The Inhibition of Retinal Ganglion Cells by Catecholeamines and γ-Aminobutyric Acid

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Summary. 1. L-Dopa, the metabolic precursor of Dopamine, was found to depress the amplitude of the evoked potential in the optic tract, when applied intravenously.

2. Electrophoretic application of Dopamine on retinal ganglion cells produced inhibition of spontaneous and light driven activity, increase of latency of light evoked excitation and occasional suppression of the antidromic invasion. Dopamine and Glutamate interacted in an antagonistic manner.

3. Noradrenaline and D-Amphetamine were likewise effective in depressing spontaneous and induced activity of ganglion cells. Serotonin was ineffective or weakly depressant.

4. The effect of electrophoretically applied GABA was similar to that of Dopamine. It differed by a faster onset, quicker reversibility and slight diminution with time.

5. Substances suspected to be transmitters by virtue of their presence in the retina are thus shown to produce the expected pharmacological effects.

Key-Words: Catecholamines — GABA — Microelectrophoresis — Retinal Ganglion Cell Activity.

HÄGGENDAL and MALMFORS (1965) interpreted the enhanced light-sensitivity of Reserpin-treated animals as due to blockade of aminergic retinal inhibitory mechanisms following depletion of catecholamines. Since Dopamine (DA) was found to be the main catecholamine in the retina [13], it was suggested that inhibitory transmission mechanisms might be dopaminergic [13]. In addition to DA, γ-aminobutyric acid (GABA) was proposed as an inhibitory retinal transmitter on the basis of its presence in retinal layers [19]. Inhibition of light induced and spontaneous activity of retinal neurons should therefore result from application of DA or GABA. Aim of the present study was to demonstrate such an effect. DA does not readily pass the blood-brain barrier [11] and must be applied either directly by iontophoresis, or indirectly by systemic injection of its precursor Dopa (1-3.4 dihydroxyphenylalanine). The latter penetrates the blood-brain barrier and is assumed to enter

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adrenergic nerve terminals causing increased synthesis and overflow of the transmitter [6]. Both methods of DA application were used in the present study. GABA, whose depressant action on retinal neurons after intraarterial injection was demonstrated previously [21], was applied electrophoretically.

**Methods**

Cats were anaesthetized by Pentobarbital (30—50 mg/i.p.), kept in a stereotactic headholder, immobilized by Flaxedil and given artificial respiration. Expiratory CO and body temperature were monitored. Pupils were dilated by Atropine. In a first series of experiments monopolar steal electrodes (tip diameter 50 μ) were stereotactically inserted into the optic tract, in order to record mass responses (evoked potentials) to bright flashes (intensity 0.07 l/flash; duration 100 μsec). The evoked potentials went into a conventional cathode follower-preamplifier system and were displayed on the oscilloscope. Responses to a series of 250 flashes were averaged by conventional averaging techniques (Cat 1000). Electoretinograms were recorded from the corneal surface by means of silverball electrodes. A dose of 10—70 mg/kg L-Dopa (Fluka) was dissolved in 10—15 ml warm physiological saline and injected slowly during 3 minutes into the femoral vein. Equal amounts of physiological saline were given as controls.

In a second series of experiments drugs were electrophoretically applied. Cornea and lens were removed; under visual guidance the multibarrel electrode was driven through the vitreous body and inserted into the retina by means of a micromanipulator. Multibarrel electrodes were prepared using methods previously described by Henz et al. (1965). Pipettes were boiled in distilled water; then the water was replaced as far as possible by the test solutions. Filled micropipettes were stored at 4°C and used 24 hours later. The microelectrophoretic method of controlling efflux of substances from drug containing barrels has been described previously in detail [17].

Extracellular spikes were recorded from single retinal units by means of a barrel containing 4 M NaCl solution. The other 3 barrels contained test solution and 3 M NaCl respectively. The latter served as a control for current effects. The neuronal signals were fed into a conventional preamplifier and displayed on the oscilloscope, where photographic records were taken from. Action potentials were converted into standard pulses, which were observed simultaneously with the spikes and counted by a rate meter. Thus firing frequency was recorded continuously on a paper recorder. Electrophoretic currents were measured with an accuracy of ± 1 nA.

For differentiation of optic nerve fiber- and ganglion cell potentials the following criteria were used:

1. Spike form and polarity [3]
2. Intraretinal location of recording site indicated by distance from retinal surface and by polarity and amplitude of the b-wave of the ERG [5]
3. Responsiveness to Glutamate

Spontaneous activity was recorded during a background illumination of 1 Lux. Light responses were evoked by intermittent diffuse illumination of the retina (duration 200 msec; intensity 10 Lux). Shocks (0.1 sec; 1/sec) were delivered by a concentric stimulation electrode, which was placed upon the optic nerve head.

Substances: Dopamine hydrochloride (0.5 M; pH 3); L-Noradrenaline hydrogen-tarttrate (0.5 M; pH 4); D-Amphetamine sulfate (0.2 M; pH 4); γ-aminobutyric acid (2 M; pH 4.5—5); monosodium-Glutamate (3 M; pH 8.4); Serotonin creatinine-sulfate (0.2 M; pH 4.0—5.0).