Stimulating the vagus nerve: memories are made of this

Psychobiologists show how the vagal pathway links hormones outside the brain to neurotransmitters inside the brain to lock in memory of emotional or stressful events.

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April 2004, Vol 35, No. 4
Print version: page 36
5 min read

University of Virginia psychologists have moved the science of memory forward, reporting that stimulating the vagus nerve, which carries sensory messages to and from the brain, releases the neurotransmitter norepinephrine into the amygdala, strengthening memory storage in limbic regions of the brain that regulate arousal, memory and feeling responses to emotionally laden stimuli.

Their findings, which appear in the February issue of *Behavioral Neuroscience* (Vol. 118, No. 1), outline the neural pathway through which hormones that are released in the body affect specific parts of the brain during meaningful or emotionally arousing events in order to strengthen memories that will later foster sentimental pleasure or torture us with relived trauma.

The researchers--psychobiologists Cedric L.Williams, PhD, Derrick Hassert, PhD, and Teiko Miyashita, PhD--conclude that the vagus nerve is the "missing link" between the hormone epinephrine *outside* the brain and the neurotransmitter norepinephrine *inside* the brain.

"It had always been puzzling how the peripheral release of epinephrine could have these central effects on memory," says John Disterhoft, PhD, editor of *Behavioral Neuroscience* and a neurobiologist at Northwestern University. "This work helps us to understand how arousal responses in the body periphery, such as fight or flight, affect the brain--which they must if they are going to enhance learning as much as they are known to do."

Armed with these new insights, scientists can now more carefully calibrate how they stimulate the vagus nerve to influence the release of norepinephrine, flood the amygdala and strengthen memory. Or they can pursue more efficient blockers to shut out intrusive memories. The implications are many, offering explanations of known phenomena and holding out hope for improved treatments.

Juicing up the brain

Given mounting evidence of vagal nerve interaction with brain biochemistry, the University of Virginia researchers sought direct experimental evidence that stimulating the nerve can cause specific changes in neurotransmitter release.

In the first of two experiments using 31 rats total, the researchers surgically implanted electrodes around the left-side vagus nerve. During surgery, they also implanted a microdialysis device that allowed them to sample the concentration of norepinephrine that is released in the amygdala during rest or following vagal stimulation.

Williams and his colleagues stimulated the vagus nerve at a level previously reported by Robert A. Jensen, PhD, his graduate adviser, to improve memory in both laboratory rats (0.4 microAmps for 30 seconds) and humans (0.5 microAmps for 30 seconds). For more than two hours, they collected brain-fluid samples every 20 minutes. In the first

experiment, norepinephrine levels increased by 71 percent in the first 20 minutes after the voltage jump and peaked after 140 minutes at a 128-percent increase above baseline. Nothing changed in the unstimulated control group.

This experiment supported the researchers' first hypothesis, that vagal nerve stimulation produces dramatic surges in norepinephrine in a brain area involved with memory storage, a finding that almost certainly generalizes to humans. What's more, Williams says, "The magnitude and time course of changes in amygdala norepinephrine almost mirrored the changes produced by the dose of epinephrine that has been shown to improve memory."

In the second experiment, the researchers injected the rats with methyl atropine, a drug that blocks the acetylcholine that is released from descending vagal fibers onto peripheral organs, 10 minutes before stimulating the vagus nerve. The blocker--which affects the descending (efferent) fibers of the vagus nerve--didn't change the release of norepinephrine any more than did a control solution of saline.

The authors conclude that the findings rule out any role played by negative feedback from the periphery and confirm that the vagus nerve--albeit the ascending fibers--is the mechanism by which peripheral epinephrine activates the release of brain norepinephrine during memory consolidation.

The research solves the mystery of how the adrenal gland could stimulate the release of norepinephrine in the brain, observers say. During stress, the adrenal medulla (near the kidneys) in humans and rats releases epinephrine into the bloodstream, famously causing the "fight-or-flight" response in the heart, lungs, stomach and elsewhere. However, epinephrine can't cross the blood-brain barrier. So what is the switch that turns on epinephrine? The vagus nerve.

The new evidence provides a close-up look at how emotional events affect the body to influence how well the brain encodes information about exciting or meaningful events. First, emotionally arousing events stimulate the nervous system to release epinephrine. Unable to get into the brain, it does the next best thing: It activates the ascending fibers of the vagus nerve, which in turn stimulate brain neurons in an area of the brainstem known as the nucleus of the solitary tract (NTS).

In this model, NTS neurons release norepinephrine into brain structures that process memory, such as the amygdala and hippocampus. Upon activation, these memory-related regions work harder to properly put the attributes of emotionally arousing experiences into long-term storage.

From vagus to specific

At their most basic, the findings help explain a prior decade of data on how stimulating the vagus nerve (either of the 10th pair of cranial nerves) improves memory processing of recently acquired information.

"These findings fit well with extensive previous evidence that epinephrine regulates memory consolidation, acting via the vagus nerve; that neurons from the NTS release norepinephrine in the amygdala; and that norepinephrine release in the amygdala plays a critical role in regulating the strength of memories," says James McGaugh, PhD, director of the Center for the Neurobiology of Learning and Memory at the University of California, Irvine, and author of the recent "Memory and Emotion: The Making of Lasting Memories" (Columbia University Press, 2003).

Adds Robert Jensen, PhD, a psychobiologist who is now interim associate provost at Southern Illinois University: "Combined with research from other laboratories, the current findings provide strong support for the idea that the neurobiological mechanisms underlying memory modulation by arousal are similar across types of memory tasks and different mammalian species."

Understanding the pathways of emotional memory can also aid clinical treatment of traumatic memories, observers note. Already, says McGaugh, recent studies show that giving propranolol, which blocks the actions of norepinephrine in the brain, to people who have had traumatic experiences decreases the development of post-traumatic stress disorder symptoms.