STUDIES ON FAST AXOPLASMIC TRANSPORT IN MAMMALIAN NERVE

METABOLIC ASPECTS

by

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ABSTRACT

The phenomenon of axoplasmic transport was first observed by Waller in 1850. Since that time it has been investigated in many different species and in various types of nerves. It has been noted that there are several different rates of transport: a fast rate of the order of 10^2mm/day and a slow rate of about 1mm/day. The substrates transported include neurotransmitters such as noradrenaline and a wide variety of proteins, peptide chains and amino acids. The soluble proteins are characteristic of the slow phase of transport while proteins in the particulate fraction are characteristic of the fast phase. The mechanism behind axoplasmic transport is as yet unknown. Studies with colchicine, however, have shown that the fast transport system may be associated with microtubules.

The relationship of this transport system to nerve energy metabolism can be examined in the light of the metabolic aspects of the primary function of nerve, the conduction of impulses. During activity as a result of electrical or cationic stimulation nerve energy metabolism undergoes some changes which presumably increase the energy available to the sodium pump. The R. Q. shifts from 0.8 to 1.0. Oxygen consumption increases to a new steady state rate. Glycolysis is somewhat inhibited due to the Pasteur Effect and noncarbohydrate sources of energy are metabolized. Inorganic phosphate levels increase and ATP and PCr are rapidly utilized. Investigations of ATP consumption under resting conditions in the intact axon and in isolated axoplasm have revealed that at least 35% is ouabain insensitive and is localized in the axoplasm. Perhaps this 'nonmembrane' energy supply is related to the axoplasmic transport system. That

metabolic energy is a requirement for the operation of the fast axoplasmic transport system is shown in these investigations.

These investigations were carried out in vitro on cat sciatic nerve using ^{3}H-leucine injected into the L7 ganglion as a ^{3}-H-protein precursor. It was shown that treatment of the nerve with inhibitors and uncouplers of oxidative phosphorylation such as NaCN and DNP block the transport system within 15 minutes of their application. Nitrogen asphyxiation also prevents the transport system from operating. The conclusion is that fast transport requires a continuous supply of energy through mitochondrial oxidative metabolism. Furthermore, this energy supply is a local one as shown by the block of transport and the damming effect in a region asphyxiated locally with petrolatum jelly. If glycolysis is blocked by treatment of the nerve with IAA the fast transport system continues for about 90 minutes but in a decrementing fashion. Addition of pyruvate or L-lactate below the point of the glycolysis block sustains the system. The degree to which they are effective is dependent on their concentrations and the degree to which pyruvate is more effective than L-lactate is dependent upon the isozymic composition of the LDH. It seems then that under the conditions of glycolysis block the nerve relies on the TCA cycle and its supply of substrates for the TCA cycle for energy to run the transport system.

The fast transport system is also sensitive to temperature changes. Within the range $8^{o}C$ - $38^{o}C$ the Q_{10} of fast transport is 2.2 which is close to the Q_{10} for most metabolic processes. Preliminary experiments on the effect of supramaximal repetitive stimulation on fast transport in vitro show that the rate of transport is reduced. The degree of the reduction is dependent on the frequency of the stimulation. Again it seems that a metabolic limitation may be operating.

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