Journal of Biomed Research

Ishizawa et al, J Biomed Res. 2022;3(1):3-5.

Commentary

A longing for flawless awakening from general anesthesia

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Received date: March 28, 2022
Accepted date: April 07, 2022

Citation: Ishizawa Y, Ballesteros JJ. A longing for flawless awakening from general anesthesia. J Biomed Res. 2022;3(1):3-5.

Abstract

Anesthetic recovery can be a critical period since neurocognitive problems such as agitation and delirium are often seen during the early recovery phase. We recently demonstrated that an α2-adrenergic agonist dexmedetomidine-induced unconsciousness and accompanying brain dynamics changes were completely and instantly reversed by the α2-adrenergic antagonist in the nonhuman primate model. Active awakening from general anesthesia using its antagonism can contribute to facilitating post-anesthesia recovery and discharge in various patients, and also potentially prevent the neurocognitive problems that are associated with anesthetic emergence and recovery. The latter possibility should be investigated in the translational animal models.

Keywords: General anesthesia, Anesthetic recovery, Unconsciousness, Consciousness, Neurocognitive function, α2-adrenergic agonist, Dexmedetomidine, 2-adrenergic antagonist

Introduction

General anesthesia just marked its 175th anniversary since diethyl ether was first used in 1846 for a surgical procedure at the Massachusetts General Hospital. General anesthesia, considered as one of the most important progresses in modern medicine, has now become safe practice for a majority of patients. However, side effects and toxicity of anesthetics and possible long-term cognitive problems after general anesthesia are still challenging issues, especially in patients of advanced age. Emergence from general anesthetic-induced unconsciousness is primarily a passive process depending on the wash-out of anesthetic gases from the lungs or metabolism and excretion of intravenous drugs. Emergence and recovery may be critical periods since some of the neurocognitive problems such as agitation and delirium are often seen during the early recovery phase.

α2-Adrenergic Agonist, Antagonist, and Anesthesia

Dexmedetomidine has been used as a part of general anesthesia regimen in the operating rooms and as a sedative in the ICU. Especially, its use for sedation in the ICU appears to be rapidly growing during the COVID-19 pandemic. Since the landmark article published by Maze and his group in 1988 [1], which demonstrated the reduction of anesthetic requirement by dexmedetomidine, the research on dexmedetomidine exemplifies the growth of successful clinical applications originated from the identification of its specific receptor mechanisms [2]. Dexmedetomidine is a highly selective α2-adrenergic agonist and is unique among currently available general anesthetics, most of which are known to act at multiple receptors in the central nervous system. Dexmedetomidine is further unique because a specific 2-adrenergic antagonist, atipamezole, is available to reverse its sedative and anesthetic effects, though its use is only approved in the veterinary practice. Our recent article demonstrated the behavioral responses and accompanying neuronal dynamics of dexmedetomidine-induced unconsciousness and recovery in unparalleled details using a nonhuman primate (NHP) model [3]. By administration of the α2-adrenergic antagonist we successfully induced immediate awakening to the top performance level and fully awake brain dynamics while dexmedetomidine was still being infused. During passive recovery without the antagonist, the state of fluctuating behavioral responses and neuronal dynamics was consistently seen and often prolonged in the NHP model, which phase was completely disappeared when the antagonist was given. This complete antagonism of the anesthetizing dose of dexmedetomidine in NHP strongly suggest a potential use of the α2-adrenergic antagonist as a reversal agent for dexmedetomidine in clinical medicine.

Such effective antagonism, however, is not available for our patients. In fact, clinical studies were conducted in 1990's to examine the effect of the α2-adrenergic antagonism to reverse the sedative and sympatholytic effect of dexmedetomidine [4-6]. Scheinin and colleagues demonstrated that impairments of vigilance and psychomotor activity by dexmedetomidine were dose-dependently reversed by atipamezole in healthy volunteers [4]. The reductions in blood pressure, heart rate, and plasma catecholamines by dexmedetomidine were similarly reversed by atipamezole, but the highest atipamezole dose showed transient sympathetic activation. The study was accompanied by an enthusiastic editorial view that it could lead to a new era of receptor-specific anesthesia [7]. The results of other clinical studies appeared to be promising with the dose-response effectiveness without serious adverse effects [5,6]. However, further clinical trials for the use of α2-adrenergic antagonists were not carried out and they remained unavailable in clinical medicine. Around that time, multimodal general anesthesia practice was not a standard practice and opioids were used heavily during anesthesia and for postoperative pain, resulting in no urgent need of non-opioid sedatives or anesthetics, such as dexmedetomidine. Additionally, the recovery from dexmedetomidine appeared to be benign compared to volatile general anesthetics and thus reversal of the effect did not seem to add further benefits to post-anesthesia patient care. More recent studies are consistent with this view and suggest lower incidence of agitation and delirium during recovery following general anesthesia with dexmedetomidine in both elderly and pediatric patients [8-10].

