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Differential Effects of Low Versus High Doses of Apomorphine on Retinal Dopamine Metabolism in Light- and Dark-Adapted Rabbits

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DRUMHELLER, A., H. HENNI, G. LAFOND, J. R. BRUNETTE AND F. B. JOLICOEUR. *Differential effects of low versus high doses of apomorphine on retinal dopamine metabolism in light- and dark-adapted rabbits.* PHARMACOL BIOCHEM BEHAV **50**(1) 83-90, 1995. – Previous electrophysiologic results from this laboratory indicate that apomorphine exerts a differential dose-related effect on rabbit electroretinograms, with low doses increasing the b-wave and higher doses decreasing this parameter. Results were interpreted as reflecting apomorphine's agonistic properties at two different receptors: 1.0 mg/kg acting at the postsynaptic site, and the lower dose, 0.01 mg/kg, preferentially stimulating inhibitory autoreceptors. The purpose of this experiment was to investigate further this hypothesis by determining retinal levels of dopamine, dihydroxyphenylacetic acid, and homovanillic acid in retinas of light- or dark-adapted rabbits treated with saline, 1.0, 0.1, or 0.01 mg/kg apomorphine intravenously. Results indicate that in dark-adapted rabbits only the highest dose tested, 1.0 mg/kg, decreased dopamine concentrations. In animals exposed to light, the lowest dose tested, 0.01 mg/kg, significantly reduced dopamine and metabolite levels, whereas the highest dose unexpectedly increased retinal dopamine turnover. Results are discussed in terms of receptor sites and the influence of lighting conditions

Retina Dopamine Autoreceptors Apomorphine Dopamine metabolism

EVIDENCE from a variety of electrophysiologic, pharmacologic, and biochemical studies strongly suggests that dopamine functions as an important inhibitory transmitter in the mammalian retina (11,12,29,49,50,58). In many species, including rat and rabbit, dopamine appears to be localized within a subset of amacrine cells (12,16,24), where its synthesis and turnover rate are regulated by light exposure (3,13,26,44,51). Binding experiments coupled with studies on agonist and antagonist effects on dopamine turnover and cyclic AMP accumulation suggest the existence of two types of dopamine receptors classified as D_1 and D_2, depending on their interaction with adenylate cyclase within the central nervous system (15,33,34,48). Both types of receptors have been identified in retinas of various mammalian and nonmammalian species (55). The existence of D_1 receptors, which are positively coupled to adenylate cyclase in retina of several species including rat and rabbit, has been convincingly demonstrated (4,5, 17,40,52,54). However, results of experiments designed to identify D_2 retinal receptors negatively linked to adenylate cyclase point to marked species differences. Although such receptors have been uncovered in several species including rat (23,52), frog (27), and hen (41), their presence has not been confirmed in rabbit (42,43,53). Nonetheless, pharmacologic experiments performed in rabbits have provided cogent data suggesting that dopamine-containing amacrine cells possess presynaptic autoreceptors of the D_2 type mediating a negative feedback inhibition that modulate the synthesis and/or release of dopamine (14,15,45).

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Results from various behavioral, biochemical, electrophysiologic, and neurochemical studies suggest that relatively low doses of apomorphine (a mixed D_1/D_2 receptor agonist) preferentially stimulate presynaptic autoreceptors, whereas higher doses stimulate postsynaptic sites (2,22,57). In a previous experiment (47), we examined the electrophysiologic consequences of pre- vs. postsynaptic receptor stimulation by investigating the effects of selective doses (0.01, 0.1, and 1.0 mg/kg) of apomorphine on the dark-adapted rabbit electroretinogram (ERG). Results indicated that the intermediate dose, 0.1 mg/kg, had no significant effect on either the latency or amplitudes of the a- and b-waves. The smallest dose of the drug significantly increased b-wave amplitudes, a result consistent with decreased dopaminergic transmission (46). Conversely, the largest dose of the dopamine agonist significantly reduced the b-wave amplitudes, implicating enhanced dopaminergic activity. These opposite effects suggest that in the retina, a relatively higher dose of apomorphine mimics the effects of dopamine at postsynaptic receptors, whereas the lower dose inhibits the action of the transmitter, possibly via interaction with presynaptic inhibitory autoreceptors. The present experiment was undertaken to better elucidate the mechanisms underlying these electrophysiologic changes by examining the effects of the same doses of apomorphine administered intravenously (IV) on levels of dopamine (DA) and its main metabolites, dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), in rabbit retinas. As dopamine metabolism is modulated by lighting conditions, we investigated the neurochemical effects of the drug in both light- and dark-adapted animals.

