Activity of the cardiac Na^+-H^+ exchanger during ischaemia

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There is dispute about whether the cardiac Na^+-H^+ exchanger (NHE1) remains active during ischaemia (Allen & Xiao, 2003). The conclusion that the NHE1 was active during ischaemia is based on the large intracellular acidosis which would be expected to drive sodium entry on NHE1 and the fact that some NHE1 inhibitors, such as amiloride, reduce the rise of $[Na^+]_i$ during ischaemia (Murphy *et al.,* 1991). However, pH_i shows no recovery during ischaemia and NHE1 inhibitor do not change the pH_i during ischaemia, which suggested that the Na^+-H^+ exchanger was inhibited during ischaemia (Park *et al.*, 1999). We took advantage of a new potent and selective NHE1 inhibitor, zoniporide (Marala *et al.*, 2002) to reassess the activity of NHE1 during ischemia.

Rats were anaesthetised with pentobarbitone and hearts were isolated and stimulated at 5 Hz. Ischaemia was induced by turning perfusion off for 30 minutes. Intracellular sodium ($[Na^+]_i$) was measured with sodium binding benzofuran isophthatale (SBFI).

In control hearts 30 minutes ischaemia increased $[Na^+]_i$ from 7.2 ± 0.2 mM to 17.3 ± 0.7 mM and reperfusion resulted in a large transient increase of $[Na^+]_i$ (peak 31 ± 2.3 mM (*n*=6)). In the presence of zoniporide (1 μM, *n=5*) present throughout ischaemia and reperfusion, ischaemia still caused a similar $[Na^+]_i$ rise to 16.2 ±0.5 mM but the large transient increase of $[Na^+]_i$ on reperfusion was abolished (peak 13.8 ± 2.4 mM). With amiloride (100 μM, *n=4*) treatment, $[Na^+]_i$ was unchanged at the end of ischemia (6.7 ± 0.7 mM) and the increase of $[Na^+]_i$ on reperfusion was abolished (peak 7.4 ± 0.3 mM).

Both zoniporide and amiloride abolished the transient increase of $[Na^+]_i$ on reperfusion, which results from activity of NHE1. However they showed different effects during ischaemia: noly amiloride abolished the $[Na^+]_i$ rise during ischaemia. Amiloride derivatives reduce the persistent Na^+ current (Chattou *et al.*, 2000). Furthermore, the rise of $[Na^+]_i$ during ischaemia is abolished by low concentrations of tetrodotoxin which inhibit the persistent Na^+ current (Xiao & Allen, 1999). Thus we propose that the ability of amiloride to prevent the $[Na^+]_i$ rise during ischaemia arises from inhibition of the persistent Na^+ current. Measurements of the effect of amiloride and zoniporide on persistent Na^+ current are required to confirm this hypothesis.

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