Nevertheless, with a recent upward trend of clinical applications of dexmedetomidine in anesthesia and intensive care, it might be a great opportunity to reevaluate a possible role of the α2-adrenergic antagonists in clinical medicine. A recent hospital registry study of a large number of patients indicated that the intraoperative administration of dexmedetomidine was dose-dependently associated with a prolonged stay in the post-anesthesia care unit (PACU) in adult patients after ambulatory surgery [11]. Discharge delays after dexmedetomidine appears to be associated with over-sedation and cardiovascular complications. In pediatric patients, a retrospective cohort analysis suggested a delay in discharge from PACU when dexmedetomidine was used as an adjuvant during propofol anesthesia for various ambulatory procedures [12]. Interestingly, the lower satisfaction scores were reported by the parents of children receiving dexmedetomidine and midazolam compared to other pharmacological regimens (propofol, propofol and midazolam, or propofol and ketamine) [13]. Parental unsatisfaction appears to be influenced by prolonged sleepiness, irritability, and unsteadiness after dexmedetomidine and midazolam. Together, these recent findings suggest that titrating reversal of the effect of dexmedetomidine by the α2-adrenergic antagonist may facilitate recovery without prolonged drowsiness and prevent discharge delay, especially in the patients after non-invasive procedures or with minimum pain.

The Brain Recovery beyond the α2-Adrenergic Mechanism

Besides the potential benefits of the α2-adrenergic antagonism in clinical medicine, our recent report with dexmedetomidine and the antagonist [3], along with our studies about other general anesthetics [14-16], suggest possibly a fundamental mechanism of how the brain transitions between the states. We show abrupt neural dynamics changes during anesthetic-induced altered states of consciousness. Loss and return of consciousness are precisely correlated with discrete neural changes with propofol and dexmedetomidine [3,15,16]. Hudson and colleagues first reported multiple metastable states during recovery from isoflurane anesthesia in rats [17]. Proekt and Hudson further characterized stochastic dynamics of neural states during anesthetic recovery [18]. In addition, abrupt or non-linear state transitions are well known during natural sleep [19-21] and in epilepsy [22,23]. These results suggest that abrupt state transitions are a fundamental manner of how the brain functions.

Although the neural dynamics change at return of consciousness following dexmedetomidine anesthesia was discrete and abrupt in our NHP model, the change induced by the α2-adrenergic antagonist was clearly more discontinuous and on-and-off [3]. The low-dimensional state space dynamics characterized this instantaneous brain transition and there was no intermediate dynamics state during recovery following the α2-adrenergic antagonist. The animals immediately resumed their top task performance, which was expected based on the immediate restoration of the brain dynamics. This is important because our translational NHP model evidenced that the primate brain is capable to switch dynamics in an on-off manner and the animal transitioned from the unconscious state to the full wakefulness, performing a task at the highest rate, in a matter of seconds. The finding opens up the possibility of future anesthetic reversal if we could establish appropriate antagonism for other general anesthetic agents.

How the anesthetic-induced unconscious state can be actively reversed has been investigated in humans and animals with a limited degree of recovery. Recently, d-amphetamine has shown to rapidly restore the righting reflex latency following dexmedetomidine administration in rats [24], suggesting that the stimulation through non-α2-adrenergic system can facilitate the arousal from dexmedetomidine. We must await further studies of the non-selective antagonism effect on cognitive behavioral functions since no correlation is shown between the recovery of the righting reflex in rodents and their cognitive recovery [25]. Moreover, behavioral specifications are largely limited to spatial or olfactory memory and non-specific locomotor activity in rodents. The rodent central nervous system is also genetically and evolutionally different from the primate one [26,27]. Especially, the neocortex is limited and the functional prefrontal cortex subdivisions, such as dorsolateral prefrontal cortex, do not exist in rodents [28,29]. Therefore, the neurophysiological mechanisms underlying the cognitive behavioral recovery require cautious interpretation in these rodent models.

Conclusion

Active awakening from general anesthesia using its antagonist can potentially contribute to facilitating post-anesthesia recovery in various patients and the α2-adrenergic antagonist is currently a promising candidate for this use. Researchers should be encouraged to continue exploration to discover appropriate antagonism for existing general anesthetics or to invent a new anesthetic drug with a matching specific antagonist. Whether active awakening can prevent the problems that may be associated with anesthetic emergence and recovery, such as delirium and perioperative neurocognitive disorders, by eliminating or shortening the immediate recovery phase using the antagonist will need future investigation in the translational animal models.

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