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Short communication

Electrical stimulation of the parabrachial nucleus induces reanimation from isoflurane general anesthesia

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HIGHLIGHTS

- We tested the hypothesis that electrical activation of the glutamatergic parabrachial nucleus (PBN) in the brainstem is sufficient to induce reanimation (active emergence) during continuous isoflurane general anesthesia.
- Emergence from isoflurane anesthesia caused a selective increase in the number of active neurons in the lateral PBN.
- The electrical stimulation of the PBN induced behavioral arousal and restoration of the righting reflex.

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ABSTRACT

Clinically, emergence from general anesthesia is viewed as a passive process where anesthetics are discontinued at the end of surgery and anesthesiologists wait for the drugs to wear off. The mechanisms involved in emergence are not well understood and there are currently no drugs that can actively reverse the state of general anesthesia. An emerging hypothesis states that brain regions that control arousal become active during emergence and are a key part of the return to wakefulness. In this study, we tested the hypothesis that electrical activation of the glutamatergic parabrachial nucleus (PBN) in the brainstem is sufficient to induce reanimation (active emergence) during continuous isoflurane general anesthesia. Using c-Fos immunohistochemistry as a marker of neural activity, we first show a selective increase in active neurons in the PBN during passive emergence from isoflurane anesthesia. We then electrically stimulated the PBN to assess whether it is sufficient to induce reanimation from isoflurane general anesthesia. Stimulation induced behavioral arousal and restoration of the righting reflex during continuous isoflurane general anesthesia. In contrast, stimulation of the nearby central inferior colliculus (CIC) did not restore the righting reflex. Spectral analysis of the electroencephalogram (EEG) revealed that stimulation produced a significant decrease in EEG delta power during PBN stimulation. The results are consistent with the hypothesis that the PBN provides critical arousal input during emergence from isoflurane anesthesia.

Emergence from general anesthesia is viewed as a passive process whereby anesthetics are discontinued at the end of surgery. Currently, there are no drugs available to actively reverse general anesthesia. Numerous sites in the brain have been shown to promote arousal. These include acetylcholine neurons in the pedunculopontine and laterodorsal tegmental areas, orexin/hyprocretin neurons in the lateral hypothalamus, dopamine neurons in the ventral tegmental area, histamine neurons in the tuberomammillary nucleus, norepinephrine neurons in the locus

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ceruleus, and others [1]. The pharmacological activation of cholinergic [2], histaminergic [3], noradrenergic [4], and dopaminergic arousal pathways [5–8], and the orexin/hypocretin neurons in the lateral hypothalamus have been reported to produce varying arousal responses during general anesthesia [9]. However, only cholinergic and dopaminergic areas have been shown to induce reanimation (active emergence) from continuous general anesthesia.

The available data suggest that it is possible to induce active emergence from general anesthesia. However, our understanding of the involvement of the brain's arousal centers in emergence is incomplete. Recent evidence has implicated the parabrachial nucleus (PBN) in promoting arousal [10,11]. The majority of neurons in the PBN are glutamatergic [12] and project to numerous areas in the brain, including the basal forebrain, hypothalamus, thalamus, amygdala, and the cortex [13,14]. Altogether, the PBN is well

