

It takes two: Double detection key for sensing muscle pain

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A new study discovers a molecular mechanism involved in pain associated with muscles. The research, published by Cell Press in the Nov. 18 issue of the journal *Neuron*, provides new insight into what underlies one of the most common, and least understood, forms of human pain.

When cardiac or [skeletal muscle](#) is not receiving enough oxygen to meet metabolic demands, a person will experience pain, such as angina, chest pain during a [heart attack](#), or leg pain during a vigorous sprint. This type of pain is called "ischemic" pain and is sensed in the body by [receptors](#) on [sensory neurons](#). It has been suggested that lactic acid, which increases during muscle exertion under conditions where oxygen is low, is a potential mediator of ischemic pain via action at acid sensing channel #3 (ASIC3). However, the acid signal it generates is quite subtle and is unlikely to act alone.

"In our study, we examined whether other compounds that appear during ischemia might work synergistically with acid upon ASIC3," explains senior study author, Dr. Edwin W. McCleskey. "We found that another compound released from ischemic muscle, adenosine tri-phosphate (ATP), works together with acid by increasing the sensitivity of ASIC3 on sensory [neurons](#)." Importantly, ATP levels have been shown to rise rapidly outside ischemic [muscle cells](#) and synergistic action of ATP and acid has been observed in animal models of ischemia.

The researchers went on to show that ATP binds to a membrane purine

receptor, called P2X, and that P2X and ASIC appear to form a molecular complex that serves to sensitize ASIC to acid. "Taken together, our results help to explain the paradox that acid appears incapable of triggering ischemic pain by itself yet buffering acid severely decreases sensory detection of ischemic pain," concludes Dr. McCleskey. "ATP, which is released from oxygen-deprived contracting muscle, increases the ability of ASICs to respond to a slight decrease in pH."

Provided by Cell Press

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