Editorial: Axonal transport and the eye

Since the earliest days of histology, it has been known that the neurons have a large amount of basophilic material in the cell body. More recently this has been shown to be due to masses of rough endoplasmic reticulum which are responsible for a high rate of protein synthesis of neurons. Since the earliest days of the microscopy of living cells in vitro, particulate movement within these cells has been recognized, particularly in neurons (Nakai, 1964). The last 30 years have seen the gradual accumulation of the knowledge required to explain these two observations. In the last 10 years in particular, the development of radioactive tracer techniques has revealed much information on the movement of protein and other substances within axons, a process termed axonal transport (Barondes, 1967). The eye and its central connexions have played a large part in the investigation of axonal flow in the normal state, and reference will particularly be made to this work here.

A large number of substances are transported along axons, including glycoproteins, mitochondria, vesicles, phospholipids, low molecular weight substances, and possibly drugs and other biologically active substances. However, the major bulk of transported material is protein. Labelling the proteins with a radioactive precursor such as 14C-leucine has demonstrated movement at different rates, some travelling rapidly at about 400 mm/day, and some slowly at about 1 to 4 mm/day. Some authors have tried to suggest that the slow (Weiss, 1972) or the fast (Ochs, 1974) are the only rates of flow, but it is clear from the movement of peaks of activity in pulse labelling experiments that there are preferential bands or rates of movement (Sjöstrand and Karlsson, 1969; Karlsson and Sjöstrand, 1971a and b; Chou, 1970; Di Giamberardino, 1971). It appears likely from the analysis of the overall patterns of distribution after pulse labelling that there are many intermediate rates of axonal transport (Bradley, Murchison, and Day, 1971; Karlsson and Sjöstrand, 1971a and b).

The fast and, to a lesser extent, the slow rates of transport are temperature dependent (Graffstein, Forman, and McEwen, 1972; Ochs and Smith, 1975), and also depend on energy metabolism (Ochs and Ranish, 1970; Ochs, 1971). The transport is an intrinsic feature of the axon, since it continues after separation from the cell body. Most of the faster-flowing material after pulse labelling with leucine consists of low molecular weight substances and proteins, and are predominantly found in the particulate fraction of nerve homogenates. The slower transported material is mainly soluble protein (McEwen and Graffstein, 1968; Kidwai and Ochs, 1969; Sjöstrand, 1970). Much of the former and more than 60 per cent of the latter is probably neurotubular protein (tubulin), and the neurotubules are thought to play a major part in axonal transport (Schmitt and Samson, 1968). The neurotubules have a similar structure to actin, and are linked to high-energy phosphate compounds. Myosin-like proteins are also found in axoplasm. It is suggested that moving material might in part roll along the neurotubules, or that the neurotubules themselves might move by a mechanism involving myosin-guanosine triphosphate-neurotubule cross bonds joining and breaking in a similar way to the sliding filament process of skeletal muscle contraction. Gross (1975) suggested a variation of this theory based on regions of differential viscosity around neurotubules (a microstream concept). As more studies are performed of the transport of individual proteins in axons, it is becoming clear that there are many relatively specific rates of flow, and that the overall pattern is due to the movement of many different molecular species.

It is known that axonal transport occurs in both large myelinated and unmyelinated fibres, although the evidence suggests that intermediate velocities are possibly slightly faster in the unmyelinated fibres (Held and Young, 1969; Sjöstrand, 1969; Gross and Beidler, 1972). Growth (Bondy and Madsen, 1971), nerve stimulation (Jasinski, Gorbman, and Hara, 1966; Kreutzberg and Schubert, 1973), and probably regeneration all lead to increased rates and possibly amounts of axonal transport. In the rabbit eye, however, no difference of axonal transport was demonstrated between animals reared in the dark and those in the light (Karlsson and Sjöstrand, 1971c). In mammals, substances are transported from the eye to the lateral geniculate body and superior corpora quadrigemina (Sjöstrand and Karlsson, 1969; Karlsson and Sjöstrand, 1971a and b, 1972), and in birds, material travels to the optic tectum (Cuenod and Schonbach, 1971).

Material is transported not only in an orthograde direction from the perikaryon to the nerve terminal, but in a retrograde direction (Kristensson and Olsson, 1973; Bunt, Lund, and Lund, 1974), and the latter may have a specificity for the transport of individual substances (Stöckel, Paravicini, and...
Axonal transport is blocked not only by a deficiency of high-energy phosphate compounds and cold, but also by vincristine and vinblastine which depolymerize neurotubules (Karlsson and Sjöstrand, 1969; James, Bray, Morgan, and Austin, 1970; Sjöstrand, Frizzell, and Hasselgren, 1970), by heavy water which stabilizes neurotubules (Anderson, Edström, and Hanson, 1972), probably by cytochalasin B which depolymerizes microfilaments (Crockos and McClure, 1972; Fernandez and Samson, 1973; McGregor, Komiya, Kidman, and Austin, 1973), and by high concentrations of local anaesthetics (Fink, Kennedy, Hendrickson, and Middaugh, 1972), but not by general anaesthetics (Fink and Kennedy, 1972).

