Neuroprotection for stroke: Progesterone treatment reduces brain mitochondrial dysfunction

Every year, six million people die from stroke and five million are left disabled. 80% of strokes are ischemic and happen when blood flow is blocked in a part of the brain, due to occlusion of brain vessel by a clot. This blockade decreases the supply of brain tissue with dioxygen (O_2) and glucose leading to a rapid death of neural cells in the area which depends on the occluded vessel. In this area called the core of the infarct the damages are irreversible. Penumbra is the zone surrounding the core of the infarct where the blood flow is less compromised. In the penumbra, cells remain viable and can be salvageable if rescued rapidly by neuroprotective agents. If not, cells in the penumbra die leading to a progressive spreading of nervous system damage. The only available treatment after stroke is the reperfusion, that it to say to remove the clot. Unfortunately, reperfusion can be used in only 5% of patients because it must be done within 4,5 hours after stroke . Beyond this time, brain cells are too altered and the reperfusion is not efficient and may increase the risk of hemorrhagic transformation. Neuroprotective drugs are urgently needed to be developed, to rescue brain cells in the penumbra and to increase the efficiency of reperfusion. Progesterone is a promising candidate. Indeed, different teams including ours showed that the administration of progesterone after an experimental stroke reduced mortality, infarct volume and neurological deficits in rats and mice. Before any potential therapeutic use of progesterone in stroke patients, we have to identify its targets and effectors. Mitochondria may be one of these targets.

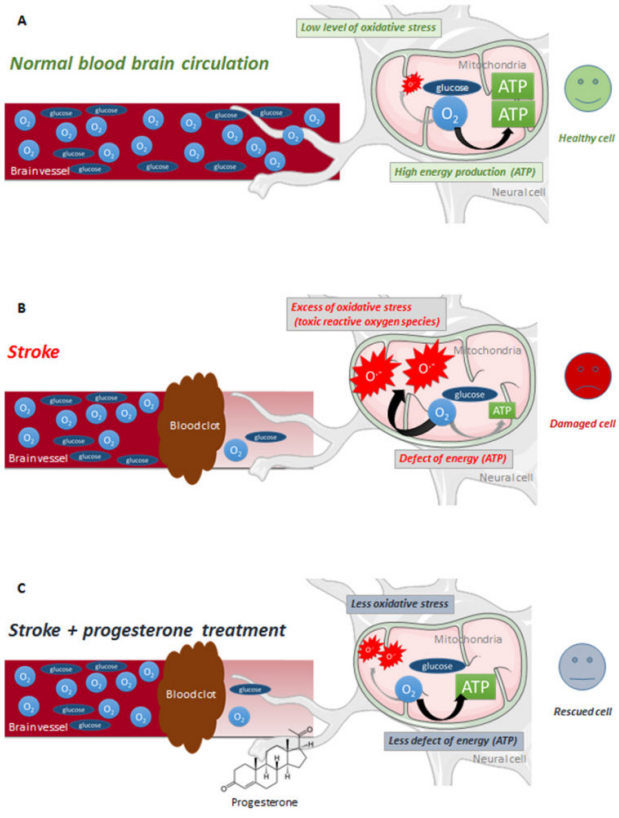

Fig. 1. Effect of stroke and progesterone on brain mitochondria function (use of dioxygen O_2 and glucose to produce ATP and control of oxidative stress)

Mitochondria are the “energy central” of the cell: they produce energy in the form of ATP (adenosine triphosphate) by using dioxygen and glucose supplied by blood. Moreover, mitochondria control the oxidative stress, i.e. the toxic effect of an excess of free reactive oxygen species. Under normal conditions, the supply of dioxygen and glucose by blood is sufficient for the adequate function of brain mitochondria (Fig. 1A). After stroke, the function of mitochondria is altered since the blood circulation is impaired. In this case, the production of energy (ATP) is decreased and the oxidative stress is increased leading to cell death (Fig. 1B).

In this study, we hypothesized that progesterone may improve the function of brain mitochondria after ischemic stroke. To test our hypothesis, we mimicked a stroke in male and female mice by occluding temporarily the middle cerebral artery using a filament. Immediately after reperfusion (taking out the filament), we treated mice either with placebo or with progesterone by intranasal administration. 6 hours after, we analyzed how mitochondria isolated from brain use dioxygen and control oxidative stress.

Two important results were obtained: Firstly, the consequences of the stroke on the use of dioxygen by mitochondria are different between males and females. This difference was not known, because almost all the previous experimental studies were done only in male animals. Future research should address the sex differences to check if the effects of stroke and of the potential treatments are similar in males and females. Secondly, we demonstrate that brain mitochondria from mice treated with progesterone show better use of dioxygen to produce ATP and less oxidative stress (Fig. 1C) than brain mitochondria from mice treated with placebo (Fig. 1B). These beneficial effects of intranasal administration of progesterone on mitochondria were observed in both, males and females, and could help to limit brain cell death, thus reducing neurological disorders after stroke.

To conclude, progesterone is a pleiotropic agent representing a promising way to protect the brain after ischemic stroke in both, men and women.

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Publication

Progesterone reduces brain mitochondrial dysfunction after transient focal ischemia in male and female mice.

Gaignard P, Fréchou M, Schumacher M, Thérond P, Mattern C, Slama A, Guennoun R

J Cereb Blood Flow Metab. 2016 Mar