Social behavior

Rats sense their human handler's fear

Learning about potential threats is critical for survival. Fear learning can happen through direct experience or through others. Like most animals, rats can acquire fear through social transmission by sensing cues from conspecifics that experience fear. According to a new study, laboratory rats can also detect human fear.

To assess whether rats have the ability to detect negative emotional states in humans, the researchers analyzed the behavior of male Wistar rats during their interaction with male caregivers who had been subjected to a fear conditioning procedure a few minutes before. The fear conditioning task experienced by the caregivers involved the presentation of colored symbols and the administration of unpleasant electrical stimulation. Previous studies employing this fear conditioning procedure have shown that it induces robust responses to the unconditioned stimulus, indicating fear acquisition.

Analysis of human–rat interactions revealed that rats responded differently to human caregivers who underwent fear conditioning and to caregivers who were subjected to the sham procedure. Notably, rats tested with the caregivers who underwent fear conditioning explored the human's hands less, spent more time exploring the cage and showed a decrease in ultrasonic communication, indicating increased anxiety.

Next, the researchers investigated the neural circuits responsible for the ability of rats to detect emotional states of humans. c-Fos immunochemistry conducted on brain sections confirmed that the centromedial and basolateral nuclei – two major parts of the amygdala, a structure critical for detecting threats and sensing conspecifics' fear – were more active in rats interacting with the caregiver who underwent fear conditioning than in rats interacting with the caregiver subjected to the sham procedure.

In a final set of experiments, the investigators performed an observational fear learning procedure in humans, in which one participant in a pair was assigned the role of a demonstrator while another was given the role of an observer. Results of the experiments showed that the observers felt empathy towards their friends receiving an electric stimulation and fMRI analysis indicated that they responded with activation of the basolateral and centromedial amygdalar nuclei.

Altogether, these results suggest that cross-species and within-species social transmission of threat information involve activation of similar neural circuits in the amygdala, indicating an evolutionarily conserved brain system for processing fear.

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Original reference: Kaźmierowska, A.M. et al. *Proc. Natl. Acad. Sci. USA* **120**, e2302655120 (2023)

Reprogramming

Optimizing in vivo reprogramming in mice

To date, the benefits of in vivo reprogramming are limited by the occurrence of detrimental side effects. A new study in *Nature Aging* reports a safer method for in vivo reprogramming in mice.

Aging is a complex process characterized by the accumulation of molecular, cellular and organ damage, leading to loss of function and increased vulnerability to disease and death. Although aging has long been considered an inevitable process, several strategies are emerging to delay and potentially even reverse it. One of these potential approaches is the restoration of youthful characteristics, or rejuvenation. The forced expression of the four transcription factors Oct4, Sox2, Klf4 and c-Myc (OSKM) can induce dedifferentiation of somatic cells and ameliorate age-associated phenotypes in mice. However, continuous OSKM expression can also lead to cancer development, teratoma formation and early mortality.

To better understand the causes of the above adverse effects, the team of researchers at the University of Lausanne characterized the phenotype of two well-studied reprogrammable mouse lines. The researchers induced OSKM expression in the 2-month-old 4Fj and 4Fs-B mice by continuously treating them with doxycycline in drinking water. After a few days, the mice displayed signs of hepatic and intestinal dysfunction, associated with decreased activity, body weight loss and premature death (median survival of 5 days and 10 days for 4Fj and 4Fs-B mice, respectively). However, the mice showed neither tumor nor teratoma formation, which suggests that hepatic and intestinal dysfunctions, not tumor or teratoma formation, are the major causes of early mortality in the reprogrammed mice.

To confirm these findings, the researchers generated a new transgenic mouse strain that expresses OSKM in the whole body, with the exception of the liver and the intestine. The mice showed none of the adverse effects associated with in vivo reprogramming, including body weight loss or abnormal activity, and could sustain longer continuous induction of in vivo reprogramming (median survival of 30 days) than 4Fj and 4Fs-B mice.

This new 4F Non-Liver/Intestine mouse model opens new avenues for safer and longer-term induction of in vivo reprogramming and for the study of organismal regeneration and rejuvenation as a strategy to improve human health and lifespan.

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Original reference: Parras, A., Vílchez-Acosta, A., Desdín-Micó, G. et al. *Nat. Aging* https://doi.org/10.1038/s43587-023-00528-5 (2023)