METHOD

Animals

Forty-eight adult, pigmented rabbits weighing approximately 2.5 kg were maintained on a 12-h light–dark cycle for at least 1 week before experimentation. Animals were removed from their home cages 3–4 h after the onset of the light cycle and were divided into two equal groups. One group was adapted to the light (approximately 500 l×) for 60 min before injection, and the other was dark-adapted for the same period. Fifteen minutes before the end of the adaptation period, animals were lightly anesthetized with pentobarbital sodium. For each lighting condition, different groups of animals (n = 6) received IV injections of either 0.9% NaCl (control group), 0.01, 0.1, or 1.0 mg/kg apomorphine in a volume of 1 ml. Thirty minutes after drug administration, animals were sacrificed and both eyes were enucleated and placed on ice. The cornea, iris, lens, and vitreous were removed, and the retina gently peeled off and stored at −80°C. For dark-adapted animals all manipulations were performed with the aid of a dim red light.

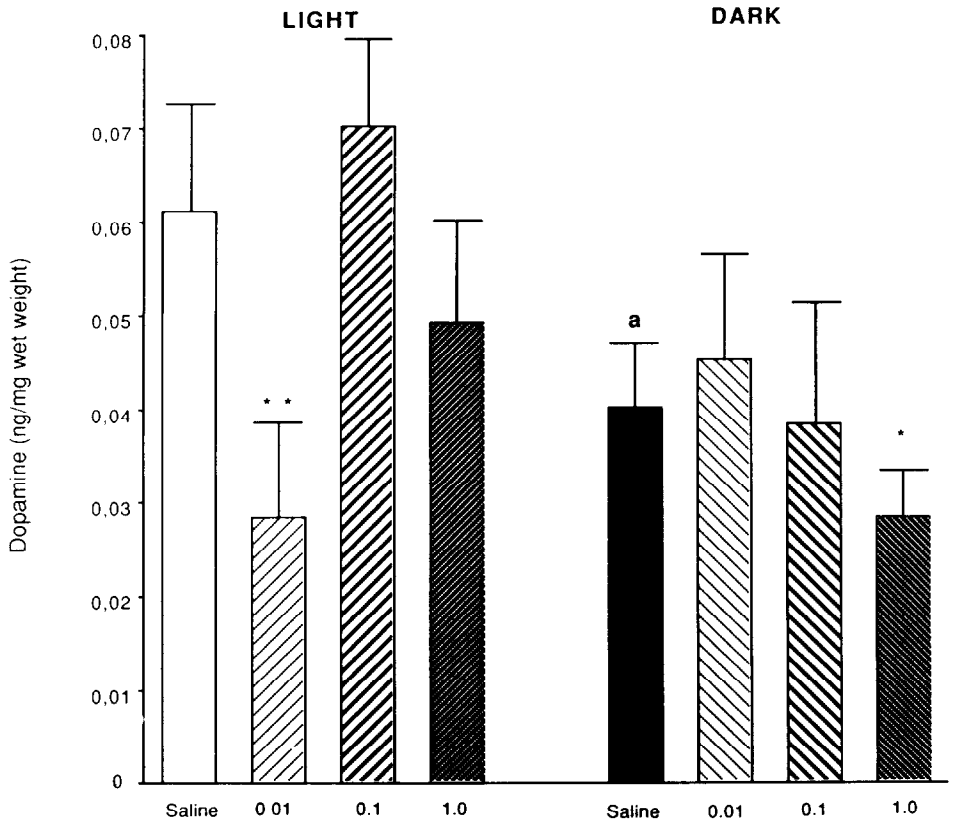

FIG. 1. Dose effects of 0.01, 0.1, and 1.0 mg/kg apomorphine vs. saline-treated controls on retinal dopamine concentrations measured in both light- (left panel) and dark- (right panel) adapted rabbits. Results are expressed as mean ± SD in nanograms per milligram wet weight. Significant differences from respective saline-treated controls are indicated by asterisks. *$p < 0.05$. **$p < 0.01$. [a]Significant differences between control groups (saline–light vs. saline–dark).

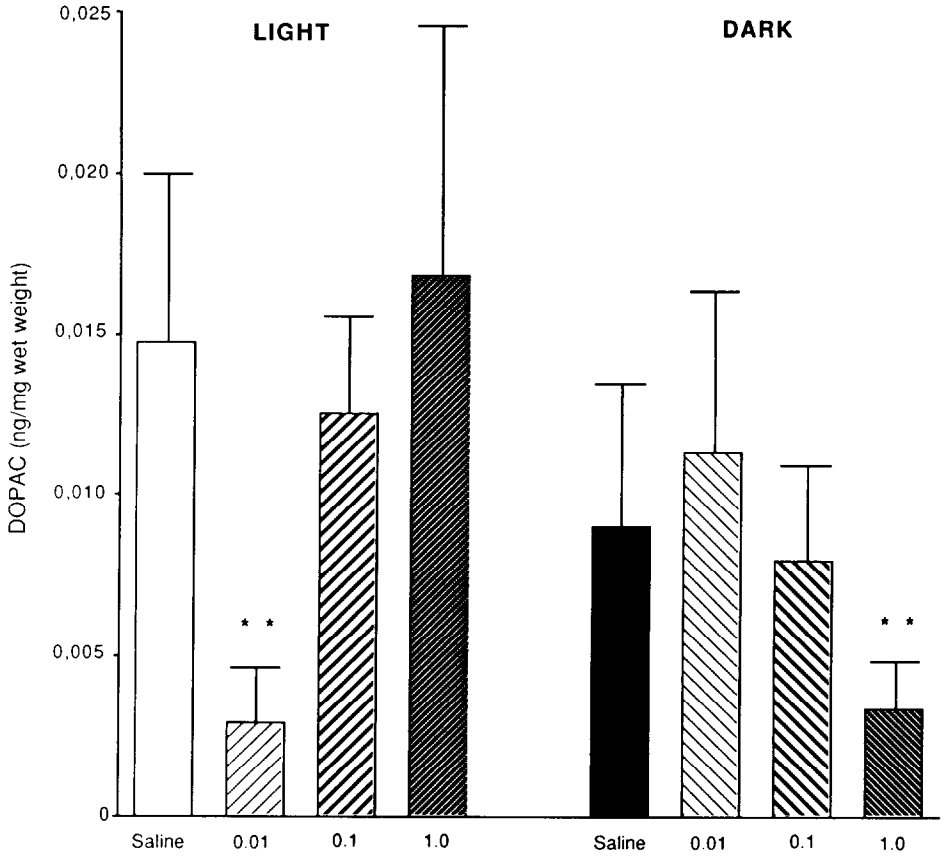

FIG. 2. Dose effects of 0.01, 0.1, and 1.0 mg/kg apomorphine vs. saline-treated controls on retinal DOPAC concentrations measured in both light- (left panel) and dark- (right panel) adapted rabbits. Results are expressed as mean ± SD in nanograms per milligrams wet weight. Significant differences from respective saline treated controls are indicated by asterisks. $*p < 0.05$. $**p < 0.01$.

