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Editorial

It is not as simple as "I will put you to sleep": A neurological perspective on sedation☆

No es tan sencillo como "Te pondré a dormir": una perspectiva neurobiológica sobre la sedación

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Comment

The editorial presented in this issue by Dr. Ramsay, "The biological cost of depressed consciousness" is an appeal for us to bear in mind the deleterious consequences of an altered state of consciousness (sedation), particularly in the Intensive Care Unit (ICU). I believe, for example, in the need to consider the significant two-way relationship between sleep disorders and Alzheimer's disease (AD), documented more than one decade ago. Sleep disorders are early indicators of dementia and may manifest before cognitive symptoms[1]. There are basically two pathological process happening in AD: the first is the abnormal biochemical processing of a transmembrane protein called amyloid precursor protein, leading to the production, among other substances, of a toxic peptide known as amyloid beta 42 (A-β42) that accumulates and forms extracellular plaques in the brain; the second is the altered tau protein, a protein associated with the microtubules which is hyperphosphorylated and aggregated in different ways in AD. Tau protein abnormalities are also found in other fatal neurodegenerative diseases causing dementia or movement disorders. Experiments in rodents and correlation studies in humans have shown that chronic changes in sleep architecture induce amyloid and tau disorders[2,3], that is to say, a fatal vicious circle.

It would appear that I have diverted from the topic, but allow me to suggest that it is not so: patients requiring sedation after head injury are commonly found in the ICU. Although war usually leaves desolation and death in its wake, the fact that a large number of combatants in Iran and Afghanistan survived severe head injury resulted in a significant increase in research about this issue in the United States. It is now known that single as well as repeated (boxers, football and rugby players, or soldiers) severe head injury is characterized by biochemical changes that are very similar to Alzheimer's disease. For example, high A-β42 may be found after severe trauma, and the two disorders may manifest in repetitive injury, although tau protein disorder is more significant (hyperphosphorylation) in the injured regions of the brain and it may progress to other regions[4]. This information is relevant because several drugs used for sedation or anaesthesia (e.g. sevoflurane, isoflurane and propofol)[5–7] have been shown in experimental studies to induce increased A-β42 or tau protein phosphorylation, or both. Up until recently it was considered that most of the tau protein abnormalities observed were not due to the anaesthetic per se but were associated with the hypothermia frequently induced in

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experimental animals, and that they were transient. But more recent information suggests that repeated or prolonged use of the anaesthetic produces hypothermia-independent irreversible tau phosphorylation[5,7].

Regarding drugs used in the ICU, specific studies of each anaesthetic/sedative are required in these and other brain homeostasis processes (including perhaps neurovascular coupling) in order to arrive at a reasonable conclusion. Briefly, neurovascular coupling refers to the fact that there is a dialogue between neurons and the vessels that supply them, in such a way that the higher the neuronal activity (greater synaptic activity) the greater the blood flow. There is also neuro-metabolic coupling, whereby neuronal metabolic rate increases (glucose and oxygen uptake) in conditions of high activity and blood flow. It was recently proposed that in some neurodegenerative diseases (Huntington's disease), neuro-metabolic de-coupling might be responsible for neuronal death[8]. Many anaesthetics cause de-coupling, although that topic is beyond the scope of this comment.

It has been determined recently that sleep acts like some sort of lymphatic system for the brain, ridding it of debris. It is actually called the glymphatic system, since the process is carried out essentially by the glia[9]. These studies have shown that sleep induces a significant increase in extracellular fluid volume in the brain and also the convective outflow of metabolites and proteins. This includes increased clearance of A-β42 and lactate. It is not known yet whether hyperphosphlyrated tau is also cleared via de glymphatic system. Interestingly, contrary to what happens with other anaesthetics, ketamine produced a similar effect as that of sleep, increasing A-β42 clearance. Based on these experiments, it has been proposed that the restorative role of sleep may be due to a functional change of the brain to a mode that facilitates the elimination of breakdown products produced during waking hours.

Another consideration relates to the dynamics of neuronal circuits during wakefulness, REM and non-REM sleep, and sedation. Studies using magnetoencephalography (MEG)[10] suggest that during REM sleep the nervous system is processing its own intrinsic neuronal information which creates a form of internal consciousness when we dream, while during waking hours it receives sensory information from the outside world which processes and modifies neuronal rhythms, creating a state of awareness – the SELF. Worth highlighting is the suggestion that the neural mechanisms by which those conscious functional states are created are very similar[10]. They are both based on synchronic neuronal activity (thalamic-cortical activity) which creates an oscillation band of approximately 40 Hz known as gamma oscillation. According to this hypothesis, wakefulness and REM sleep are electrically similar in terms of the 40 Hz oscillation, although a key difference is that sensory stimuli are unable to change the origin or location of the 40 Hz activity. The opposite is true in the waking state. In contrast, during delta sleep (non-REM) there is no predominant gamma band but, similar to REM sleep, the sensory input is unable to change the brain's electrical frequencies.

During sedation, both functional states associated with the gamma band are abnormal, and the short and long-term cognitive consequences of that condition are yet to be elucidated. What is known is the frequent clinical observation that moderate dementia cases worsen after anaesthesia and it is impossible to predict which patients will recover to their initial state after this happens.

A paper published recently by professor F. Plum et al. focused on the study of patients in a vegetative state[11], a cognitive clinical syndrome characterized by the presence of endogenous sleep-wakefulness cycles with no evidence of consciousness, which ensues following severe head trauma, hypoxia or any other severe systemic insult. Using PET scans, video EEG, MRI and MEG, the researchers found that some patients responded to sensory stimuli with coordinated focal cortical activation. However, despite the use of state-of-the-art methodology, it was not possible to find evidence that these residual functional modules could generate a state of consciousness. This suggests that consciousness requires large-scale comprehensive brain function.

To conclude, I would say that it is important to think twice before deciding to alter the functional state of the brain through the use of a sedative drug. I hope I have been able to convey the thought that sedating a patient is not an easy decision. Like in the famous Chinese novel of novels, Chin P'ing Mei, many characters mentioned here have to be taken into consideration or revisited in order to understand the whole story.

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Conflicts of interest

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