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"Optoanesthesia": The Application of Transcranial Photobiomodulation to General Anesthesia

Chung-Min Tsai

Social Alternative Service, Northern Region Senior Citizen's Home, Ministry of Health and Welfare, Taiwan
Email: d119102012@tmu.edu.tw

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Abstract

General anesthesia relies on pharmacological anesthetics. However, some side effects of anesthetics have been observed. Non-pharmacological transcranial photobiomodulation (tPBM) as an adjuvant treatment may reduce the dosage of pharmacological anesthetics while maintaining anesthetic depth. The inhibitory effects of tPBM in terms of central nervous system depression render it a potential approach for inducing general anesthesia. Alteration of quantum processes of neuronal microtubules, the mechanisms of general anesthesia on consciousness, may occur in response to tPBM treatments. Further, tPBM as an adjuvant treatment may facilitate the distribution of the pharmacological anesthetics in the brain. The analgesic effects of photobiomodulation (PBM) are acknowledged, and PBM has been used for regional analgesia. However, whether tPBM can be used for general anesthesia is unknown. Here, I define "optoanesthesia" as "the use of tPBM for general anesthesia". I hypothesize that optoanesthesia can act as a means of general anesthesia. Supporting evidence in the form of unconsciousness, amnesia, and immobilization is provided in this paper. In addition, the tPBM-induced frequent yawning (a manifestation of transient arousal-shift during the continuing loss of consciousness during induction of general anesthesia) observed incidentally in my previous study of tPBM preconditioning for seizures also supports the hypothesis. I further discuss the issues with respect to the pharmacokinetics, parameters of optoanesthesia such as wavelength and targeted brain regions, and apparatus design, as well as the compatibility of the optoanesthesia and the Bispectral Index Monitoring System during surgery. Future research is needed to prove this hypothesis.

Keywords

Optoanesthesia, Transcranial Photobiomodulation, General Anesthesia

1. Introduction

General anesthesia is currently induced mainly using pharmacological anesthetics administered via inhalation and intravenously. However, these agents have some drawbacks. Specifically, inhalational anesthetics have side effects such as sevoflurane-induced hypotension and sevoflurane-induced delirium and agitation [1], desflurane-and-sevoflurane-induced respiratory complications [2], while intravenous agents have side effects such as propofol-induced apnea [3] and hypotension [4], and etomidate-induced myoclonus [5]. Nonpharmacological approaches to be used as adjuvant treatments combined with current pharmacological anesthetics are thus needed, to facilitate reducing the dosage of pharmacological anesthetics while maintaining anesthetic depth.

Photobiomodulation (PBM), previously termed "low-level laser/light therapy" [6], refers to the use of red to near-infrared (NIR) light to induce biological alterations in organisms that result from the interactions of photons with molecules in cells or tissues [7]. It is generally accepted that mitochondrial cytochrome *c* oxidase (CcO) is the primary photoreceptor of PBM [8] [9]. Transcranial PBM (tPBM) is the application of PBM transcranially. Photons of laser light or from a light-emitting diode (LED) in the red to NIR wavelength administered during tPBM treatments penetrate the scalp, skull, and dura, and reach the brain. The wavelength 808 (or 810) nm exhibits the best light penetration in human brain tissue when compared with the wavelengths 660 nm, 940 nm, and 980 nm [10] [11]. This technique has been applied in several neurological diseases [12], such as stroke [13], traumatic brain injury [14], Alzheimer's disease/dementia [15], Parkinson's disease (PD) [16], epilepsy [17]-[22], and depression [23]. It is a safe and noninvasive approach and has no known side effects, apart from one report of a mild increase in diastolic blood pressure [24].

The tPBM technique produced inhibitory effects in the cortex and hippocampus of normal healthy rats [25], while tPBM monotherapy attenuated seizures in peripubertal (808 nm wavelength) [17] [19] and adult rats (750 nm) [21]. In addition, tPBM (808 nm) add-on therapy combined with valproic acid attenuated pentylenetetrazole (PTZ)-induced seizures [18]. Further, Tsai [20] proposed the use of tPBM as an add-on therapy to be used with general anesthetics to treat pediatric refractory status epilepticus and super refractory status epilepticus. These tPBM add-on strategies may reduce the demand for/dose of general anesthetics, thereby reducing the side effects of anesthesia. Although not all anesthetics are anticonvulsant, some are proconvulsant, and virtually every anesthetic has both proconvulsant and anticonvulsant properties [26], tPBM has anticonvulsant effects in that it inhibits abnormal electric discharge, thus partially meeting the requirements for anesthetics—central nervous system depression [27].

