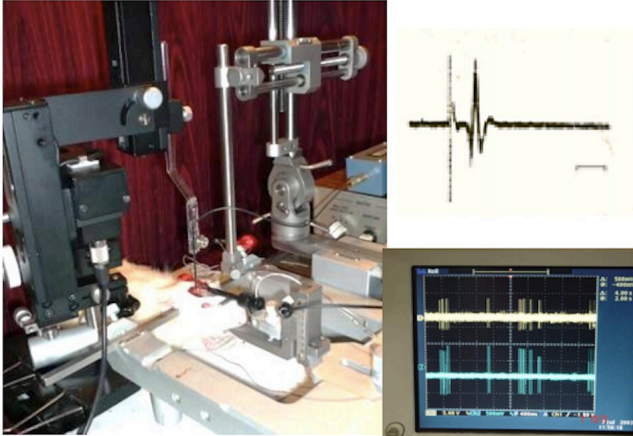


Ketone 2-heptanone reduces inhibitory control of the amygdala in the mouse brain

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Single-unit extracellular recording. When the amygdala is electrically stimulated, neurons in the mPFC exhibit a brief period of activation, followed by a silent period and then an afterdischarge. Credit: Contreras & Gutiérrez-García.

Alarm pheromones are substances that send danger signals to different parts of the brain. When these signals are perceived by other pheromones of the same class, they can act as cues that alert humans or animals about a potential danger.

In the brains of humans and other animals, fear is known to be regulated by several areas and networks, including [basolateral amygdala](#) (BLA) nuclei and their connections with prelimbic (PL) and infralimbic (IL) regions of the medial prefrontal cortex (mPFC). Past studies have found that when rats are stressed and confronting potentially dangerous situations, the concentration of a ketone called 2-heptanone in their urine is high.

Moreover, when rats in a non-stressed state detect the odor produced by 2-heptanone, they immediately react, become alarmed and/or try to avoid specific stimuli. The ketone also appears to modify [neuronal activity](#) in the rat brain's limbic

connections.

Researchers at Universidad Nacional Autónoma de México and Universidad Veracruzana have recently carried out a study on rats aimed at better understanding the role of 2-heptanone in fear regulation. Their findings, published in Elsevier's *Neuroscience Letters*, could ultimately improve the current understanding of anxiety disorders and potentially pave the way toward the development of more effective treatments for these disorders.

"Studies of cerebral actions of pheromones allow a better understanding of the neurobiological basis of the behavioral response when confronting this chemical cue. 2-heptanone was initially described in insects," Carlos M. Contreras and Ana G. Gutiérrez-García, the two researchers who carried out the study, told *Medical Xpress* via email. "For a long time, however, its presence in mammals was ignored. We and other research groups detected it in mammals' urine, including rodents and humans."

Alarm pheromones are vital to the survival of species and are generally picked up in the form of odors (i.e., by olfactory routes). Most vertebrates, animals that possess a backbone or spinal column, have two main olfaction-related sensory systems. Their primary olfactory system is based on sensory receptors that are located in the nasal epithelium, on the superior turbinate (structure inside the nasal cavity).

"These sensory receptors connect to the [olfactory bulb](#), and the olfactory bulb then connects to the pyriform cerebral cortex and temporal lobe of the amygdala," Contreras and Gutiérrez-García explained. "In the accessory olfactory system, sensory receptors are in the [vomeronasal organ](#), located in the nasal septum. The vomeronasal organ then projects to the dorsal portion of the olfactory bulb, and neuronal fibers connect to amygdala nuclei."

Information collected by both olfactory systems (i.e., the main and accessory systems) converge on nuclei of the amygdala, a region of the brain involved in the integration of emotions, motivations and emotional behaviors. The amygdala is known to play a crucial role in the control of fear and anxiety, and consequently also in anxiety disorders.

