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 (100\(\mu\)M) 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 \(\mu\)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.