With respect to mechanisms through which tPBM induces general anesthesia, I proposed that tPBM has the potential to alter consciousness reversibly as well and that tPBM may alter the quantum processes in microtubules that underly

consciousness [28]. General anesthesia alters consciousness reversibly [29]. Hameroff and Penrose [28] proposed in the mid-1990s that "*consciousness depends on biologically 'orchestrated' coherent quantum processes in collections of microtubules within brain neurons*" [28]. With respect to the role of microtubules in anesthesia, it was suggested more than 50 years ago that microtubular proteins are susceptible to reversible depolymerisation caused by anesthetics [30]. Recent studies have confirmed that general anesthetics bind to and affect microtubules [31] [32] [33]. Craddock *et al.* [34] suggested that anesthetics act on quantum channels in the microtubules of brain neurons. Recently, Staelens *et al.* [35] demonstrated that PBM (810 nm) modulates the microtubules in living cells. In response to tPBM treatments, alteration of quantum processes may occur in the microtubules within the neurons of the brain regions that are related to general anesthesia.

Further, tPBM as an adjuvant treatment may facilitate the distribution of pharmacological anesthetics in the brain. Moro *et al.* [36] speculated that PBM has an arousal-dependent effect. When PBM is applied during wakefulness, it stimulates neuronal function; boosts mitochondrial activity and gene expression; influences α, β, and γ, waves; improves neuronal survival; and enhances neuroprotection against distress and neurodegenerative diseases. When it is applied during sleep, PBM may be more effective for the clearance of cerebral spinal fluid (CSF). They further suggested that PBM may increase the permeability of aquaporin-4 in astrocytes, thereby increasing the flow of CSF. Based on this proposal that PBM has arousal-dependent effects of PBM, in the induction and maintenance phases induced using current intravenous and inhaled anesthetics, the patients' arousal condition is closer to sleep than to wakefulness, so the administration of tPBM may enhance the distribution of the pharmacological anesthetics by increasing the flow of CSF. Therefore, tPBM may have a synergistic effect on general anesthetics when it is administered during the induction and maintenance phases.

With respect to regional analgesia, the local analgesic effects of PBM have been used in dental surgery to reduce injection pain [37] [38], and a positive analgesic outcome was noted [39]. Local anesthetic effects of PBM during pediatric dental procedures have also been confirmed [40]. Further, PBM administered in the form of laser acupuncture with a wavelength of 808 nm induced analgesic effects in an animal model of postsurgical pain [41]. In humans, PBM administered as laser acupuncture with a wavelength of 810 nm relieved postoperative pain in patients with traumatic rib fractures and this was confirmed in a randomized-controlled trial (RCT) [42]. In the setting of general anesthesia, tPBM (810 nm) had been reported to ameliorate mice with a perioperative neurocognitive disorder caused by isoflurane inhalation anesthesia [43]. Tsai [44] speculated in 2021 that "*tPBM might possess general anesthetic effects on the brain*". However, the use of tPBM as a form of nonpharmacological general anesthesia has not yet been explored.

Here, I define "optoanesthesia" as "the use of tPBM for general anesthesia". This nonpharmacological method of general anesthesia may be useful as an adjuvant treatment to be combined with current anesthetics in general anesthesia.

2. Hypothesis

I hypothesize that optoanesthesia can act as a means of inducing general anesthesia. This hypothesis can be divided into three secondary hypotheses:

1) Optoanesthesia is effective;

2) Optoanesthesia can be used as an adjuvant treatment to induce general anesthesia; and

3) Optoanesthesia can be used as the sole treatment to induce general anesthesia.