Biochemical Determinations

Retinas from each rabbit were combined and homogenized in 400 μl $HClO_4$. After centrifugation the supernatant was aspirated and analyzed immediately by HPLC (Beckman Instruments, San Ramon, CA) for the contents of DA, DOPAC, and HVA. Dopamine and its metabolites were separated isocratically on a 4 mm × 10 cm, 3 μ reverse-phase column protected by a short precolumn. The column eluate was monitored by an LC 2A electrochemical detector (BAS, West Lafayette, IN) equipped with a glassy carbon electrode and operated at an applied potential of 0.65 V. The eluting solvent was a mixture of 0.1 M sodium acetate, 0.02 M citric acid, and methanol (92/8 v/v), pH 4.0, containing 0.3 mM EDTA and 0.05 mM sodium octylsulfate. Analyses were performed at room temperature at a flow rate of 1.5 ml/min.

Contents of retinal DA, DOPAC, and HVA were quantified by comparing peak heights obtained from injections of retinal homogenates to those obtained from injection of known quantities of standard solutions. Injection volumes for standards and retinas remained constant at 80 μl.

Data Analysis

All data were analyzed by two-way analysis of variance for nonrepeated measures. Data were further analyzed by posthoc Tukey *a*-tests to determine differences between all means, and by Dunnett's tests within each adaptation group to determine differences from control data (61).

Results are expressed as retinal concentrations of DA, DOPAC, and HVA in nanograms per milligram wet weight, as well as the ratio of metabolites (DOPAC, HVA) to amine (DA). It has been suggested that the use of metabolite-transmitter ratios provides a simple, reliable, and noninvasive measure of neurotransmitter use (1,35,56)

RESULTS

As illustrated in Figs. 1-5, the effects of apomorphine are both dose- and condition-dependent.

Light Adaptation

The lowest dose of the drug, 0.01 mg/kg, significantly decreased retinal concentrations of DA (Fig. 1) and its main metabolites, DOPAC (Fig. 2) and HVA (Fig. 3), in light-adapted rabbits. The metabolite-to-amine ratios (Figs. 4 and 5) were also significantly reduced by this dose. In contrast, the largest dose of apomorphine studied, 1.0 mg/kg, produced a marked increase in HVA levels, as well as the ratio, HVA-DA, under these conditions. Although both dopamine and DOPAC concentrations remained constant, the ratio DOPAC-DA was significantly elevated. The intermediate

