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Macrophage-dependent IL-1beta production induces cardiac arrhythmias in diabetic mice

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One of the most serious complications of diabetes, heart arrhythmias, is now on its way to be prevented and combated. Researchers from the Federal University of Rio de Janeiro (UFRJ) in partnership with investigators from University of Bonn, Universidad del Pais Vasco, Universidad de La Plata, FIOCRUZ and UNICAMP, show how the disease affects the heart and how the process can be reversed with two promising drugs. The findings have just been published in the October issue of the journal *Nature Communications*.

Heart problems are responsible for 65% of the deaths related to diabetes. The most common disorder in these cases is ventricular tachycardia (a dysregulation in the heart rhythm). This work, coordinated by Prof. Emiliano Medei, from the Institute of Biophysics Carlos Chagas Filho and CENABIO at UFRJ, confirms that the increase in blood glucose causes a specific inflammation, which directly affects the heart.

To investigate this process, researchers caused diabetes in wild-type mice and mutant animals unable to produce a specific type of inflammation related to production of IL-1-beta substance. Both had similar increases in blood glucose, but only those typically inflamed- the wild-type mice—had altered heart rate. Furthermore, mutants which do not produce IL-1 beta suffered much less from arrhythmias even when under effect of caffeine or dobutamine, drugs that promote ventricular tachycardia.

The researchers found a large amount of circulating IL-1-beta and

especially in the hearts of common diabetic mice. They also observed that IL-1-beta alone altered heart function when given to healthy rat hearts (without diabetes), or human heart cells.The good news is that the group also tested successfully two drugs that specifically inhibit this inflammatory process: MCC-950 and anakinra. The first blocks IL1-beta production, while the latter prevents it from having active effects in the body cells and is already being used to treat some autoimune diseases, such as rheumatoid arthritis. The team managed to even reverse the cardiac alterations in diabetic mice.

"It is noteworthy that inflammation is an important tool to fight infections, which usually ends when the 'intruder' is removed. In the case of diabetes, there is no infection. Persistent hyperglycemia stimulates the immune system to produce a constant inflammation, with great production of IL-1-beta—"we found inflammation to be the link between arrhythmias and diabetes", explains Medei. "I believe that the new therapeutic tools that we propose in this study are very promising to treat the heart disease caused by diabetes" he says.

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