3. Supporting Evidence

The characteristics of general anesthesia are amnesia, unconsciousness (hypnosis), analgesia, and immobilization [45] [46]. The analgesic effects of tPBM are discussed above. With respect to unconsciousness, cortical and subcortical effects are involved in the mechanisms of anesthetics-induced unconsciousness [46]. Among the pharmaceuticals that exhibit cortical effects, propofol, pentobarbital, ketamine, isoflurane, enflurane, and halothane inhibit spontaneous action potentials in the cortical neurons [46]. Similarly, tPBM induces a transitory reduction in the excitability of the designated cortex (primary motor cortex, or M1 [47]). In subcortical areas such as the thalamic reticular nucleus (TRN), cortical activity was suppressed during isoflurane anesthesia under TRN stimulation [46] [48], and sensitivity to propofol via GABA type B ($GABA_B$) receptors is increased under TRN stimulation [49] [50]. Correspondingly, Radwan *et al.* [51] speculated that tPBM mimics benzodiazepine and barbiturates in its blocking effect on $GABA_B$ receptors (*i.e.* tPBM acts as a positive modulator of $GABA_B$ receptors [18]).

Amnesia elicited by etomidate is caused by the modulation of GABA type A ($GABA_A$) receptors in the hippocampus [52] [53] [54]. The study by Tsai *et al.* [18] study indicated that tPBM can also modulate $GABA_A$ receptors by attenuating the noncompetitive antagonism of PTZ toward the $GABA_A$ receptor complex in postsynaptic principal cells.

Immobilization can be induced by the action of $GABA_A$ agonist in the mesopontine tegmental anesthesia area (MPTA) [55] [56]. Coincidentally, Tsai *et al.* [18] speculated that tPBM could act as a positive modulator of $GABA_A$ receptors, and this is equivalent to considering tPBM as a $GABA_A$ agonist. Therefore, one of the more important brain regions targeted in optoanesthesia is the MPTA.

Tsai [44] observed incidentally that during 60-minute tPBM preconditioning behavioral observations, frequent yawning was observed in rats subjects to tPBM treatment (808 nm) 60 minutes prior to a PTZ injection. Up to 11 times of

yawning per rat were observed in rats received tPBM preconditioning, and it was more frequently compared to yawning frequency observed in rats subjected to a sham treatment 60 minutes prior to the PTZ injection (up to 6 times per rat, unpublished data). Further, rats in the tPBM treatment group tended to be sleepier than those in the sham treatments group, although some rats in the latter group did also sleep during the 60-minute observation period (unpublished data). Yawning during the intravenous induction of general anesthesia with thiopental or propofol indicates a transient arousal-shift during the continuing loss of consciousness [57]. Such yawning responses may occur one minute after the injection of thiopental or propofol, with an occurrence rate of approximately 50% [58]. Upper-airway collapse during the induction of anesthesia coincides with increased yawning, while upper-airway muscle dilation and decreased yawning caused either by either teeth clenching or opioids administrations coincides with obstructive sleep apnea-like symptoms [59]. Yawning after tPBM administration mimics the yawning that is elicited by thiopental or propofol administration during induction of general anesthesia.

4. Discussion

With respect to pharmacokinetics of optoanesthesia, since the tPBM photons do not "dissolve" in the blood flow and are not absorbed by the alveolar, its pharmacokinetics are presumably different from those of current pharmacological anesthetics. I now discuss the physiological basis of the pharmacokinetics of tPBM. The tPBM photons are absorbed by the CcO in brain cells (such as neurons, astrocytes, and microglia). Although there is no direct distribution of the photons around the rest of the body, the distribution of adenosine triphosphate (ATP), red blood cells (RBC) carrying oxygenated hemoglobin, and neurotrophic factors (as a result of direct mediation by the tPBM photons) within the blood flow would distribute. It has been reported that tPBM increases regional blood flow [60] [61]. In particular, the regional blood flow in brain regions such as the reticular formation may increase in response to tPBM treatments. Since tPBM increases ATP production, the quantity of non-synaptic and non-vesicular ATP released into the bloodstream [62] would increase. Further, tPBM also increases changes in the concentration of oxygenated hemoglobin Δ[HbO] and neurotrophic factors. Accordingly, the quantity of ATP, Δ[HbO], and neurotrophic factors may increase in the brain regions related to general anesthesia. In addition, GABA release (which mimics the action of propofol in the induction phase [63]) in the pontine reticular formation may increase following tPBM treatment. This conjecture is based on the study by Tsai *et al.* [17] that tPBM (808 nm) preserved GABAergic interneurons (parvalbumin-positive interneurons, PV-INs) in the hippocampus from status epilepticus-induced or PTZ-induced apoptosis and preserves the neurites of the PV-INs surrounding pyramidal cells. Considering that the tPBM photons are absorbed by mitochondrial CcO, and probably by other proposed photoreceptors as well, there may be no accumula-

