Effects of Some Psychotropic Drugs on the b-Wave of the Electroretinogram in Isolated Rabbit Retina

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Abstract—The role of dopaminergic and cholinergic functions in the genesis of an electroretinogram is unclear. The present study was carried out to elucidate the direct actions of some psychotropic drugs in isolated rabbit retinas. Methamphetamine and apomorphine decreased dose-dependently the b-wave amplitude at a dose of 10^{-7} to 10^{-5} g/ml. On the other hand, chlorpromazine and haloperidol, as well as atropine and amitriptyline, increased dose-dependently the b-wave amplitude at the same dose range. These data support the idea that dopaminergic and cholinergic systems play an important role in the genesis of the ERG.

Recently, histochemical and neurochemical studies have demonstrated that the dopaminergic, cholinergic and GABAergic neurons locate in the mammalian retina, and that dopaminergic amacrine cells make synapses with other cholinergic and GABAergic amacrine cells in the inner plexiform layer of the retina (1–4). The role of these neurons in the genesis of an electroretinogram (ERG), however, is still unclear. Some neurotransmitters (NTMs) cannot enter the central nervous system (CNS) through the blood-brain and blood-retina barriers (5). In addition, their metabolic rate is fast and the duration of effects is very short. Therefore, for investigating the function of the NTMs in the CNS, their agonists, releasers, precursors, uptake inhibitors, depletors and antagonists are often used. Several reports have been published with regard to the effects of psychotropic drugs on ERG in mammalian animals. These drugs, however, affect not only the retina and other CNS systems but also affect the circulatory system. It has been reported that changes in O_{2} and CO_{2} concentrations and Na^{+} and K^{+} ion levels in the circulatory tissue fluid also influence the ERG b-wave (6, 7). In the isolated mammalian retina, few studies of psychotropic drugs have been reported except for those on the retinal GABAergic system (8, 9). The present study was carried out to elucidate the direct actions of psychotropic drugs using isolated retina and to get a deeper understanding of possible correlations between the genesis of ERG and dopaminergic and cholinergic neurons in the mammalian retina.

Male albino rabbits, 6 months old, were purchased from Shimizu Laboratory Supply. The animals were housed in a room having a constant 12/12 hr light-dark cycle for 1 month. The pupils of both eyes were dilated by instillation of 0.5% tropicamide. The animals were then anesthetized with urethane (1 g/kg, i.p.) and were dark-adapted for 3 hr before the operation. The eye was enucleated under dim red light and hemisected, and the vitreous body was lifted away. The posterior half of the eyecup which was designated as the isolated retina was maintained at 31°C in the perfusion medium described previously (9). ERG recordings were conducted in an electrically shielded dark room, using a Zn-ZnSO_{4} electrode (9). A photic stimulator (SLS4100, Nihon Kohden) was used to present a xenon lamp flash.
stimulus of 0.3 joule in intensity. The lamp was placed about 30 cm in front of the isolated retina where the illumination was about 4.7 lux sec (stroboscopic photometer II, Minolta). ERGs were amplified by a bio-physioamplifier (1205D, Sanei), transformed A/D by a signal processor (7T07A, Sanei) and plotted with an X-Y recorder (8U11, Sanei). The time constant of the amplifier was 0.3 sec for recording the b-wave.

Stable ERGs with less than 5% variation resembling in vivo ERG could be recorded from the isolated rabbit retina for about 1 hr or more. A typical ERG in the isolated rabbit retina is shown in Fig. 1. All drugs tested were dissolved in saline and added accumulatively at intervals of 10 min. Photo stimuli were given at intervals of 2 min. ERGs were recorded 10 min after the addition of drugs. Three or more preparations were used to test the dose-response curve of each drug using the orthogonal contrasts after the two-way analysis of variance with the preparation and the dose as factors and to calculate the mean of each dose (10). Methamphetamine (MAPT), a dopamine (DA) releaser, at concentrations of $10^{-7}$, $10^{-6}$ and $10^{-5}$ g/ml, decreased the b-wave amplitudes to 86.6%, 66.8% and 64.3% of the control before the addition, respectively (Fig. 2A). Apomorphine (APD), a DA agonist, decreased the b-wave amplitude as potently as MAPT. In contrast, chlorpromazine (CPZ) and haloperidol (HAL), DA antagonists, increased the b-wave to 143.3% and 125.2% of the control at the maximum concentration of $10^{-5}$ g/ml, respectively (Fig. 2B). At the same concentration, atropine (ATP), an anticholinergic drug, and amitriptyline (AMT), a monoamine uptake inhibitor, also increased the b-wave amplitude as potently as DA antagonists, HAL and CPZ.

Starr (11) observed using an in situ perfusion technique that local administration of DA decreased the b-wave amplitude in rabbits. Jagadeesh et al. (12, 13) also showed that APO (i.v.) decreased the b-wave amplitude, while CPZ (i.v.) increased it in rabbits. These in vivo and the present in vitro studies suggest that dopamine-like substances decrease the b-wave amplitude, while dopamine antagonistic drugs increase it in rabbits. However, it has been reported that systemic administration of levo-dopa (precursor of DA) together with carbidopa increased the b-wave amplitude in humans and rats (9, 14, 15), and that thioridazine also decreased it in humans (16). McMillen and Shore (17) studied the effect of HAL on the brain caudate nucleus neurochemically and observed that HAL increased the content of DA metabolites and decreased that of DA in rats, but in rabbits, there was no change. Thus, they pointed out species differences...
between these animals. Many reports have been published concerning electrophysiological and neurochemical studies in the mammalian retina, but most of them employed rabbits as the experimental animals. Considering this, comparative studies between rabbits and other species appear to be important in studying retinal function.

AMT and CPZ increased the b-wave amplitude like ATP in the present study, but these drugs are known to possess potent anticholinergic effects (18, 19). An increase in the b-wave amplitude by an anticholinergic drug was also confirmed in humans (16). Fornaro et al. (20) reported that imipramine, which has a weaker anticholinergic activity and a stronger inhibitory activity on monoamine uptake than AMT, caused no changes in the ERG of human. Considering these reports, it is suggested that the increasing actions of AMT and CPZ on the b-wave amplitude may not be caused by either their monoamine uptake inhibition or antagonistic effect on DA, but may be due to their anticholinergic effect. The findings in this study are in agreement with those by systemic administration, and they suggest that these drugs may directly affect the rabbit retina. However, as psychotropic drugs possess antiserotonergic and antihistaminergic activities (19) in addition to dopaminergic and anticholinergic activities, the effects of these psychotropic drugs on ERG remain to be further studied pharmacologically.

Fig. 2. Effects of methamphetamine (A) and chlorpromazine (B) on b-wave in isolated rabbit retina. The retinogram was evoked by 0.3 joule light flashes at intervals of 2 min. Vertical calibration bar, 50 μV; horizontal time bar, 80 msec. \( \Uparrow \): photo stimulus. a: a-wave. b: b-wave.

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