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NYU dental researcher to study 'mitochondrial permeability transition'

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Stroke and heart attack are severe medical conditions that affect millions of people worldwide. They occur when blood supply to the tissue is interrupted. This lack of blood supply can cause extensive damage leading to permanent injury and/or death. It has been found that at the elementary cellular level, damage to the individual cell is caused by the loss of mitochondrial function - in a phenomenon known as the Permeability Transition. Thus, if the occurrence of Permeability Transition can be blocked, we may be able to protect the affected tissue against damage.

Unfortunately, it is impossible to develop effective treatments without knowing the detailed molecular nature underlying the Permeability Transition.

"Mitochondrial Permeability Transition Pore (mPTP) is a large, non-selective channel located in the mitochondrial inner membrane," explains Dr. Pavlov. "It has been established that prolonged opening of mPTP during stress conditions leads to an increase in permeability of the mitochondrial membrane and a disruption of energy generation (in the form of ATP, the principal molecule for storing and transferring energy in cells), eventually causing cell death. mPTP opening is the central event leading to tissue damage during stroke."

Dr. Pavlov notes that blocking mPTP by pharmacological agents can be highly protective. However, current knowledge of the channel ("pore") part of mPTP remains incomplete. The central goal of the current

proposal is to test the hypothesis that formation of the functional conducting channel of the mPTP requires the presence of non-proteinaceous polymers of inorganic polyphosphate and polyhydroxybutyrate in combination with the C-subunit and Ca2+.

"The ultimate goal of the project," says Dr. Pavolov, "is to define the core molecular components of the Permeability Transition."

Toward this end, a sequence of experiments will use electrophysiology to study the activity of the purified mPTP channel, followed by investigating the molecular composition and assembly of mPTP by using a number of analytical approaches, including immunochemistry and mass spectroscopy. Finally, the researchers will use wild-type and genetically modified cultured neurons and stable cell lines to investigate interactions between C-subunit, polyphosphate, and polyhydroxybutyrate during mPTP activation in living cells.

"In the future," says Dr. Pavlov, "this new knowledge will lead to opportunities to design novel treatment strategies which will specifically target these non-proteinaceous components of the pore, effectively preventing mPTP opening and protecting against tissue damage that causes heart attack and stroke."

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