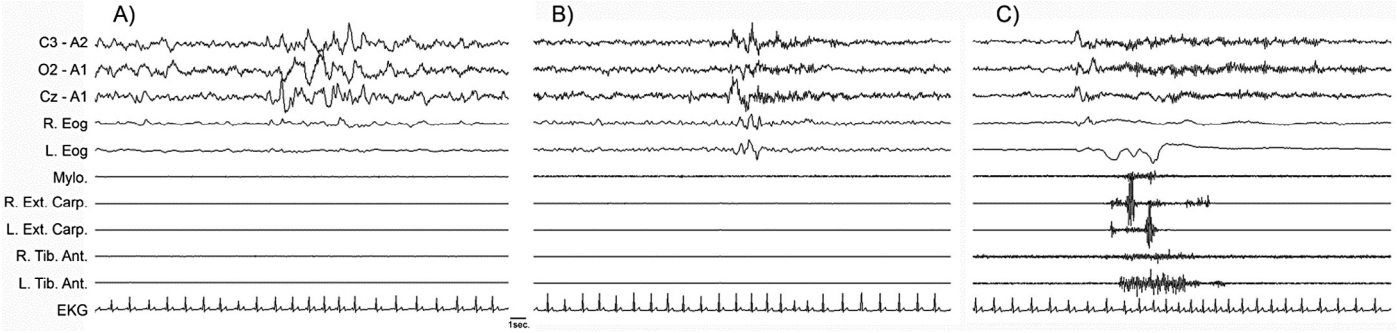

Fig. 1. Polygraphic recordings of: (A) EEG-synchronisation type of microarousal (subcortical arousal); (B) EEG-desynchronisation type of microarousal (cortical arousal); and (C) 'phase d'activation transitoire' arising from non-rapid eye movement (NREM) sleep. The three types of arousal are associated with autonomic changes (early increases and late decreases in heart rate, as evident from the electrocardiogram recording, EKG). Electroencephalogram (EEG): C3-A2, O2-A1, Cz-A1. EOG, electrooculogram; Ext. Car., Extensor Carpi muscle; L, left; Mylo., mylohyoideus muscle; R, right; Tib. Ant., Tibialis anterior muscle.