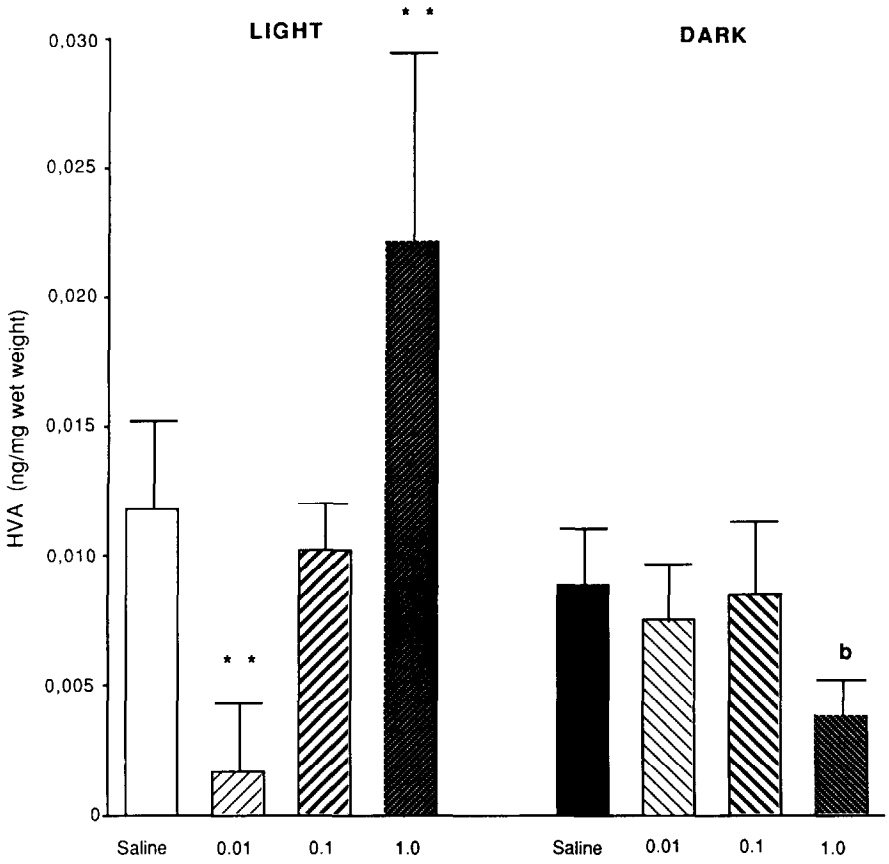

FIG. 3. Dose effects of 0.01, 0.1, and 1.0 mg/kg apomorphine vs. saline-treated controls on retinal HVA concentrations measured in both light- (left panel) and dark- (right panel) adapted rabbits. Results are expressed as mean ± SD in nanograms per milligrams wet weight. Significant differences from respective saline-treated controls are indicated by asterisks. $*p < 0.05$. $**p < 0.01$. [b]Statistical significance not assessed ($n = 4$).

dose, 0.1 mg/kg, of the agonist did not significantly alter any neurochemical measures.

Dark Adaptation

As seen in Fig. 1, DA levels were significantly reduced in retinas of dark-adapted, saline-treated animals compared with retinas of animals maintained in the light. Although both DOPAC and HVA levels were lower in dark-adapted animals, this tendency did not reach statistical significance (Figs. 2 and 3). The lowest dose of apomorphine did not significantly affect any measure under dark-adaptation conditions. However, 1.0 mg/kg of the agonist produced significant decreases in both DA and DOPAC levels, as well as the ratio of DOPAC to DA (Fig. 4). The statistical significance of the apparent decrease in HVA was not assessed, as the retinal levels of this metabolite in two animals were below the detection limits of the apparatus. Again, the intermediate dose of apomorphine produced no neurochemical changes.

DISCUSSION

Electrophysiologic, neurochemical, and behavioral effects of apomorphine in the central nervous system are diverse and highly dose-dependent. Comparison of results obtained in various laboratories is virtually impossible because of the variety of techniques used, including in vitro vs. in vivo measurements, species differences, time course of effects, and regions studied. The data presented here provide ex vivo evidence for the existence of retinal pre- and postsynaptic receptors capable of regulating dopaminergic transmission. A low (0.01 mg/kg) dose of systemically administered apomorphine significantly attenuated dopamine metabolism in light-adapted retinas. Similar dose-related effects have been reported in striatal tissue, both in vivo and in vitro (32,62). Furthermore, results of a recent study indicated that the purported D_2 selective dopamine agonist, quinpirole, significantly decreased both dopamine and DOPAC levels in light-adapted rat retinas (23). These results have been interpreted as evidence for the presence of presynaptic autoreceptors that, when stimulated, inhibit the synthesis of dopamine. Although this inhibitory effect is generally attributed to presynaptic receptor occupancy, it cannot be ruled out that certain presynaptic agonists, including apomorphine, exert a direct inhibitory action on tyrosine hydroxylase (TH) by competing for the pterine cofactor (6,18,21,25,45). In the present study, the effects the lowest dose (0.01 mg/kg) of the drug in dark-adapted retinas might provide indirect support of this possibility. It is known that in the dark, TH affinity for its co-factors and its activity are

greatly reduced (28). Thus, it might be argued that the lack of effect of 0.01 mg/kg on dopamine metabolism in the dark occurs because apomorphine cannot exacerbate the already-diminished interaction of TH with its co-factor. However, on a functional level, the results of our previous electrophysiologic study indicated that this dose of the drug significantly increased the b-wave amplitude of the dark-adapted rabbit ERG, a finding consistent with decreased dopaminergic transmission. This might be a consequence of a postsynaptic action of this small dose of apomorphine, as recent reports have shown that intraperitoneal administration of similar doses of apomorphine (20–100 μg) increases a retinal cAMP-regulated protein kinase inhibitor, thus diminishing the physiologic effectiveness of the transmitter (42,43).