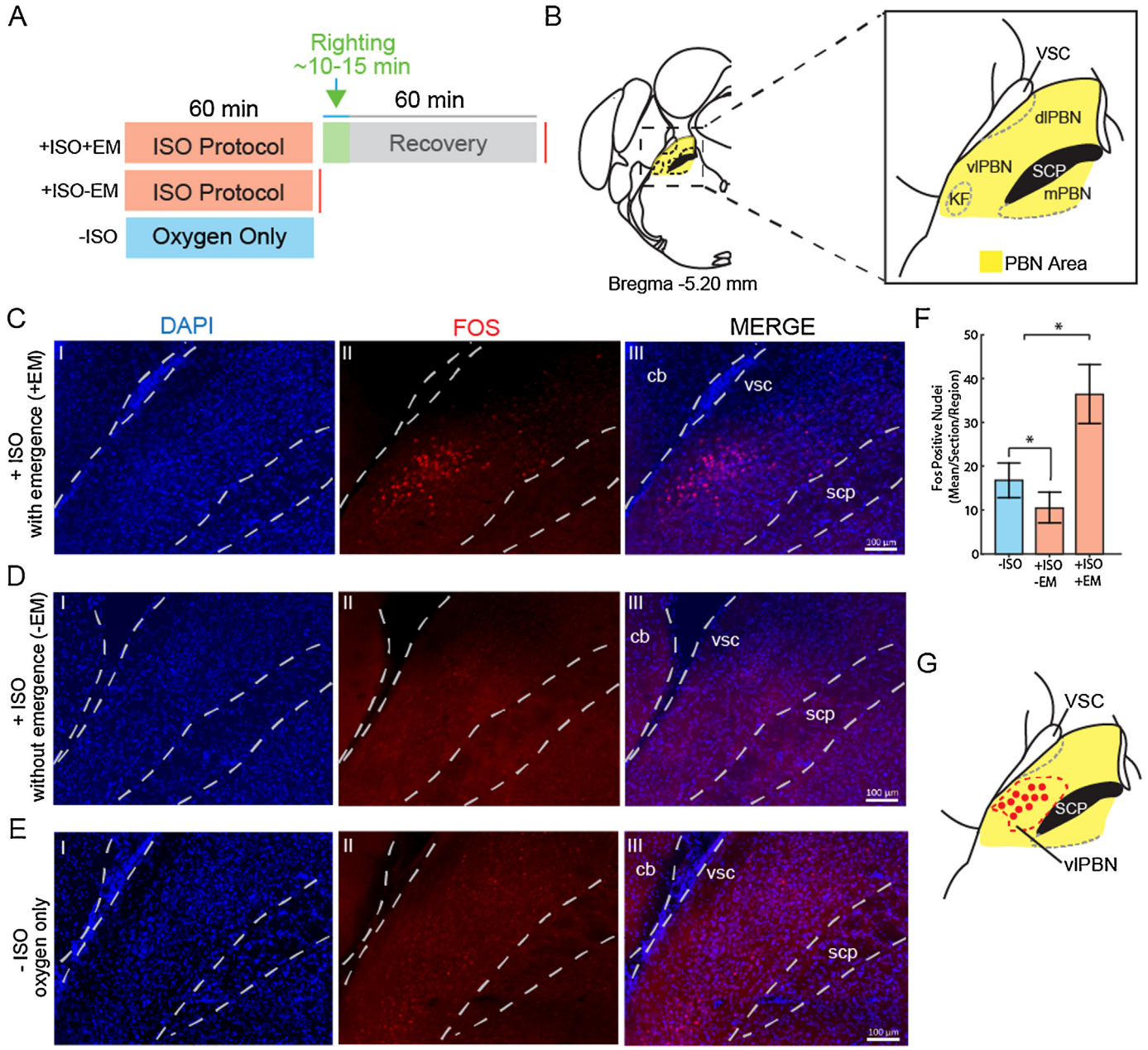

Fig. 1. c-Fos expression in the PBN after exposure to isoflurane with or without emergence. (A) Experimental protocol for quantifying the number of c-Fos positive nuclei in three groups of mice. The first group (+ISO + EM) underwent passive emergence from the isoflurane anesthesia protocol shown in A, and had return of righting before being sacrificed. The second group (+ISO – EM) underwent the same isoflurane anesthesia protocol and was sacrificed before emergence. The last group (-ISO) received only oxygen. (B) A coronal section representation showing the PBN area and local structures in mouse. (C) DAPI stained, c-Fos stained, and merged images from +ISO + EM mice. The c-Fos image shows a visible cluster of c-Fos positive nuclei in the lateral PBN. (D) DAPI stained, c-Fos stained, and merged images from +ISO-EM mice. c-Fos staining shows a comparative lack of positive nuclei. (E) DAPI stained, c-Fos stained, and merged images from awake mice that were only exposed to oxygen. (F) A coronal section schematic showing the PBN area as well as the superior cerebellar peduncle (SCP), the lateral PBN and accompanying c-Fos positive nuclei are shown as red circles. (G) Mean number of c-Fos positive nuclei for each section and region across the three groups of animals. The c-Fos positive nuclei count for the +ISO + EM group was significantly higher (*) than the +ISO-EM and –ISO groups. The c-Fos positive nuclei count for the –ISO group was also significatly higher than the +ISO-EM group. Error bars indicate 95% confidence intervals around the mean. *Abbreviations*: dorsolateral Parabrachial Nucleus, dlPBN; ventrolateral Parabrachial Nucleus, vlPBN; medial Parabrachial Nucleus, mPBN; Kolliker-Fuse Nucleus, KF; Ventral Spinocerebellar Tract, VSC. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)