Neurochemistry

Is GABA the neurotransmitter for some photoreceptors?

from Stephen Yazulla

A SERIES of papers published last year in *Nature* and discussed in these columns[1] caused major revision of a long-held hypothesis about photoreceptor transduction. Now, again in *Nature*, photoreceptors are the focus of another controversy. Nishimura *et al.* on page 753 of this issue[2] report that the synaptic terminals of about 25 per cent of the rod and cone photoreceptors in the monkey retina show immunoreactivity to antisera against γ-aminobutyric acid (GABA) and its biosynthetic enzyme L-glutamate decarboxylase (GAD). These authors suggest that GABA may be a neurotransmitter in a select population of rod and cone photoreceptors. If correct, the report is highly controversial: either it will require a major revision of our views on photoreceptor synaptic physiology; or, if incorrect, it means that the use of immunocytochemical labelling as a technique to localize neurotransmitter systems in neural tissue must be questioned.

Vertebrate photoreceptors constantly release transmitter in the dark. The effect of light is to hyperpolarize the photoreceptor, with a consequent reduction in transmitter release[3]. There is general agreement that the transmitter (s) of vertebrate photoreceptors are depolarizing (excitatory) to horizontal cells (second-order neurones) — a leading candidate for such a transmitter is the excitatory amino acid L-glutamate[4,5]. GABA, however, tends to function as a hyperpolarizing (inhibitory) neurotransmitter in many parts of the nervous system, including the retina[6]. Thus, the implication of GABA in photoreceptor transmission by Nishimura *et al.*[2] appears diametrically opposed to the generally accepted hypothesis, which is founded on a very large database obtained by electrophysiological, biochemical and pharmacological means in the retinas of many vertebrate species[7]. It is unfortunate that the present data were obtained in monkey retina, a preparation for which there are no supporting physiological data, nor are there likely to be any in the forseeable future.

To establish a chemical as a neurotransmitter, several criteria must be fulfilled, of which the demonstration that the candidate and its biosynthetic enzyme are present, as suggested in the present report, are only two. Primate retinas, because of cost, supply and viability *in vitro*, are much less amenable to the kinds of manipulations required to obtain supportive physiological data needed to satisfy criteria such as measurement of transmitter release and physiological action on postsynaptic neurones. Herein lies the value of non-primate and non-mammalian retinas for the study of retinal function.

A further issue raised by the new report involves the validity of immunocytochemical protocols to mark or label neurotransmitter-specific pathways. There has recently been an explosion in the number of published papers that use immunocytochemical localization techniques to identify putative transmitter-specific neurones and pathways. Despite the care with which many antisera are produced and characterized, there are a host of posssible artefacts that can lead to false-negative or false-positive results. Artefactual staining can be produced, for example, by cross-reactivity of the antisera with tissue proteins, impurities in the antisera and nonspecific staining of necrotic or damaged tissue.

The data of Nishimura *et al.* are adequately controlled for such artefacts, with reliable and apparently valid staining in a class of neurones in which there is no other evidence for GABAergic transmission. If one chooses not to accept the data of Nishimura *et al.*, then doubt must be cast on all existing published immunocytochemical data for which adequate controls appear to have been done. The degree of such concern, which does exist, seems to depend on the transmitter system under study. For each system, many different antisera are available from different laboratories that use different protocols; they can be directed against the degradative or synthesizing enzymes of the transmitter, its receptor molecule or the transmitter itself. Thus, details in the localization of a transmitter system often differ depending on the antisera used, although the different antisera were presumably raised against the same antigen.

As an example, the GABAergic system in the retina has been studied using antisera against the GABA biosynthetic enzyme GAD. There are at least six GAD antisera currently in use which were

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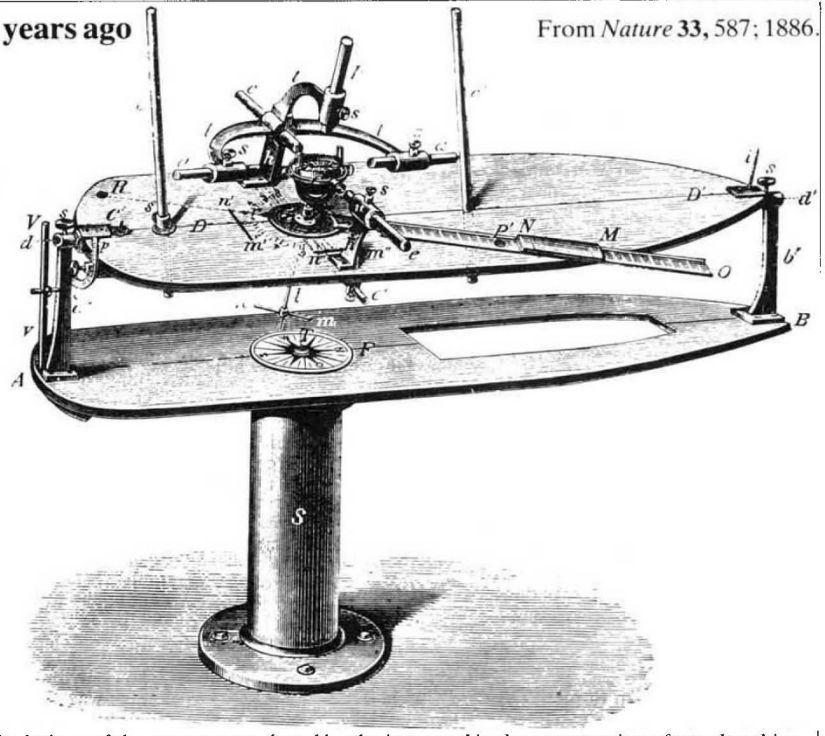

THE deviations of the compass produced by the iron used in the construction of wooden ships was a source of considerable perplexity to the navigators of the last and early part of the present centuries; and no sooner were these difficulties overcome than the building of ships entirely of iron commenced. One of the most important contributions to magnetical science as regards iron ships was made by Sir George Airy (late Astronomer-Royal) in a paper published in the *Phil. Trans. Royal Society* for 1830 who invented the system of correction by magnets and soft iron, which is universally practised in the present day. This system of correction, coupled with the analysis described in the "Admiralty Compass Manual," provides the means of correcting a compass even in position on the 'tween decks of our armour-plated ships of war. Different forms of models have been used for instruction in the magnetism of iron ships considered. The illustration above is a woodcut of the original model taken from Paper No. 2 of the *Archiv der Deutschen Seewarte*, VI. Jahrgang, 1883, where an account of the experiments to be made with it is given in full detail.