nase release, was between $5 \times 10^{-9}M$ and $1 \times 10^{-8}M$. This effect on enzyme release by IAA was reversible; that is, when granulocytes were washed after incubation with IAA, opsonized zymosan-induced release of histaminase was similar to that released from cells first incubated in buffer alone. Inhibition of release was not dependent on an effect of IAA on phagocytosis (another stimulus for enzyme release) since IAA also inhibited release from cells treated with cytochalasin B at concentrations that block phagocytosis. The IAA had no effect on opsonized zymosan-induced granulocyte release of β-glucuronidase, myeloperoxidase, or lysozyme (data not shown) (*13*).

Inhibition of granulocyte histaminase release by IAA was compared to the effects of other products of histamine catabolism, imidazole compounds, and amines, as shown in Table 1. Histaminase release was inhibited 50 percent by the histamine methyltransferase metabolite, 1-methyl-4-imidazoleacetic acid at $10^{-4}M$ concentration, a K_i 10,000 times greater than the K_i for IAA. The K_i for imidazole, histidine, and urocanic acid were indeterminate, but were more than 10,000 times that for IAA. Histaminase release was inhibited 10 percent or less at the highest concentration of these agents tested. The K_i for histamine, as well as other amines, cadaverine, spermine, and spermidine were greater than 1000 times that for IAA.

Lysosomal enzyme release from granulocytes (*14*) and histamine release from mast cells and basophils are modulated by intracellular concentrations of cyclic nucleotides (*15*). Imidazole enhances mediator release, perhaps because of decreased concentrations of mast cell adenosine 3′,5′-monophosphate (cyclic AMP) (*16*). To test whether agents known to modulate cellular levels of cyclic AMP and guanosine 3′,5′-monophosphate (cyclic GMP) would affect granulocyte histaminase release, we conducted the following experiments. Adrenergic or cholinergic agents, a phosphodiesterase inhibitor, exogenous dibutyryl cyclic AMP and cyclic GMP were each incubated with granulocytes for 20 minutes at 25°C and then during exposure to opsonized zymosan (2.5 particles per cell).

For each agent, at the highest concentrations that could be tested, only minimal inhibition of histaminase release was observed. The K_i was, therefore, indeterminate. However, incubation of granulocytes with isoproterenol in the presence of a phosphodiesterase inhibitor led to inhibition of histaminase release (Table 1). Under these conditions, the K_i for isoproterenol was 100 to 200 times that of IAA.

These data provide evidence for an indirect feedback inhibition by imidazoleacetic acid of histaminase release from granulocytes. Physiological concentrations of IAA, the principle end product of the action of histaminase on histamine, block enzyme release. Related compounds were at least 1000 times less potent inhibitors of histaminase release. Histamine and IAA may play a role in eosinophil chemotaxis (*17*). Since the eosinophils also contain histaminase (*3*), stimuli for release of the enzyme may, therefore, indirectly affect the accumulation of eosinophils at an inflammatory site.

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23 April 1979; revised 7 June 1979

Heavy Metals Affect Rod, But Not Cone, Photoreceptors

Abstract. *Low concentrations of lead, mercury, or cadmium depress the amplitude of the rod receptor potential in the perfused bullfrog retina. Responses from the cones were not affected. The data implicate the rods as a lesion site in animals exhibiting scotopic vision deficits as a result of heavy metal poisoning.*

Vision deficits in human and nonhuman primates after exposure to either lead (Pb^{2+}) (*1, 2*) or methylmercury (*2, 3*) have been attributed to decreases in the rod-mediated, scotopic, visual system as opposed to the cone-mediated, photopic, visual system. There is little doubt that at least some of the reported deficit is due to a central lesion (*2, 3*). However, some retinal involvement is suggested by a report describing decreases in the amplitude of the b wave of the electroretinogram (ERG) as an early indicator of Pb^{2+} toxicity in occupationally exposed workers (*4*). To determine whether the deficits caused by Pb^{2+} and mercury (Hg^{2+}) involve rod or cone photoreceptors (or both), we studied the isolated, perfused bullfrog (*Rana catesbeiana*) retina. We report here that inorganic Pb^{2+}, Hg^{2+}, and cadmium (Cd^{2+}) affect the rod, but not the cone, photoreceptors.

