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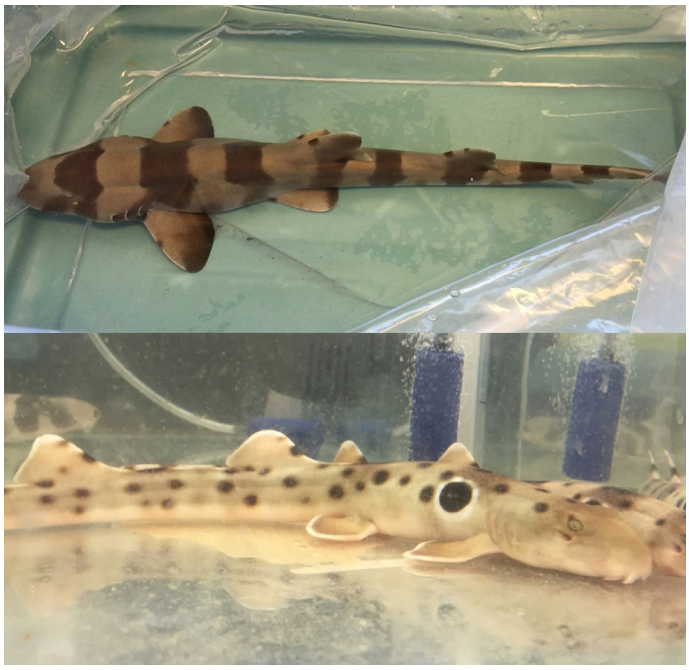
INSIDE JEB

Shark lessons for stroke and heart attack victims



A grey carpet shark (top) and an epaulette shark (bottom). Photo credit: Jules Devaux.

When humans suffer a stroke or heart attack, the supply of oxygen to the brain is interrupted, with disastrous consequences. 'This is because mitochondria, famously referred to as the "powerhouse of the cell", rely on oxygen and can no longer make sufficient energy [ATP] for our cells', says Jules Devaux from the University of Auckland, New Zealand. He adds that medics would love to find a way to prevent such damage. Fortunately, Mother Nature has already done the experiment.

'Some species have evolved and survive in environments that become anoxic [lose all of their oxygen]', says Devaux, adding that creatures such as epaulette sharks and grey carpet sharks survive in conditions that are equivalent to experiencing daily strokes, yet sustain no brain damage. However, the fish depend on contrasting survival strategies. Grey carpet sharks bank oxygen in stored red blood cells – like SCUBA tanks – ready for later use, while epaulette sharks shut down their metabolism to conserve energy and go into a coma-like state. Knowing this, Devaux, Anthony Hickey, also at the University of Auckland, and Gillian Renshaw from Griffith University, Australia, investigated how mitochondria from the brains of the two sharks cheat death when the coral pools that they inhabit become anoxic and their oxygen supply is cut off.

Collecting brains from both species, Devaux measured how the mitochondria consumed oxygen when functioning normally. Next, he tested their oxygen consumption when he cut off the oxygen and then reintroduced it; most damage occurs when oxygen floods back into the mitochondria after a period of anoxia. The team also knew that a substance called succinate accumulates in mitochondria when they are deprived of oxygen, wreaking havoc when oxygen returns and the mini power packs consume the substance rapidly. So, Devaux recorded the oxygen consumption of mitochondria that had received a dose of succinate before he turned their oxygen supply back on. Recalling the day-long experiments, he laughs 'It was certainly hard to stay in the lab on sunny summer days on the Australian Gold Coast while the surf was on'.

Not surprisingly, the mitochondria of the epaulette sharks, which shut down their metabolism when oxygen is scarce, coped well. They sustained little damage and resumed oxygen consumption when oxygen was returned after a period of anoxia. The cell structures also reduced their succinate consumption, which may protect them from damage when oxygen floods back in. However, the mitochondria were unable to convert all of the energy released by oxygen into ATP, 'although, we showed that part of the oxygen conversion may help to transfer the newly produced energy to the cell for its own use', Devaux says.

In contrast, the mitochondria of the grey carpet sharks were slightly more vulnerable and consumed less oxygen, as predicted. The sharks have a lower risk of running out of oxygen – thanks to their SCUBA-like oxygen storage – making it less essential for their mitochondria to develop alternative protection mechanisms when their oxygen supply runs down.

But what hope do the sharks hold for clinicians wishing to treat stroke and heart attack victims? Devaux thinks that they could be a great model for these human diseases as the fish live at relatively high temperatures (~34°C), close to our own body temperature, unlike other anoxia-tolerant animals, which allow their body temperature to fall close to zero when oxygen is scarce during hibernation. And he suggests that clinicians look into ways of reducing succinate levels in the mitochondria of human stroke and heart attack victims, as the reduction in the epaulette sharks' succinate consumption seems to offer them some protection.

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Devaux, J. B. L., Hickey, A J. R. and Renshaw, G. M. C. (2019). Mitochondrial plasticity in the cerebellum of two anoxia-tolerant sharks: contrasting responses to anoxia/re-oxygenation. *J. Exp. Biol.* **222**, jeb191353.

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