The function of axonal transport is still debated. Jakoubek (1974) produced calculations which indicated that the amount of protein transported was approximately that required to replace axolemmal and axonal proteins. Thus axonal transport might be thought to be simply the process required to replace the normal turnover of structural and other proteins of the cell, the phenomenon of transport being particularly well seen because of the unusual geometry of the neuron. In addition it is worth remembering that by virtue of its elongated shape, the neuron has a very high surface-to-volume ratio, and thus has an unusually high axolemmal protein turnover. Several studies have shown that material moving by axonal transport becomes incorporated into axolemmal and synaptic membranes including synaptic vesicles (Droz, 1973; Koenig, Di Giambertardino, and Bennett, 1973; Giorgi, Karlsson, Sjöstrand, and Field, 1973; Marko and Cuenod, 1973; Krygier-Brévard, Weiss, Muhl, Schubert, and Kreutzberg, 1974; Droz, Rambourg, and Koenig, 1975). The role that axonal transport plays directly in synaptic function is not certain. Blockage of axoplasmic flow causes some of the features of postsynaptic denervation of skeletal muscle (Albuquerque, Warwick, Tasse, and Sansone, 1972). There are several reports of material passing across the synaptic gap to become incorporated into the trans-synaptic cell (Grafstein, 1971; Alvarez and Püschel, 1972; Korr and Appeltauer, 1974; Appeltauer and Korr, 1975), although the amount is relatively small and its functional role uncertain.

In a number of neural diseases the distal parts of the axons suffer the earliest and major degeneration (dying back neuropathies) (Cavanagh, 1964). It seems likely that impairment of axonal transport may be the basis of this distal degeneration. To date the results of studies of axonal transport in axonal neuropathies are conflicting, and their significance uncertain. Pleasure, Mishler, and Engel (1969) reported absent slow axonal transport in the dorsal roots of cats with acrylamide neuropathy, although transport in the peripheral branches and in triorthochresyl phosphate neuropathy were normal. Bird, Shuttleworth, Koestner, and Reinglass (1971) reported impairment of slow axonal transport in mice with an inherited anterior horn cell degeneration (the wobbler). However, Bradley and Williams (1973) found only minor changes of rate and amount of both slow and fast axonal transport of protein in acrylamide, triorthochresyl phosphate, and vincristine neuropathies and concluded that they were not sufficient to explain the neural degeneration. James and Austin (1970) found no abnormality of axonal transport in difluorophosphonate neuropathy. Bradley and Jaros (1973) found no significant abnormality of fast or slow transport of protein in wobbler mice. However, they found an increase in fast and a decrease in slow transport of protein in murine muscular dystrophy where there are abnormalities of the spinal nerve roots (Bradley and Jenkinson, 1973). This finding was extended by Komiya and Austin (1974) who found a decrease in the 'super fast' (2000 mm/day) and an increase in the fast rate of protein transport, while Tang, Komiya, and Austin (1974) found an increased rate of the fast transport of cholesterol and phospholipids in the sciatic nerve of dystrophic mice. Jablecki and Brimijoin (1974) showed that there was a decreased rate of the transport of dopamine-β-hydroxylase in dystrophic mouse sciatic nerve, this enzyme being transported according to their results at slow rates.

Mendell, Saido, Weiss, and Savage (1976) have recently reported a decrease in the fast rates of transport of protein in methyl n-butyl ketone neuropathy, which is associated with marked axonal swelling from neurofibrillary accumulation. It seems likely that in all cases with axonal swellings, including neuraxonal dystrophy, a significant abnormality of axonal transport is to be expected.

There are very few studies of axonal transport in diseases of the eye. Grafstein, Murray, and Ingoglia (1972) studied mice with hereditary degeneration of the visual receptor cells, in which there is a 20 per cent reduction in the number of retinal ganglion cells. The amount of material transported at both fast and slow rates was reduced by about a half, and the rate of movement of slower transport of material was reduced by about one-third. Because the eye has been relatively neglected for the investigation of the part that axonal transport may play in disease, the paper by McLeod (see page 551) is particularly welcome. He mentions that in the experimental situation he has found localized opaque swellings of the retinal ganglion nerve fibres at the edge of infarcts, due to the accumulation of mitochondria, and has gone on to demonstrate similar opaque nerve fibre swellings in human
retinal infarcts where part of the retina remains viable. The opaque axons are situated at the edge of the infarcts, and the accumulation of axoplasm is essentially similar to that seen above a ligature. Although studies of axonal transport are virtually impossible to undertake in man, further studies of axonal transport in degenerative diseases of the retina in animals are awaited with interest.

References

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