The dissected retina, minus pigment epithelium, from a dark-adapted bullfrog was positioned in a chamber and perfused (*5*) with Ringer solution containing 100.0 m*M* NaCl, 2.0 m*M* KCl, 5.0 m*M* glucose, 0.4 m*M* $MgCl_2$, 0.4 m*M* $CaCl_2$, 10.0 m*M* sodium aspartate, and 20.0 m*M* tris-maleate buffered to *p*H 7.8. Sodium

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aspartate was present in the perfusing solution to suppress the PII and proximal PIII components of the ERG and to isolate the distal PIII or late receptor potential (*6*). Temperature was maintained at 18.0° ± 0.2°C by a Lauda K-2/R water bath. A gravity flow controller (IVAC model 200) held the perfusion rate at 0.2 ml/min. Two silver-silver chloride electrodes, positioned on opposite sides of the retina, carried responses to a capacitance-coupled amplifier (time constant, 0.5 second). Responses were displayed on an oscilloscope (Tektronix model 5112). After perfusion of the retina for either 30 or 60 minutes with the control Ringer solution, the retina was further perfused for an equal period with a solution containing the chloride salt of either Pb^{2+}, Hg^{2+}, or Cd^{2+} (1 to 50 μM). After each experimental perfusion, the retina was again perfused with the control Ringer solution in order to examine the reversibility of the effects.

The light stimulus was a 250-msec flash of white light. With the exception of the experiment concerned with sensitivity, where various stimulus intensities were necessary, the intensity was 47 $\mu W/cm^2$ in all cases. Rod responses were separated from cone responses by the two-flash method (*7*). Thus, the first flash produced a response that contained contributions from both rods and cones. The second flash, identical to the first but administered 10 seconds later, produced a pure and maximal cone response (*7*). The isolated rod contribution was then calculated by subtracting the amplitude of the cone response from the amplitude of the first response.

The Pb^{2+} caused a reversible, concentration-dependent decrease in the amplitude of the rod response but had no effect on the cone potential (Fig. 1A); thus, 1.0 μM Pb^{2+} produced no decrease in rod response amplitude while the 5.0 μM and 12.5 μM Pb^{2+} produced a 9 and a 20 percent decrease, respectively. In one of the two experiments where the effect of 1.0 μM Pb^{2+} was tested, some decrease in rod response was seen. A decrease in rod response amplitude was observed in each of four experiments where 5.0 μM Pb^{2+} was used (9 to 24 percent decrease, the mean being 16 percent). Five experiments with 12.5 μM Pb^{2+} showed a mean decrease in rod response of 23 percent with a range of 20 to 28 percent. In the three experiments with 50 μM Pb^{2+}, rod responses decreased by 26, 31, and 36 percent, respectively (the mean decrease was 31 percent). It is significant that the lower concentrations used in this experiment are of similar magnitude to those found by Fox *et al.* in the brains of suckling rats that had been exposed to lead (that is, the nursing mothers' drinking water contained lead) and that showed altered development of the visual system when the concentrations of lead in the blood were comparable to those of children not yet showing symptoms of lead poisoning (*8*).

The Pb-induced decreases in the amplitude of the rod receptor potentials are not necessarily indicative of an alteration in threshold sensitivity of the receptors, and therefore the amplitude-intensity relationship was examined to determine threshold (*7*). The absolute sensitivity after treatment of a retina with 12.5 μM Pb^{2+} decreased by 0.7 log unit (Fig. 1B). The same result was seen in an identical experiment on a second retina from a different frog.

