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EDITORIAL VIEW

Time of the day, anesthesia and cognition: a neuro-protective approach

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ABSTRACT

Anesthesiologists have always been concerned about the post anesthetic effects on brain and the possibility of neurocognitive dysfunction. Neurocognitive effects have been observed in all ages especially with long duration anesthetics. Experimental studies on animals have also suggested detrimental effects on brain and cognitive functions are also altered negatively. This might be due to the fact that the proteins responsible for cognitive processes are also altered by the anesthetics. Studies have also shown that proteins responsible for cognitive functions show circadian variations, i.e. their levels are different during different time points of the day. It is suggested that if the anesthetics are given while the proteins (which are responsible for cognitive function) are at peak, effect of anesthetics might be less. For this reason, there is a need to study the effect of anesthetics with/without surgery at different time points of the day to determine any variation of cognitive effects at different day times.

Key words: Anesthetics; Circadian rhythm; Cognition; Neuroprotection; Brain proteins; Time of the day

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Anesthetics and Cognition

Studies have revealed that millions of individuals go through surgical procedures every year under general or local anesthesia.[1] Anesthetics have been implicated in short and long terms alteration in cognitive functions in all ages. Experimental studies on laboratory animals have shown that anesthetics may be responsible for neurotoxicity and are implicated in brain protein changes leading to cognitive dysfunctions.[2] Any alteration in the neurotropic factors like Brain Derived Neurotropic Factor (BDNF) are associated with cognitive impairment.[3] Studies have shown a relationship between anesthetics and BDNF and a link has been observed in BDNF and postoperative delirium.[4] In addition to BDNF, some other proteins too, are implicated in cognition like extracellular signal regulated kinases (ERK) and these proteins have also been affected by the anesthetics.[5]

Daily variation of brain proteins

The rhythms which are about a day are called circadian rhythms and are endogenously driven not only at physiological levels but also at molecular level.[6] These rhythms are altered by the external environmental factors called zeitgebers. Zeitgebers are the factors, stimuli that are capable to alter the circadian clock like the daylight, stressors, temperature, humidity etc.[7] Studies have shown that various proteins follow a circadian rhythms i.e. certain proteins are at peak at one time point of the day and low at other time points. There is evidence that the circadian variation of the proteins is regulated by the central pacemaker that is present in the supra-chiasmatic nucleus (SCN) of hypothalamus.[8] The proteins which have been implicated in cognitive processes like BDNF have shown daily variations in human plasma.[9] Mitogen activated protein kinase and cyclic adenosine monophosphate play important role in learning and memory formation and these proteins also follow daily variation in circadian fashion and it has also been studied that hippocampal dependent long term memory depends on circadian profile of these proteins.[10] Further, it has also been shown that memory performance varies during different times of the day. It is shown to be parallel to the daily variation of extracellular signal regulated kinase.[11] As these proteins vary during the day i.e. their plasma

levels are different according to the time of the day, so these proteins might respond to zeitgebers differently at different time points of the day.

How time of the day for anesthesia is important?

All brain proteins which have been involved in neuro plasticity, long term potentiation ancognition follow a circadian rhythm. At certain time point of the day, such proteins like BDNF, ERK are at peak and at other time point these proteins have been observed at nadir. The physiological processes and linked behaviors are also altered according to the time of the day, e.g. memory performance has been observed at peak around zeitgeber time 5 (ZT5, five hours after light on period).[11] This is because, the proteins responsible for cognition are at peak around ZT5. So, it might be possible that these protein may respond to anesthetics differently at different time points of the day. Therefore, if the anesthesia procedures are planned in respect of the circadian profile of the brain proteins, there may be less neurotoxicity and less dysfunction in cognitive abilities. It is proposed that anesthetics might have less detrimental effect if anesthesia is given in light period, as brain proteins are at peak after light on period and can protect the brain and so, less detrimental effects on cognition. To confirm it, we need to study the effect of anesthetics with/without surgeries at different time points of the day. Anesthetics may also affect the brains in another way by effecting the neurotransmitters which have been involved in circadian rhythms. A review[12] on number of studies indicated that many anesthetics on a variety of organisms either in vivo or in vitro effect the neurochemicals which are involved in circadian rhythms. It also reviewed that patients with surgeries under anesthesia experience sleep issues post operatively. Data on lab animals also indicate that the anesthetics can alter circadian rhythms, leading to alterations of molecular clock. This showed that anesthetics have been implicated in disruption of circadian clock which in turn has shown alterations in neuronal architecture and a decrease in cognitive flexibility.

Concluding that anesthetics may have varied effect on cognition at different time points of the day. This should be further studied through in vivo experiments in animals by injecting the subjects with anesthetics at least at six different time point to investigate any circadian effect. This research may be implicated in minimizing the detrimental effects of anesthetics on brain and cognition.

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