MICROGLIA

Uncovering the role of microglia in anesthesia

Cao, K., Qiu, L. et al. *Curr. Biol.* **33**, 2187–2200.e6 (2023)

To date, most studies have focused on the contribution of neurons in anesthesia. A new study in *Current Biology* presents the first evidence that microglia ± the brain-resident immune cells ± also contribute to anesthesia.

Anesthesia is a prerequisite for most surgical procedures in both animals and humans. General anesthetics induce loss of consciousness by suppressing neuronal activity, but the precise mechanisms are unclear. Here, Cao, Qiu and colleagues used different mouse models, pharmacological and chemogenetic approaches to demonstrate the role of microglia in anesthesia.

The investigators initiated this study after noticing that mice treated with PLX5622, a microglia-depleting reagent, recovered faster from anesthesia than controls. The team further showed that PLX5622-treated mice showed a reduction in the time taken to recover the righting reflex after injection of various anesthetic agents (such as pentobarbital and ketamine) compared with control mice. Analysis of a genetically modified mouse line in which microglia were selectively ablated confirmed that microglial depletion accelerated the recovery of consciousness from anesthesia. By contrast, chemogenetic activation of microglia delayed recovery from anesthesia. Further analysis of microglia-depleted mice showed that analgesia and hypothermia ± two reactions associated with anesthesia ± were also impaired in the absence of microglia.

To understand how anesthesia affected microglia, the investigators performed single-cell RNA sequencing of microglia isolated from non-anesthetized and anesthetized mice. The analysis revealed that anesthesia primarily upregulated chemotaxis and migration, two important microglial pathways which could be involved in the modulation of anesthesia. Pharmacological or genetic inhibition of the $P2Y_{12}$ receptor ($P2Y_{12}R$) ± a purinoceptor selectively expressed in microglia and involved in microglial motility and migration ± decreased the time to recover the righting reflex and attenuated hypothermia in pentobarbital-injected mice compared with control mice, recapitulating the effects observed in microglia-depleted mice.

Altogether, these findings demonstrate that microglia actively participate in multiple processes of anesthesia. In their report, the investigators explain that $P2Y_{12}R$-might be important for microglia± neuron interactions and to reduce the activity of arousal-promoting neurons during anesthesia. ãTargeting microglia and $P2Y_{12}R$ may serve as a potential strategy to fine-tune the depth and duration of anesthesia in clinical practice and facilitate anesthetic monitoring in modern medicineë they conclude.

Alexandra Le Bras

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