Past studies have identified two different roles of anxiety, a 'healthy' or adaptive role and a maladaptive one. In normal levels, anxiety can be seen as a helpful emotion that allows animals and humans to select useful strategies for surviving [dangerous situations](#). When baseline levels of anxiety become too high, however, it can become a maladaptive and highly disabling emotion.

"Our general working hypothesis was that a chemosignal that produces alertness toward a dangerous situation produces more efficient strategies to cope with danger," Contreras and Gutiérrez-García explained. "In other words, when a given substance produces the emotion of fear, then there must be a neurobiological process that allows selection of the most efficient behavioral response for survival."

When examining the effects of a given behavioral situation or stimulus on neuronal activity, most neurobiologists focus on a single cerebral region at a time. Recently, however, researchers have started to study the effects of behavioral situations, chemicals and pharmaceutical drugs on two or more cerebral nuclei simultaneously.

One of the techniques most used by neuroscientists is single-unit extracellular recording. As suggested by its name, this technique allows researchers to record the electrical activity of individual neurons under different conditions or in different situations.

"As an extension of this procedure, neurons from one nucleus are stimulated electrically, chemically, or pharmacologically, and the neuronal response of another nucleus that is anatomically or functionally linked to the first nucleus is recorded," Contreras and Gutiérrez-García said. "Such neuronal responses can be synaptic, paucisynaptic, or polysynaptic, providing information about the

responsivity of these two cerebral nuclei."

For a while now, neuroscientists have considered single-unit neural activity as elusive to statistical analysis. In contrast, the technique used by Contreras and Gutiérrez-García, which records neuronal responsivity, enables rigorous and systematic statistical analyses of two interconnected cerebral nuclei under the influence of specific behavioral, hormonal and pharmacological variables.

"This methodology is even a step beyond the analysis of the Fos protein," Contreras and Gutiérrez-García said. "The Fos technique indicates that there is indeed neuronal activity, but it is not possible to discern whether such activity is excitatory or inhibitory because both are influenced metabolically. The methodology we used, on the other hand, allows the precise detection of increases, decreases, or no changes in the excitatory or inhibitory response of two anatomically related structures to behavioral, hormonal, and pharmacological influences."

The amygdala is known to be connected to other brain structures in the brain's frontal and temporal lobes, including the hippocampus. Combined, these structures regulate emotions and emotional memory, both of which are known to be dysregulated in people with anxiety disorders.

"The amygdala also has reciprocal connections with the medial prefrontal cortex (mPFC), where strategies are selected and elaborated that promote survival of the individual and consequently the species," Contreras and Gutierrez-Garcia said. "Under basal conditions, the amygdala regulates activity of the mPFC. If the amygdala is very active, however, then inhibition of the mPFC would increase, which would prevent selection of the best strategy."

The recent study carried out by this team of researchers gathered interesting new insight about the regulation of fear in mice. Specifically, the team found that in rats, the organic compound 2-heptanone reduces inhibitory control of the amygdala over the mPFC. The brain then adaptively reacts to an alarm substance and allows

selection of the best response (e.g., avoidance, flight, or escape).

In the future, these findings could inspire new studies specifically assessing the role of 2-heptanone in the regulation of fear and the selection of useful behavioral responses.

Ultimately, they could inform the development of more effective treatments for anxiety disorders and other psychiatric disorders marked by high levels of anxiety and maladaptive behavioral responses to fear.

"The methodology outlined in our paper has many applications," Contreras and Gutiérrez-García said. "Our interest has largely been studying the neurobiology of emotions. We focus on the neurobiological basis of anxiety (hence, studies of alarm substances) and depression as clinical entities. There is still much we do not know about the neurobiological bases of anxiolytic and antidepressant treatments and the participation of gonadal hormones in these processes."

More information: Carlos M Contreras, Ana G Gutiérrez-García, 2-Haptonone reduces inhibitory control of the amygdala over the prelimbic region in rats, *Neuroscience Letters*(2021). DOI: [10.1016/j.neulet.2021.136201](https://doi.org/10.1016/j.neulet.2021.136201).

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