The inhibitory effect of the higher dose of apomorphine, 1.0 mg/kg, on dopamine metabolism in dark-adapted retinas is consistent with behavioral findings and neurochemical data generated from other central nervous system regions. From these studies it has been proposed that higher doses of this mixed agonist interact directly with postsynaptic receptors, activating a still-unknown negative feedback loop affecting dopamine synthesis (32,60,62). It has been shown that cAMP is more readily stimulated by DA agonists, including apomorphine, in the dark-adapted rabbit retina, probably as a result of receptor supersensitivity generated by the lack of light (43). Also, in the dark, contrary to the effects of low doses, high doses of apomorphine (1–10 mg/kg) reduce the activity of a retinal cAMP regulated protein kinase inhibitor (42,43). Taken together, these findings indicate that high doses of apomorphine further enhance the inhibitory effect of darkness on retinal dopamine synthesis and release. The increased postsynaptic stimulation produced by the drug is concordant with our electrophysiologic findings of significantly decreased ERG b-wave amplitudes in dark-adapted animals.

The neurochemical effects of 1.0 mg/kg apomorphine on light-adapted retinas were unexpected. Although levels of DA and DOPAC were not significantly altered, the concentration of HVA nearly doubled. Furthermore, the ratios of both DOPAC and HVA to dopamine were also increased, suggesting that the turnover of dopamine is significantly enhanced by this dose of apomorphine (Figs. 4 and 5). These findings are in contrast to the report of diminished dopamine metabolism in rat retina after the administration of high doses (10 mg/kg) of apomorphine under similar conditions (7). In this regard, electrophysiologic and biochemical data generated from in vitro retinal preparations have demonstrated that apomor-

