A Dynamic Model of a Two-Synapse Feedback Loop in the Vertebrate Retina

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Abstract

The theoretical properties of synapses such as those in the retina which operate on graded potentials are developed using work on tetrodotoxin-treated synapses as a basis. A linearized model of a two-synapse negative feedback loop analogous to the bipolar-amacrine feedback loop in the retina possesses a frequency response which develops an increasingly prominent resonance peak at higher input levels and under some circumstances shows instability. Psychophysical studies have shown that the visual system also exhibits this behaviour suggestive of progressive underdamping in a harmonic oscillator. Evidence in favor of the hypothesis that resonance originates in the loop is presented, the conclusions being that the loop functions to tune the retina to a range of temporal frequencies.

Introduction

The vertebrate retina contains an exquisite arrangement of synapses at the output aspect of the bipolar cell, a radially oriented, so-called short-axon neurone interposed between the receptors on the one hand, and the main output neurone of the retina—the ganglion cell—on the other (Dowling and Boycott). One half of a curious double or bifurcated synapse transmits the output signal of the bipolar cell to the ganglion cell, while the other half diverts a replica of this signal to a process of an ancillary short axon neurone, the amacrine cell, in this case tangentially oriented (and which receives similar inputs from a number of spatially distributed bipolars). This amacrine cell process immediately synapses back onto the bipolar in close proximity to the double synapse, thus forming a loop no greater than 1 \mu in length, and as such, presumably subserving a highly specific function (Fig. 1). Despite Walls' dictum that "everything in the vertebrate eye means something" none of the functional specificity demanded by the anatomy has yet been assigned to the loop. One role suggested by Dowling was that it exerted the rapid type of gain control seen experimentally in studies of light adapta-

Fig. 1. Diagram of synaptic relationships between retinal elements: receptors (R), bipolars (B), ganglion cell (G), horizontal cell (H), amacrine cell (A). Arrays of receptors and bipolars are represented by a single cell so that the degree of divergence or convergence of the signal is not shown. Direction of synaptic transmission indicated by either continuous arrows, or interrupted when synaptic function is uncertain or inconstant. Synapses having a presynaptic origin in radial cells in general have a positive effect on signal transmission whereas for tangential cells the converse is in general true. Also shown is a diagram based on electronmicroscopy of the bipolar terminal with amacrine and ganglion cell processes seen in cross section. Presynaptic aggregates of vesicles and membrane thickening serve to delineate synapses. In the circuit diagram is shown the model representation of bipolar and amacrine "cells" as (semi-infinite) RC cables terminated by the equivalent circuit of postsynaptic membrane. Depolarization of one terminal operates on the variable conductance of the other (see text).

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output of many, if not all, bipolars is sure evidence of its importance. It is the purpose of this paper to attempt to answer the question as to function by shifting the emphasis to the dynamic properties of the loop, there being a considerable amount of evidence, for example, of oscillatory phenomena in the retina suggestive of a feedback loop. Because of experimental limitations, the approach is of necessity theoretical through use of a model which, nevertheless, is anchored as firmly as possible in the experimental data of synaptic and retinal physiology and psychophysics. Progress reports of this work have been reported briefly elsewhere (Abernethy, 1970, 1971).

The Model

The major assumptions and properties of the model are described below; the mathematical development is left to the appendix. The basic assumption is that these short-axon neurones transmit signals by means of graded potentials, rather than all or none “spikes”, and that synapses respond to these potentials by graded changes in rate of transmitter release. This assumption is compatible with the fact that “slow” potentials dominate electrophysiological recordings from these cells. Such spikes as do occur are always superimposed on slow potentials and, furthermore, selective blocking of spikes by tetrodotoxin does not interfere with the transmission of light-induced potentials to the ganglion cell (Murakami and Shigematsu). Accordingly the bipolar cell, the amacrine cell process, and ganglion cell dendrite, are all assumed to function as simple RC cables of uniform radius and semi-infinite extent. Two phenomena have been excluded for simplicity, namely, voltage-dependent conductance changes and the stochastic nature of transmitter release. The model is based on bipolars which depolarize at the “on” of light but hyperpolarizing bipolars could be included if it is assumed that they are equivalent to bipolars depolarizing at the “off” of light. Amacrine-to-ganglion synapses have also been excluded from this treatment.

Synapses are assumed to consist of two types of specialized nerve membrane forming the boundaries of a space, the synaptic cleft. The membrane is specialized presynaptically for depolarization-coupled transmitter release and postsynaptically for transmitter-induced conductance changes. The contents of the space are well mixed, i.e., there is no transmitter diffusion delay. A deterministic synaptic transfer function relating input (presynaptic) and output (postsynaptic) depolarization has been developed and based as far as possible on experimental work. Two first order differential equations describing transmitter release and the effect of transmitter on postsynaptic membrane respectively have been used [Eqs. (6), (7a)]. The first equation embodies the exponential relationship between rate of transmitter release and presynaptic depolarization first described by Liley. The second is analogous to an equation developed for drug-receptor interaction (Leibovic and Sabah) and assumes that opening of conductance channels in the postsynaptic membrane is proportional to the product of free transmitter concentration and the fraction of receptors “unoccupied”, whereas channel closure is dependent on the fraction of receptors “occupied” by transmitter (as might be expected if destruction of transmitter results from a membrane-bound or intracellular enzymatic process). Finally, postsynaptic conductance changes are converted to depolarization using cable theory. Representation of postsynaptic membrane is simplified by using a version of the standard nerve membrane equivalent circuit comprising a variable conductance “channel” in series with an ionic battery (Rall). The distinction between excitatory and inhibitory synapses is assumed to rest on the magnitude and polarity of the e.m.f. of this battery, being large and positive for excitatory and small and negative for inhibitory synapses. This equivalent circuit is assumed to terminate the proximal end of a semi-infinite cable representing the relevant post synaptic neurone.

Steady State Analysis

Synaptic Transfer Function

Representing a synapse in the fashion described above, the effect of progressive increase in the rate of transmitter release on postsynaptic conductance gives rise to postsynaptic depolarization which is an S-shaped function of presynaptic depolarization [see Eq. (11) and Fig. 2]. The shape of the curve is determined essentially by two parameters both of which can be assigned values which are more or less in accord with physiological facts. One parameter, b, defines the maximal slope of the middle segment of the S-curve and the other, a, shifts the curve along the input axis. This theoretical steady-state curve can be fitted satisfactorily to experimental curves (albeit non-steady-state) derived by Katz and Miledi (1967) using graded 1, or 18 msec input pulses and measuring the peak output potential of tetrodotoxin-treated preparations of the squid giant synapse. The experimental curves differ from the theoretical only in that they begin to saturate at slightly lower input potentials. Two sets of a, b values derived from data