Blocking sodium current reduces the rise in intracellular calcium concentration during hypoxia in rat hippocampal neurons

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It is believed a marked rise in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) is the leading cause of irreversible cell damage during hypoxia. There is increasing evidence that an increase in intracellular Na^+ concentration ($[Na^+]_i$) is also involved. Whether there is a relationship between the rises in $[Na^+]_i$ and $[Ca^{2+}]_i$ remains controversial. We have studied this relationship in cultured hippocampal neurons (cells were obtained from rapidly decapitated newborn rats) by recording $[Ca^{2+}]_i$ before and during hypoxia or exposure to ion channel blockers in cultured hippocampal neurons using the Ca^{2+} indicator fluo-3-AM. The fluorescence of fluo-3 was monitored within single cells before and during hypoxia to track changes in $[Ca^{2+}]_i$. It has been shown that low concentrations of the Na^+ channel blockers TTX (1 nM) or lidocaine (10 nM) block persistent Na^+ current but not the transient, inactivating Na^+ current responsible for action potentials[1]. We found that these drugs effectively blocked the hypoxic rise in $[Ca^{2+}]_i$. In contrast, blocking Ca^{2+} channels with cadmium (100µM) did not prevent the hypoxic rise in $[Ca^{2+}]_i$. These results suggest that the persistent Na^+ influx is making a major contribution to the $[Ca^{2+}]_i$ rise during hypoxia. A rise in $[Na^+]_i$ could influence $[Ca^{2+}]_i$ by influencing removal of Ca^{2+} from cells by the Na^+-Ca^{2+} exchanger. To test this hypothesis, we examined the effect of an Na^+-Ca^{2+} exchanger inhibitor, KB-R7943 (5 ì M), and found that it reduced the hypoxic rise in $[Ca^{2+}]_i$. These results support the hypothesis that hypoxia causes an increase in $[Ca^{2+}]_i$ by increasing persistent Na^+ current and consequently $[Na^+]_i$ and this then depresses removal of Ca^{2+} so that $[Ca^{2+}]_i$ rises.

(1) 1. Hammarstrom AK and Gage PW. Inhibition of oxidative metabolism increases persistent sodium current in rat CA1 hippocampal neurons. J Physiol 510 (Pt 3): 735-741, 1998.