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Popular arthritis drug may disrupt heart rhythm, UB research finds

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Celebrex, a popular arthritis drug that blocks pain by inhibiting an enzyme known as COX-2, has been shown in laboratory studies to induce arrhythmia, or irregular beating of the heart, via a novel pathway unrelated to its COX-2 inhibition.

University at Buffalo researchers discovered this unexpected finding while conducting basic research on potassium channels.

They found that low concentrations of the drug, corresponding to a standard prescription, reduced the heart rate and induced pronounced arrhythmia in fruit flies and the heart cells of rats.

The drug inhibited the normal passage of potassium ions into and out of heart cells through pores in the cell membrane known as delayed rectifier potassium channels, the study showed.

“The adverse effects of drugs like Celebrex and Vioxx based on their selective inhibition of COX-2 currently are a topic of intense discussion in the medical community,” said Satpal Singh, Ph.D., associate professor of pharmacology and toxicology in the UB School of Medicine and Biomedical Sciences and senior author on the study. Vioxx was withdrawn from the market in September 2004.

“We now have shown an important new effect of Celebrex through a totally different pathway, one that is unrelated to the drug’s effect as a pain reducer,” Singh said. “The adverse effect arising from this

unexpected mechanism definitely needs to be studied more closely, because the potassium channels inhibited by the drug are present in heart, brain and many other tissues in the human body.

The research was supported by grants from the National Science Foundation to Singh and Randall D. Shortridge, Ph.D., UB assistant professor of biological sciences, to analyze the basic properties of potassium channels.

Aware that COX-2 inhibitors had been shown to produce cardiovascular side effects, the researchers first tested whether Celebrex would affect the heart in fruit flies, a good animal system for studies on heart in other species, including humans.

“When we found an effect on the fly heart, we began looking for the underlying mechanism,” said Singh. “We searched the fly genome and were surprised to find that these flies don’t have cyclooxygenases, the enzymes targeted by Celebrex.

“Because the main effect of the drug in our study was induction of arrhythmia, and arrhythmia is often the result of ion-channel dysfunction,” continued Singh, “we examined the drug’s effect on potassium channels and other ion channels in their models and were struck by the strong inhibition of the potassium channels.”

The researchers now are examining the underlying molecular mechanisms responsible for the drug’s action and its effect on other ion channels that play a prominent role in setting the rhythm of the heart.

“We are trying to determine whether the drug binds directly to the channels or to some other molecule, and if it acts by blocking the pore of the channel through which potassium ions travel or by some other mechanism,” Singh said.

Source: University at Buffalo