# Two neurotransmitters are linked to unusually aggressive behaviour in male mice

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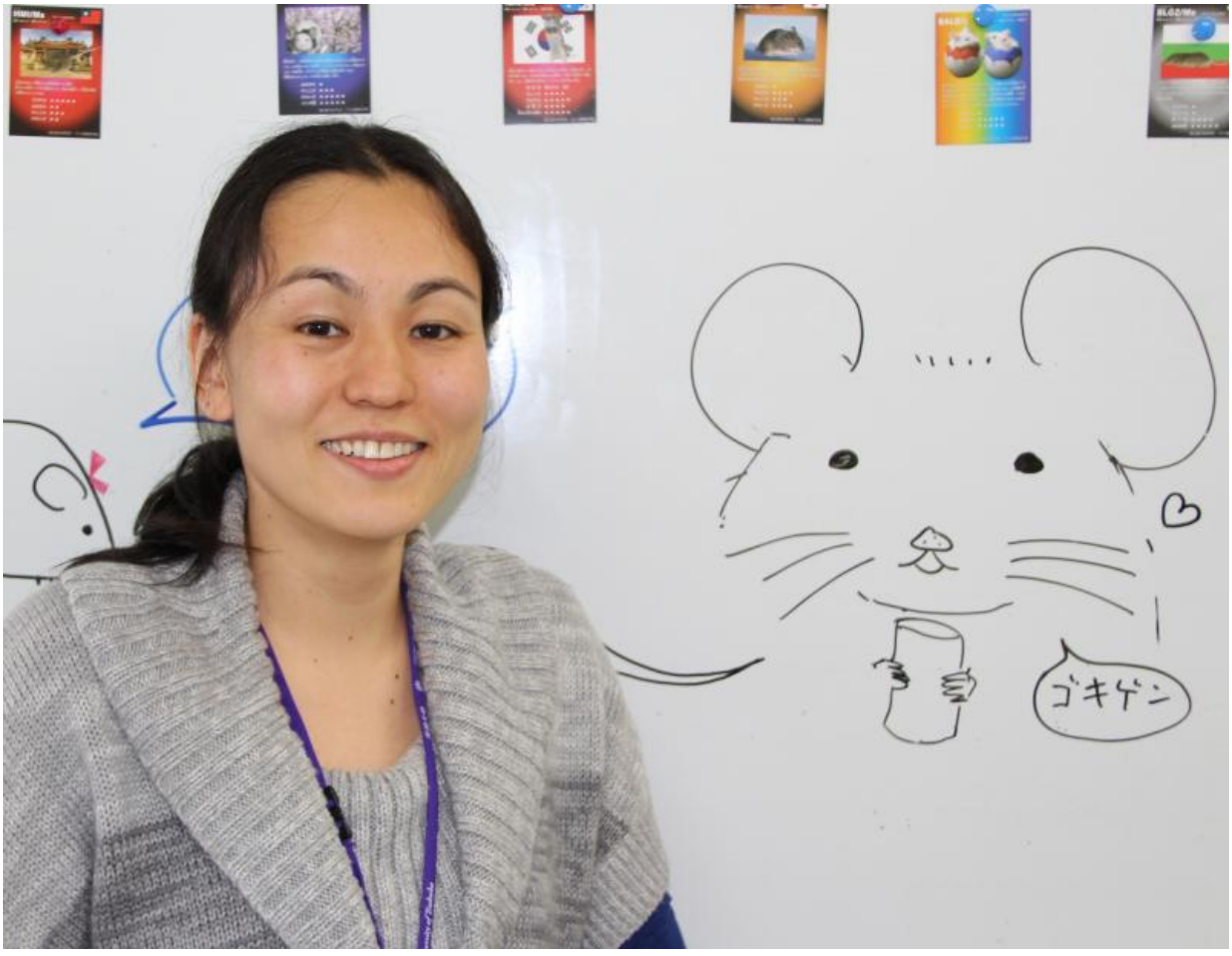


Aki Takahashi

How do some of us manage to control our violent tendencies while

others cannot? Research led by University of Tsukuba behavioural neuroscientist Dr Aki Takahashi and Dr. Tsuyoshi Koide from the Mouse Genomics Resource Laboratory in the National Institute of Genetics may help to address this question. She and her team of international collaborators found that an increase in the levels of two neurotransmitters, glutamate and serotonin, in key parts of the brain is linked to intense aggression in male mice.

In mice, especially in males, as in many other animal species, aggressive behaviors have evolved as adaptations to deal with danger and with competition for resources such as mates, food and shelter. When this adaptive species-typical aggression escalates to intense aggression, it becomes destructive or maladaptive. Due to similarities in the neurobiology of aggression between rodents and humans, studies in mice may eventually help us to understand and even treat antisocial, violent and psychopathic behavior in humans.

Dr Takahashi's research, recently published in the *Journal of Neuroscience*, focused on a part of the brain called the dorsal raphe nucleus (DRN). The DRN is located in the lower, most primitive part of the brain and contains the largest collection of serotonin-producing neurons in the brain. Serotonin, sometimes known as the 'happiness hormone', has been implicated in the control of aggression more than any other molecule in the brain, in several species ranging from invertebrates to humans. The activity of the serotonin-producing neurons in the DRN is controlled by serotonin itself, as well as by other neurotransmitters such as glutamate and γ-aminobutyric acid (GABA). The DRN receives glutamate from many brain areas, including the medial pre-frontal cortex, a part of the brain targeted in the procedure known as frontal lobotomy. Several types of psychiatric illnesses such as anxiety disorders and depression, as well as aggression, are linked to an imbalance between the levels of glutamate and GABA.

Measuring aggression in mice involves introducing an intruder mouse into a resident mouse's homecage and observing the type and levels of aggression that ensue. For example, normal aggressive behavior includes threatening postures and acts while escalated aggression results in an increased frequency and intensity of biting. For the first time, an in vivo microdialysis study, in which the DRN areas of the brains of living mice were implanted with a probe that can both microinject drugs and collect samples of brain fluid, showed changes in glutamate input in the DRN during aggressive behavior in male mice. Using a clever combination of genetically-engineered mice and in vivo microdialysis, the researchers

showed that glutamate release increased in the DRN during an aggressive encounter.

Serotonin release was also increased within the DRN, as well as in the medial pre-frontal cortex during escalated aggression, but this increase in serotonin release was not observed when animals were engaged in normal adaptive aggression. Glutamate input to the DRN is thus critical for an escalation in aggressive behavior, and causes a surge in serotonin

released from the DRN. The precise role of this glutamate input, as well as its origin, remains to be clarified.

Studies such as this may provide in future the targets needed to develop therapeutic interventions for those of us with extreme antisocial behaviors and psychiatric illnesses.

Dr. Takahashi, Assistant Professor in the Laboratory of Behavioral Neuroendocrinology, fell in love with the Japanese Fancy Mouse, a mouse strain used in this type of research, when she was a graduate student in the University of Tsukuba and visited Dr. Koide at his laboratory. This mouse was domesticated as a pet in Japan a few hundred years ago. She then decided to change her major from psychology to behavioral genetics. She said "I'm interested in the mechanism of escalating an adaptive species-typical aggressive behavior. From this research we plan to examine which activation pattern or inhibition of the serotonin system can affect which type of aggression."

**More information:** "Glutamate Input in the Dorsal Raphe Nucleus As a Determinant of Escalated Aggression in Male Mice," *Journal of Neuroscience*, 22 April 2015, 35(16): 6452-6463; DOI: 10.1523/JNEUROSCI.2450-14.2015