tion of photons in the brain or the rest of the body. Notably, Moro *et al.* speculated that biophotons may be involved in the mechanisms of tPBM [36]. If so, then there would be the issue of biophotons accumulation to be addressed. With respect to the clearance of wastes products caused by pharmacological anesthetics and excess neurotrophic factors, tPBM promotes the glymphatic system during treatments [64]. It also increases the permeability of the blood-brain barrier under healthy conditions.

Different ranges of wavelengths in tPBM treatments in combination with different targeted brain regions might have different or even opposite effects in the human brains. The wavelength-brain region combinations in tPBM treatment that 780 nm [21], 808 nm [17] [19], 830 nm [25] [51], 850 nm, 905 nm [47] and 980 nm [65], targeting the precentral gyrus and anterior paracentral lobule (M1), temporal cortex, hippocampus, limbic system, TRN, reticular formation, and brain stem may have suppressive effects toward brain state arousal. In contrast, tPBM with wavelengths longer than 1000 nm, such as 1064 nm, targeting the prefrontal cortex boosts brain state arousal, with effects that manifest as cognitive enhancement [66]. Former wavelength-brain region combinations may be more suitable for optoanesthesia.

The tPBM apparatus available varies in appearance and purpose, in terms of the targeted brain regions. McGee *et al.* [67] designed a tPBM apparatus they called the "PDNeuro Helmet" for patients with PD, with 20 points of light sources including the 2nd cervical vertebrae (C2) points in the sub-occipital region corresponding to the brain stem. The locations of the points closely match those of the corresponding pontine reticular formation. Zomorrodi *et al.* demonstrated that tPBM with "Vielight Neuro Gamma" (known as Neuro Gamma) modulates gamma oscillations [68], and the brain regions targeted by the Neuro Gamma and the Neuro Gamma 3 (Brain) [69] include the temporal lobe. The design of a tPBM apparatus for optoanesthesia targeting the brain stem (especially the MPTA) and the temporal lobe could refer to the design of the PDNeuro, the Neuro Gamma, and the Neuro Gamma 3 (Brain) [69]. Notably, the forehead (corresponds to the prefrontal cortex) should be avoided when designing the tPBM apparatus for optoanesthesia.

The administration of optoanesthesia does not conflict or interfere with the use of the Bispectral Index Monitoring System (BIS) [70] during surgery. The first and second patches of the BIS are applied on the forehead, at points corresponding to the prefrontal cortex. However, the third patch is located in the temporal region. I, therefore, recommend that the patch or probe of the tPBM device placed contralaterally to the site of the third BIS patch. Using this arrangement, the tPBM patch or probe would correspond to the hippocampus (which is contralateral to the side on which the temporal BIS patch is placed), thalamus, limbic system, and the posterior neck around 1st cervical vertebrae-C2, corresponding to the pontine reticular formation and the brain stem. Considering the neuroanatomical distance between the BIS and tPBM patches or probes, there should

be no conflict or interference between them.

In vitro, *in vivo*, and human studies, as well as clinical trials including RCTs, are thus needed to test the hypothesis I have proposed here.

5. Conclusion

I have proposed a hypothesis that "optoanesthesia can act as a means of inducing general anesthesia". Supporting evidence includes the fact that tPBM can induce a transitory reduction in cortical excitability, which resembles the effects of pharmacological anesthetics in suppressing spontaneous action potentials in cortical neurons. The fact that tPBM elicits yawning resembles the effects of intravenous anesthetics. Further studies are needed to prove this hypothesis.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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