Intracellular Transport in Axonal Microtubular Domains
I. Theoretical Considerations on the Essential Properties of a Force Generating Mechanism

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Summary
In this article the mode of force generation of axoplasmic transport is examined on theoretical grounds. We use as criteria the experimental evidence available, the biophysical boundary conditions, energetical feasibility, and earlier theoretical treatments of this topic. The following results are obtained:

1. Comparison of the energy available and the energy required to move organelles through the viscous cytoplasm shows that the viscosities reported preclude such movement of larger vesicles or mitochondria. This suggests that transport should occur in microregions of low viscosity.

2. For ultrastructural, pharmacological, and biochemical reasons such low viscosity regions are expected to be located around microtubules.

3. Out of the 11 theoretical possibilities to generate the driving force we had to rule out four because of obvious violations of verified data. Four other modes of force generation would require one or several additional transport mechanisms to explain the entire phenomenon. Models which imply streaming of low viscosity axonal regions are found to be in good agreement with the experimental findings.

4. The comparison of intracellular sites for the location of the force generating mechanism suggests that they are located at the microtubular surface.

We have shown that the properties of axoplasmic transport fit most easily the concept that the proposed low viscosity domains be located around microtubules and microtubule bundles and that these domains represent streaming regions of cytoplasm. This concept is found to be in agreement with the presented list of criteria any hypothesis of axoplasmic transport must satisfy.

Keywords: Axoplasmic transport; Force generating mechanism; Microtubules; Nerve cell; Saltatory movement; Viscosity.

1. Introduction
The phenomenon of intracellular transport of organelles and soluble cellular components along the processes of nerve cells is called axoplasmic transport. Axoplasmic transport shares a number of its properties with other motile phenomena including saltatory particle movement (Rebhun 1972), mitotic chromosome movement (Brinkley and Brenner 1982), movement in chromatophores (Schlwa 1981) and other types of motility (Morre 1982). Yet, despite intensive research in all these areas, we still lack convincing data about the molecular mechanisms underlying this phenomenon. On the other hand, a great variety of models have been proposed over the years, many of which are still in debate. The general properties of the phenomenon can be compiled from a large body of experimental evidence which has been recently reviewed (Schwartz 1979, Grafstein and Forman 1980, Weiss 1982 a, Weiss 1982 b) so that a list of the most important properties will suffice for this article (Table 1). The characteristic velocities of different molecules and organelles have been summarized by Baitinger et al., (1982).

It is not known whether the properties listed result from one unitary mechanism or whether several mechanisms work simultaneously. However, since most dynamic properties of retrograde and anterograde transport are very similar (Smith 1982) and since differences among different velocity groups are more gradual than abrupt
Table 1. General properties of axoplasmic transport dynamics

1. Virtually all axonal constituents tested have been found to be transported. This includes low molecular weight material, lipids, mucopolysaccharides, tRNA, peptides, proteins (soluble and particulate), all axonal organelles as well as exogenous material (colloidal gold, lectins, tetanus toxin, viruses). Different molecules or organelles move at their characteristic transport velocities ranging from 0.2 to 410 mm/day at 37°C.

2. The apparent selectivity is due to processes in the cell body preceding transport such as packaging, initiation or specific uptake from extracellular space.

3. Transport is directed and may be anterograde (leaving the cell body) or retrograde (towards the cell body).

4. Visible transported organelles move in a saltatory fashion with rapid movements and longer periods of rest. Therefore, the velocity of the population is less than the actual particle saltation velocity.

5. Endogenous or artificial obstructions of the axon cause accumulation of anterogradely and retrogradely transported material at their respective sides. At least part of the anterogradely moving material is reversed at such obstructions.

6. The material separation during rapid transport is roughly size dependent. Particles attain the highest population velocities, while free macromolecules and especially free low molecular weight materials trail behind.

7. Population transport velocities remain constant with time.

8. Transport velocities, especially the $u_{\text{max}}$, are linearly temperature dependent (within physiological limits), but are little influenced by the length or diameter of the axon, functional type of axon, animal species, or by the electrical activity of the neuron.

9. In tracer experiments, a moving asymmetric peak and a tailing region (saddle, plateau) are observed. Peak broadening in rapid transport cannot be ascribed only to diffusion.

(WEISS and GROSS 1982), we have to assume the existence of one mechanism until we are forced by experimental evidence to abandon that concept. Since most of the evidence available, including our own experimental results, is derived from studies on anterogradely moving material of the more rapid velocity range from 20 to 410 mm/day (at 37°C), we will address mainly this aspect of the transport phenomenon. Slow transport (from 0.2 to 20 mm/d) will be discussed in a future report in this series.

In this article we examine possible modes of force generation and the essential properties of the mechanism of force generation. The results of such a study are expected to aid the search for the unknown molecular counterparts of what we call here very generally the “force generating enzymes”. Furthermore, we want to identify those models of force generation which best fit the properties of the phenomenon to use as the basis for our subsequent quantitative theoretical studies. To this end we use as criteria (i) the experimental evidence available, (ii) the biophysical boundary conditions in the axonal cytoplasm (axoplasm), (iii) the energetic feasibility, and (iv) earlier theoretical treatments of the topic (ODELL 1976, RUBINOW and BLUM 1980).

2. Energetic Boundary Conditions

Axoplasmic transport is an active process driven by high energy phosphate, most probably ATP, which is derived from oxidative phosphorylation (for review see OCHS 1976). Diffusion does not contribute significantly to transport beyond the first few millimeters (COPELAND 1976, WEISS et al. 1980). In order to decide which of the many proposed modes of force generation are energetically feasible, we have first to compare their energy requirements with the energy available.

Almost all hypothetical transport mechanisms suggest that the transported material is moved through stationary cytoplasm (SCHMIDT 1968, OCHS 1971, HESLOP 1974, KERKUT 1975, PORTER et al. 1979, STEARNS 1980, ELLISMAN 1982, SMITH 1982). Cytoplasm is, however, known to be a gel of high viscosity. Values between $1.5 \times 10^4$ and $10^6 \text{cP} \times$ (ABE 1965, BIONDI et al. 1972, RUBINOW and BAKER 1979) have been reported for macroviscosities, i.e., viscosities that affect organelles in transit, whereas the microviscosities that affect only low molecular weight solutes are similar to the viscosity of water (HAAK et al. 1976, RUBINOW and BAKER 1979, SCHMIDT et al. 1983). It is, therefore, reasonable to first of all estimate the amount of material that can be moved through stationary axoplasm on the basis of the estimated energy available. Such estimates have not been made by the authors of other transport hypotheses.

Organelle transport allows a relatively simple analysis of the energy requirement. Thus, only organelle motion is considered without implying that only organelles are transported, since at the present time the data do not allow us to assume that all moving material must be

* $1 \text{cP} = 0.01 \text{ Poise} = 1 \text{ g cm}^{-1} \text{s}^{-1}$. 