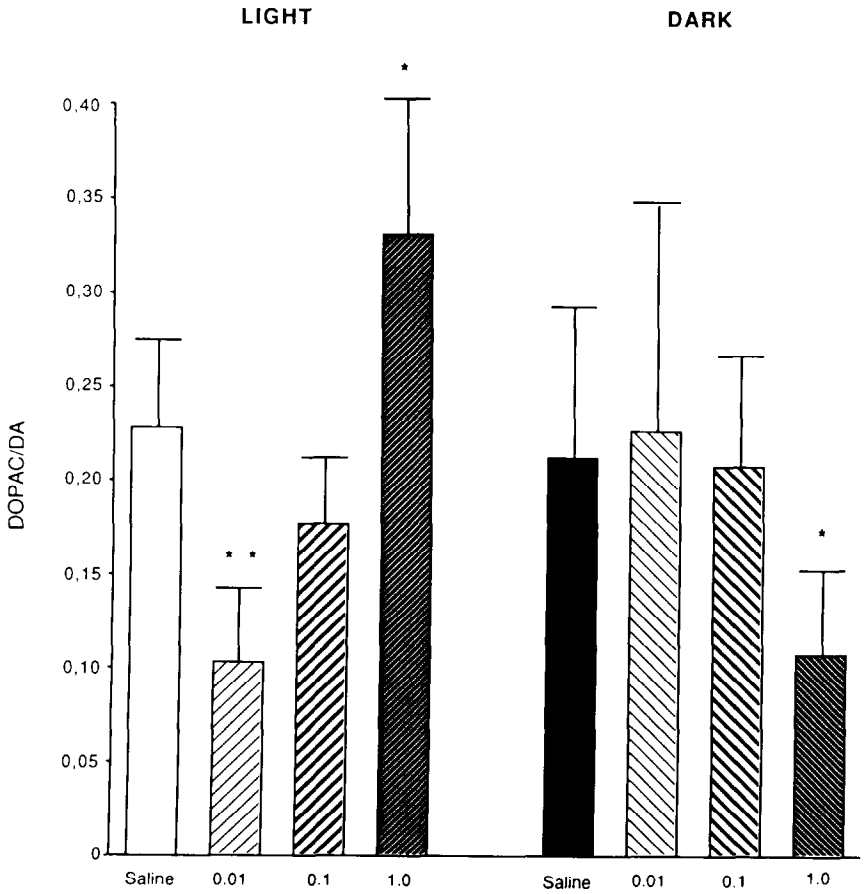

FIG. 4. Dose effects of 0.01, 0.1, and 1.0 mg/kg apomorphine vs. saline-treated controls on the ratio of DOPAC to dopamine in retina calculated for both light- (left panel) and dark- (right panel) adapted rabbits. Significant differences from saline treated controls are indicated by asterisks. $*p < 0.05$. $**p < 0.01$.

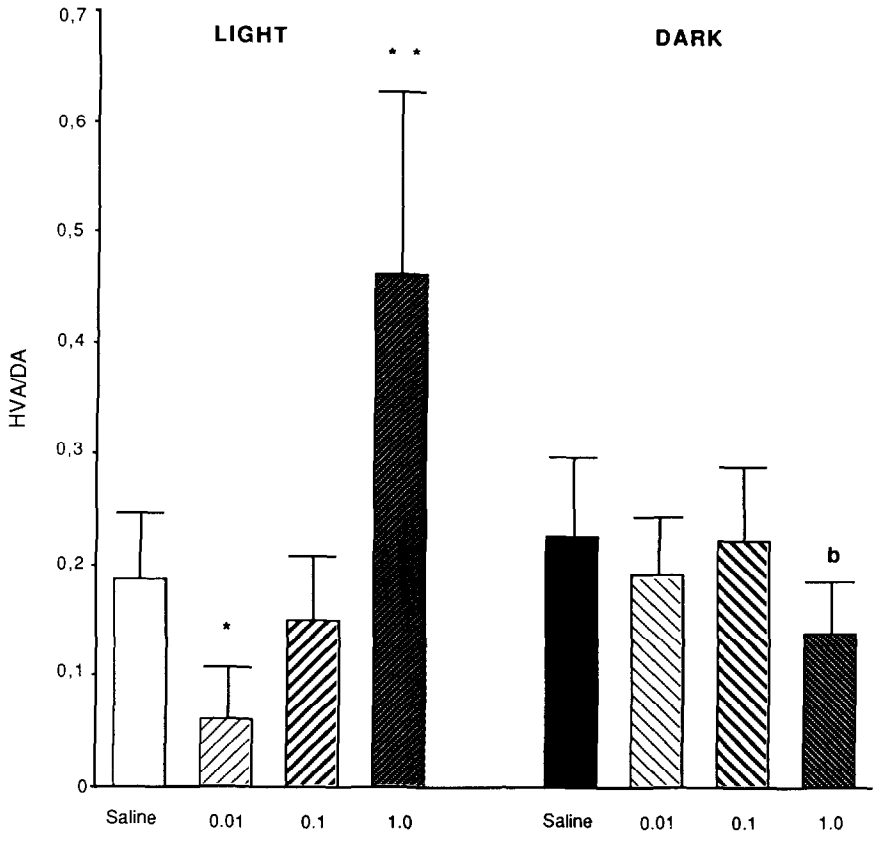

FIG. 5. Dose effects of 0.01, 0.1, and 1.0 mg/kg apomorphine vs. saline-treated controls on the ratio of HVA to dopamine in retina calculated for both light- (left panel) and dark- (right panel) adapted rabbits. Significant differences from saline-treated controls are indicated by asterisks. $*p < 0.05$. $**p < 0.01$. *b*Statistical significance not assessed ($n = 4$).

