Abstract During prolonged depolarization of excitable cells, some voltage-activated, tetrodotoxin-sensitive sodium channels are resistant to inactivation and can continue to open for long periods of time, generating a “persistent” sodium current ($I_{NaP}$). The amplitude of $I_{NaP}$ is small [generally less than 1% of the peak amplitude of the transient sodium current ($I_{NaT}$)], activates at potentials close to the resting membrane potential, and is more sensitive to Na channel blocking drugs than $I_{NaT}$. It is thought that persistent Na channels are generated by a change in gating of transient Na channels, possibly because of a change in phosphorylation or protein structure, e.g. loss of the inactivation gate. Drugs that block Na channels can prevent the increase in $[Ca^{2+}]_i$ in cardiac cells during hypoxia. Hypoxia increases the amplitude of $I_{NaP}$. Paradoxically, NO causes a similar increase in $I_{NaP}$ and the effects of both can be inhibited by reducing agents such as dithiothreitol and reduced glutathione. It is proposed that an increased inflow of Na⁺ during hypoxia increases $[Na^+]_i$, which in turn reverses the Na/Ca exchanger so that $[Ca^{2+}]_i$ rises. An increase in $I_{NaP}$ and $[Ca^{2+}]_i$ could cause arrhythmias and irreversible cell damage.

Keywords Hypoxia · Sodium channels · Inactivation · Sodium current

Persistent sodium current

In the classical description of the ionic basis of action potentials, Hodgkin and Huxley (1952) described voltage-activated sodium currents that activate rapidly and then inactivate more slowly within tens of milliseconds. Some years later, tetrodotoxin (TTX)-sensitive plateau potentials were recorded in cerebellar Purkinje neurons (Llinás and Sugimori 1980) and TTX-sensitive inward rectification in neocortical neurons (Stafstrom et al. 1982). The results pointed to a TTX-sensitive, voltage-activated sodium current that did not inactivate rapidly in these neurons.

A couple of years later, the newly available single-electrode voltage clamp was used to record the persistent sodium current for the first time directly in mammalian neurons (French and Gage 1985). A similar “threshold sodium current” was recorded at about the same time in squid axon (Gilly and Armstrong 1984). A more comprehensive description of the persistent sodium current in neurons in the CA1 region of hippocampal slices appeared several years later (French et al. 1990). Because the current was so small, it was necessary to subtract current traces recorded before and after exposure of cells to high concentrations of TTX to be certain that currents recorded were indeed sodium currents and not due to drifts in leakage current with time. It was found that the maximum amplitude of the persistent sodium current was less than 1% of the maximum amplitude of the transient sodium current, that it activated at more negative potentials than the transient sodium current, and that it was resistant to inactivation even during depolarizations lasting many seconds. Although the current is small, its resistance to inactivation means that it can produce significant changes in $[Na^+]_i$ if it turns on for many seconds.

A similar persistent sodium current was also recorded in skeletal muscle (Gage et al. 1989) and cardiac muscle (Saint et al. 1992). Persistent sodium current is probably responsible for the fibrillations commonly seen in denervated skeletal muscle. Several heritable forms of myotonia and periodic paralysis are caused by impaired inactivation of sodium channels causing a persistent sodium current that may either initiate abnormal bursts of action potentials (myotonia) or cause paralysis by
Effects of hypoxia

There is mounting evidence that an increase in persistent sodium current is an early and fundamental event in hypoxia. Drugs that selectively block this current might reduce damage to cells during ischaemia or hypoxia. The shortage of effective drugs that can be used to prevent this damage is largely due to our lack of information about the exact sequence of biochemical events linking insufficient oxygen supply to cell death (Lipton 1999).

Oxygen is required for the survival of cells because of its central role as the final acceptor of electrons in the mitochondrial respiratory chain, making the synthesis of ATP possible via oxidative phosphorylation. Even transient localized oxygen deficits, such as those that occur during head injuries or unstable coronary syndromes, can produce irreversible cell damage. The high lipid content and oxygen metabolism of the brain render it particularly vulnerable to oxidative damage. This may be a result of increased levels of free radicals or compromised defences (e.g. antioxidant levels) against the radicals in the brain during hypoxia. Normal cellular defences against hypoxia include a high intracellular content of reduced glutathione (GSH) and a low content of oxidized glutathione (GSSG). This keeps protein thiol groups in the reduced state. The tissue content of GSH is decreased whereas that of GSSG is increased during hypoxia and this creates a situation where SH groups may be modified.

Neuronal hypoxia

Neuronal death caused by decreased or interrupted O2 delivery has been attributed to changes in intracellular pH, decreased ATP levels, free radical production, increases in [Na+]i and/or [Ca2+]i, and to membrane depolarization (Lipton 1999). These changes are accompanied by activation of damaging proteases and phospholipases and release of free radicals. Neuronal cell death may be described as having three stages: (1) early intracellular ionic and chemical changes, (2) activation of damaging enzymes and (3) changes in cellular functions and structures, eventually leading to cell death. The delay before cell death occurs varies greatly (from minutes to hours or weeks), depending on the nature of the insult and the cell type. Dying cells release chemicals that endanger cells in the surrounding area (penumbra) where blood flow is not completely cut off. These surrounding cells are in a state of "shock" and either survive or die, depending on what happens in the minutes to hours that follow. A large number of the damaging changes occurring in the neurons are secondary to an increase in intracellular Na+ levels (Lipton 1999).

Cardiac hypoxia

Arrhythmias

Although cardiac muscle appears to be more resistant to hypoxia than neurons, more than half the deaths following an ischaemic episode occur suddenly and have been attributed to arrhythmias. The cause of these arrhythmias is not well understood (Carmeliet 1999). It is known that electrophysiological changes occur rapidly following ischaemia without any evidence of irreversible membrane damage, indicating that the underlying mechanisms are likely to be due to transient biochemical and ionic alterations within or near the sarcolemma of the ischaemic myocyte. It has been suggested that abnormalities of action potentials (afterdepolarizations), which become prominent following cardiac hypoxia or ischaemia, may trigger the arrhythmias. Two kinds of afterdepolarizations have been described: an early afterdepolarization occurring during repolarization of an action potential and a delayed afterdepolarization occurring when repolarization is complete or nearly complete. The ionic mechanisms responsible for these afterdepolarizations are not well understood. It has been assumed that they are caused by a net increase in inward currents that are activated under hypoxic or ischaemic conditions. Computer models suggest that small increases in a persistent sodium current would cause significant lengthening of the action potential duration (Sakmann et al. 2000) that may cause lethal arrhythmias. Early afterdepolarizations are depressed by a reduction in external Na+ concentration ([Na+]o) and by the specific Na+ channel blocker TTX (Coraboeuf et al. 1980), suggesting that a TTX-sensitive Na+ current is involved. Consistent with this idea, veratridine, which causes persistent activation of Na+ channels, induces early afterdepolarizations which can be completely eliminated with TTX. Interestingly, the Na+ channel blocker TTX abolishes early afterdepolarisations in myocytes obtained from heart failure patients (Maltsev et al. 1998). Delayed afterdepolarizations are Ca2+-dependent events that are evoked by a variety of conditions that induce intracellular Ca2+ overload and are thought to play a role in reperfusion arrhythmias.