Blood-brain barrier governs ant behavior by altering hormone levels, study shows

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Major (larger) workers which typically do not forage, and Minor (smaller) workers which do most of the foraging for the colony. Credit: Karl Glastad

In many animals, including ants, the blood-brain barrier (BBB) ensures normal brain function by controlling the movement of various substances

in and out of the brain. Researchers reporting in the journal *Cell* on September 7 have made the unexpected discovery that the BBB in carpenter ants plays an active role in controlling behavior that's essential to the function of entire ant colonies. The key is production in the BBB of a particular hormone-degrading enzyme.

"In these ants, the BBB produces a special version of the enzyme Juvenile hormone esterase (Jhe), which degrades Juvenile Hormone (JH3)," says Karl Glastad, the co-lead author along with Linyang Ju, both in the lab of senior author Shelley Berger in the Perelman School of Medicine at the University of Pennsylvania in Philadelphia.

"Typically, Jhe enzymes are secreted into the hemolymph (insect blood); however the copy produced by the ant BBB is retained in the cells of the BBB where it controls the amount of JH3 hormone entering the brain of the worker ant," Ju says.

JH3 hormone is known to promote foraging among social insect workers. Different types of worker ants within the same colony do very different "jobs." The new findings show that this results, in part, from different levels of the JH3-degrading enzyme in their BBB, leading to different levels of the hormone JH3 in the brain.

The finding underscores how a single protein expressed in the right place at the right time can have major effects on individual behaviors underlying complex societies, the researchers say. And it isn't just ants; the researchers already have evidence that similar mechanisms may play a role in mouse behavior, too.

The researchers made the discovery after applying single-cell RNA sequencing to understand differences in gene activity across cells in the brain in two ant behavioral castes: foragers and soldiers. Their analysis revealed that the gene encoding Jhe, the degrading enzyme for the

hormone JH3, was found only in BBB cells. It also showed striking differences between the BBB cells of foragers and soldiers. They wanted to know more about what it meant for ant behavior.

Their studies show that intentional manipulation of the level of the Jhe degrading enzyme reprograms the brain and complex behaviors that differ between ant castes, switching the soldier caste to foraging behavior. They went on to show in Drosophila fruit flies that Jhe enzyme is naturally outside of cells. When they made the fly BBB express the ant version of the Jhe enzyme, they saw behavioral changes similar to those observed in the ants.

"Differences in expression of this single enzyme [Jhe] between the BBB of different castes control the hugely important decision to forage or to stay inside the nest for defense as soldiers and can even reprogram flies to change food-seeking behavior," Glastad said.

To see if similar mechanisms apply in other animals, the researchers also analyzed published data from a panel of mouse endothelial cells, including those from the mouse BBB. They found that mouse BBB cells also expressed several hormone-degrading enzymes at higher levels than any other endothelial cell type. Most notably, these include enzymes that degrade the hormone testosterone.

"This suggests that gating hormone entry into the brain by the BBB is a function extending well beyond ants and that gating a hormone differentially between behavioral conditions as seen in ants may exist in other organisms, including mammals," Berger says.

In future studies, the researchers say they want to learn more about the origin and prevalence of this mechanism and whether it is a convergent strategy to control behavior outside of ants.

More information: Shelley L. Berger et al, Hormonal gatekeeping via the blood brain barrier governs caste specific behavior in ants, *Cell* (2023). DOI: 10.1016/j.cell.2023.08.002. www.cell.com/cell/fulltext/S0092-8674(23)00856-5

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