phine can act as an antagonist of dopamine at the D_1 postsynaptic receptor (20,30,31,37). If the same holds true for in vivo apomorphine activity, then this could explain the increased turnover of dopamine reported in this study, as it has been shown repeatedly that acute blockade of postsynaptic receptors results in increased synthesis and release of neurotransmitter (19,36,38). However, the antagonistic effect of apomorphine demonstrated in these studies was minimal, and occurred only at doses of the drug markedly higher than that used in the present study. Also, as our results demonstrate, this dose of the drug behaves as a postsynaptic receptor agonist in the absence of light stimulation. An alternative explanation for the increased metabolism of dopamine under these conditions resides in the morphology of the dopamine-containing amacrine cells. It has been shown that, whereas inhibition of impulse flow as well as apomorphine retarded the disappearance of DA in the striatum of α-methyl-*para*-tyrosine–treated animals, neither treatment influenced DA release and metabolism in the substantia nigra (39). These findings suggest that in the brain, cell body metabolism functions independently of both impulse flow and postsynaptic receptor events. In retina, the amacrine cells constitute the site of both synthesis and release of dopamine, and might react to postsynaptic receptor blockade and activation in a manner similar to the substantia nigra. As such, even if apomorphine is acting as a DA agonist on postsynaptic retinal receptors, the amacrine cells continue to function normally in response to the physiologic stimulus, light. It is thus possible that light is so potent a dopamine releaser, it overrides an hypothesized inhibitory feedback loop thought to be responsible for the decrease in dopamine metabolism after the administration of relatively large doses of apomorphine in other CNS regions. In this regard, data have been presented suggesting that TH activity in the retina is modulated by two independent mechanisms, one of which is light-dependent (8,9). Furthermore, a 2.0 mg/kg dose of the drug did not attenuate TH activity in light-adapted retinas (10). Nonetheless, this argument does not explain why the concentrations of metabolites increased rather than remained steady, as would be expected if only the synthesis of dopamine were affected. However, results of an earlier in vitro study demonstrated that a purportedly selective autoreceptor agonist, 3-PPP, which significantly reduced dopamine synthesis, also induced dopamine release at high doses (45). In the present study, although the metabolites and their ratios to dopamine were elevated, the concentration of dopamine was indeed 20% lower in animals treated with the highest dose of the drug (Fig. 1), again suggesting that synthesis proceeded at a slower rate than release. Together, these findings indicate that the control of dopamine metabolism in the retina is more complex than in other CNS regions. Obviously, further work with selective agonists and antagonists is necessary to define the relative contributions of light- and receptor-

mediated events in the regulation of dopamine synthesis and release.

Finally, the lack of effect of the intermediate (0.1 mg/kg) dose of the drug probably reflects apomorphine's composite nature, whereby the drug is simultaneously activating pre- and postsynaptic receptors, resulting in no net change in transmitter level. Similar effects of concomitant D_1/D_2 on cAMP accumulation have been reported (41,59).

In conclusion, the results of this study provide ex vivo neurochemical evidence for the existence of both postsynaptic and presynaptic dopamine receptors. The decreased concentrations of dopamine and its metabolites produced by the administration of 0.01 mg/kg apomorphine to light-adapted animals are consistent with the hypothesis that low doses of apomorphine preferentially stimulate inhibitory dopaminergic autoreceptors, indicating that retinal dopamine containing amacrine cells function similar to dopamine neurons in other regions of the CNS. The inhibitory effect of 0.01 mg/kg apomorphine was not obtained in dark-adapted animals, probably because of the already significantly lower basal levels of dopamine, as well as the deactivation of tyrosine hydroxylase under these conditions. The effects of the higher dose of the drug, (1.0 mg/kg) are more difficult to explain, but might be due to an antagonistic effect of apomorphine on postsynaptic retinal receptors. More likely, any agonistic effects of this dose of apomorphine at postsynaptic sites are masked by the amacrine cell's sustained response to light, because the expected effects of 1.0 mg/kg apomorphine are evident in dark-adapted retinas.

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