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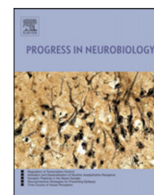

Fast intra-axonal transport: Beginning, development and post-genome advances

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A B S T R A C T

The review describes the initial experiments suggesting a fast intra-axonal transport of transmitter related substances, in addition to the "classic" slow flow. Early experiments were mainly conducted in the peripheral adrenergic system, focusing on transport of amine storage granules, the extent of the vast sympathetic adrenergic system and the importance of axonal transport of amine granules for the adrenergic system. Further, it describes important advances obtained from studies of other neuron systems regarding local axonal protein synthesis, motor proteins and new insights regarding relation between faults in the transport machinery and some neuropathological conditions.

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Foreword: This review article will recall the early experiments indicating the existence of fast intraneuronal transport, the follow-up studies that gave an extended view on the adrenergic system, and the development of methods that allowed systematic comparisons between the fate of different substances and organelles in the peripheral nervous system. Further development of the field opened with progress in molecular biology, and the burst of knowledge following the mapping of the human genome as well as the genome of important model experimental animals. This enabled the "fishing" of molecules of possible importance for various phases of the transport phenomenon. In this later part review articles are referred to as well as some original publications that the author found especially important. A vast number of publications have been published, especially during the last decade, and hopefully the authors who were not cited in this review will have understanding.

The European Union has sponsored much research in intra-neuronal dynamics, and several meetings and conferences have been held. The first was held at Schloss Elmau in Bavaria 1981 and resulted in two monographs: "Axoplasmic Transport", edited by D.G. Weiss and "Axoplasmic Transport in Physiology and Pathology", edited by D.G. Weiss and A. Gorio, printed by Springer Verlag in 1982. The following meeting was a satellite symposium of the 30th congress of the International Union of Physiological Sciences, held at the University of Calgary, Canada in 1986. The proceedings, printed in 1987 as volume 25 of the series "Neurology and Neurobiology", were edited by R.S. Smith and M.A. Bisby and the volume was printed by Alan R. Liss Inc., New York, with the title "Axonal Transport".

Starting in 2002 in Rostock-Warnemunde, Germany ("Molecular Aspects of Axonal Transport – Nerve Growth and Regeneration"), a series of three conferences supported by the European Union were held. The unifying theme was Intra-Neuronal Transport and Communication. The following meetings were held at Kristineberg Marine Station, Sweden ("Molecular Aspects of Neuro-Degenerative Diseases") and in 2005 in Barcelona, Spain ("Molecular Aspects of Ageing and Development, Toxicology and Neuroimmuno- Communication"). Excellent presentations and intense and stimulating discussions took place at these meetings, and the three organizers of these meetings (Brady, Dahlström and Blasi), decided to invite the speakers to submit papers and reviews that were assembled in a special issue of J. Neuroscience Research, vol. 85, number 12, 2007. The reader may consult this issue, bearing in mind that development has advanced a great deal since then.

1. Introduction

1.1. Historical comments

The view on the nervous system has undergone dramatic changes since the beginning of the 20th century. Due to the absence of morphological techniques to observe small morphological details below 1 μm, it was assumed that the autonomic peripheral nervous system was a diffuse syncytium, which embedded presumed effector organs in a non-defined fluid-like medium. Myelinated fibres could be observed and traced, using lipid stains, like Sudan black or osmium tetroxide, which stained the myelin sheaths. But, the autonomic nerves, being non-myelinated, were eluding observation.

The peripheral autonomic nervous system (ANS) was classically divided in the sympathetic and the parasympathetic system on a physiological basis. In 1904, Elliott (1904), experimenting on frogs, suggested that adrenaline (A = epinephrine) was the chemical substance that mediated the effect of nerve impulses from sympathetic nerves to the effector cells. After the concept of chemical neurotransmission was accepted, these nerves were named "adrenergic" by Sir Henry Dale in 1933 (Dale, 1933), the suffix – ergic meaning "using as transmitter". In mammals the peripheral sympathetic adrenergic nerves use noradrenaline (NA = nor-epinephrine) as transmitter instead of A, as demonstrated by Ulf von Euler in 1946 (Euler, 1946). In the central nervous system (CNS), where NA-containing as well as A-containing neurons exist; the terms adrenergic and noradrenergic therefore have to be used when dealing with the brain.

Von Euler's studies, published in 1946 (Euler, 1946), demonstrated that tissue homogenates from sympathetic ganglia and sympathetically innervated tissues, contained a substance that pharmacologically was identified as NA. However, the exact cellular localization of this catecholamine (CA) was not known, since microscopically identified structures that could be connected to a transmitter function had never been observed. However, in 1946, Hillarp (1946) was able to present microscopic pictures of a widely ramified network of thin unmyelinated fibers using a special modification of the, at the time, generally practiced methylene blue staining protocol (Fig. 1a). Also sympathetic ganglia were found to contain such nets of varicose fibers (Fig. 1b). Hillarp, in his thesis of 1946, presented strong arguments that this net of varicose fibers represented the morphological components that mediated transmitter effects in autonomically innervated tissue (Hillarp, 1946, 1959).

1.2. The histochemical fluorescence method of Hillarp and Falck

The full structure of the adrenergic neuron was clarified in the 1960s, when Falck et al. (1962) succeeded in developing a histochemical fluorescence method that made possible, for the first time in scientific history, the exact cellular and intracellular localization of a transmitter. This histochemical fluorescence method used gaseous paraformaldehyde to initiate a ring closure of the side arm of the CA molecule, resulting in a strongly fluorescent isoquinoline. After using this method on an air dried preparation of a rat's iris a brilliantly green fluorescent varicose network of NA containing adrenergic nerve terminals could be seen in the fluorescence microscope (Fig. 2a). This method could also demonstrate the other CAs (dopamine-DA- and A) with similar fluorescence spectra, as well as serotonin (5-HT), whose reaction product emitted a strong yellow fluorescence (see Jonsson, 2009) in nerve cells and in mast cells (Fig. 2b). The method was subsequently used for many kinds of tissues, and was the basis for the first mapping of the neuronal pathways in the brain that use NA, DA or 5-HT as transmitter (see Fuxe et al., 2009). These studies were carried out during 1962–1969 at the dept. of Histology, Karolinska Institute, in Stockholm, Sweden. (for a narrative description of the development of this method see Dahlström and Carlsson (1986) and Dahlström (1996)).

2. The initial observations in lesioned nerve fibers, suggesting fast transport of amines

During the mapping of the central NA, DA and 5-HT containing pathways, we (Dahlström and Fuxe) made use of several methods for tracing nerve cells bodies to their nerve terminal areas. It was known from earlier light microscopic studies that nerve fibers reacted in typical ways to trauma, for instance, after sectioning their axons. The phenomenon was known as Wallerian degeneration (Waller, 1852). Some days after the trauma the severed axon shrunk, the distal stump disintegrated, the remains removed by macrophages, and the nerve endings supplied by the cut axons degenerated. The cell body appeared swollen (chromatolysis), and the axon stump still connected with the cell body increased in diameter.

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