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'Long-shot' discovery may lead to advances in treating anxiety, memory disorders

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(PhysOrg.com) -- An unexpected discovery by UCLA life scientists holds promise for the future development of treatments for post-traumatic stress disorder and other anxiety disorders, and potentially for Alzheimer's disease and other memory-impairment diseases.

The researchers, led by UCLA professor of psychology Michael Fanselow, have discovered what may be a completely unexplored drug target for the treatment of anxiety disorders. The research is published Jan. 7 in the journal *Science*.

Normally, when people or animals experience a frightening event, they learn to fear the place of the event and any signals that were present at the time. This occurs because the nerve cells in certain brain regions increase their ability to excite or stimulate one another, said Fanselow, a member of UCLA's Brain Research Institute.

Most neuroscience research has emphasized how this phenomenon occurs through chemical communication among neurotransmitters flowing across synapses — the space between neurons. However, there are also small, inhibitory neurons in these regions as well, which have direct electrical contact with one another through connecting channels known as "gap junctions," Fanselow said. Gap junctions are very common in invertebrates but rare in mammals, where they are found on only certain inhibitory interneurons.

"Because of this, no one has looked at the importance of these gap

junctions for learning, memory and emotion," Fanselow said. "We hypothesized that these gap junctions may be very important. Because the gap junctions cause the inhibitory neurons to fire together, they may cause these inhibitory neurons to act as a pacemaker for the excitatory neurons, making them fire at the same time so they are better able to make fear memories."

Fanselow's research team used several drugs in rats that block the gap junctions and found that they disrupted critical rhythms in the dorsal hippocampus — the brain region most involved in cognition — and prevented fear memories for places from forming. The drugs could block the formation of fear of places when given after the frightening experience.

Neuronal gap junctions may be an unexplored drug target for the treatment of anxiety disorders such as PTSD; they hold promise because giving a regular injection of drugs in a cavity near the abdomen worked as effectively as an injection directly into the brain. In addition, the injections worked when given right after the frightening experience.

"Because we don't know when a person will experience trauma, treatments that can work after the experience hold more promise," Fanselow said.

"The brain has many processes we have not yet explored," he added. "Understanding them and how they normally work can open up new approaches that may help in very prevalent and debilitating diseases, such as anxiety disorders and memory disorders."

Neuronal gap junctions form where inhibitory neurons touch one another. They are like an opening between nerve cells, a gap in the membranes separating the cells from one another; they let the electrical activity in one neuron affect the neuron it touches.

"Our research shows a way that neurons can coordinate their activity, and this coordination is critical for memory formation," Fanselow said. "Perhaps if we had a way of enhancing gap junction function, we may improve memory formation by facilitating gap junctions when memory is impaired by diseases such as Alzheimer's. However, we have not shown this yet."

"I was completely surprised by this discovery," he said. "I really thought we were taking a long shot and was surprised that gap junctions were not only playing a role but that their importance was so great.

"The formation of fear memories is the major cause of anxiety disorders. These disorders are very common and can be very debilitating. Gap junctions appear to be key in coordinating the activity of the network of neurons that produce fear memories, specifically, and probably other memories, generally, as well."

The lead author on the Science paper is Stephanie Bissiere, an assistant researcher in Fanselow's laboratory, who last week was selected as a recipient of a Young Investigator Award from the National Alliance for Research on Schizophrenia and Depression.

Other co-authors are Moriel Zelikowsky, a graduate student in Fanselow's laboratory; Ravikumar Ponnusamy, an assistant researcher in Fanselow's laboratory; Nate Jacobs, a former UCLA undergraduate who is currently a graduate student at UC Irvine; and Hugh Tad Blair, a UCLA associate professor of psychology.

Provided by University of California Los Angeles

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