Two experiments were performed with $HgCl_2$. Like Pb^{2+}, Hg^{2+} caused a decrease in rod response amplitude but did not affect the cones (Fig. 2A). In contrast to the effect of Pb^{2+}, that of Hg^{2+} was not reversible. The kinetics of the effect of Hg^{2+} (Fig. 2A) were different from those of Pb^{2+} (Fig. 1A) in that the onset of the decrease in rod response amplitude was much delayed with Hg^{2+} (Fig. 2A). The transient increase in rod response amplitude that occurred shortly after exposure

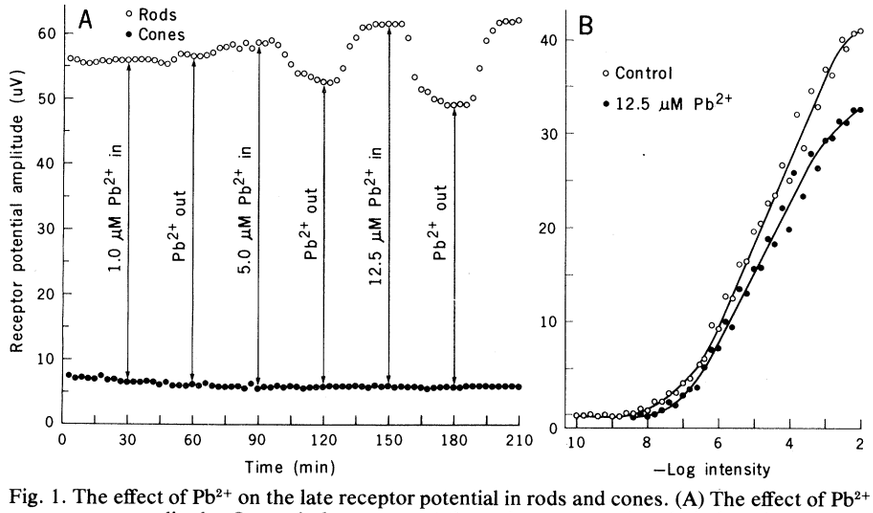

Fig. 1. The effect of Pb^{2+} on the late receptor potential in rods and cones. (A) The effect of Pb^{2+} on response amplitude. Open circles represent the rod response; closed circles, the cone response. Pairs of stimuli were applied at 3-minute intervals. There were nine separate experiments with nine frogs. (B) The effect of Pb^{2+} on rod sensitivity. Open circles represent the data under control conditions. Control values were obtained before and after exposure to Pb^{2+}, and each data point is the mean of the two readings. Closed circles represent the data during perfusion of the retina with a Ringer solution containing 12.5 μM Pb^{2+}. Thresholds were determined by the ascending and descending method of limits (*21*).

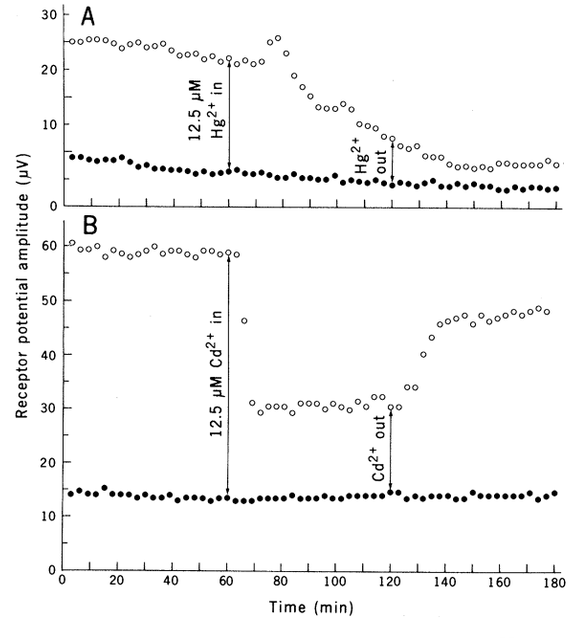

Fig. 2. The effect of Hg^{2+} and Cd^{2+} on the amplitude of the late receptor potential in rods and cones. Open circles represent the rod response; closed circles represent the cone response. (A) Data from an experiment with 12.5 μM Hg^{2+}. (B) Data from an experiment with 12.5 μM Cd^{2+}.

to Hg^{2+} (Fig. 2A) was seen in both Hg^{2+} experiments. A similar transient effect of Hg^{2+}, as well as its irreversibility, has been observed in other in vitro systems (*9*).

In view of the results with Pb^{2+} and Hg^{2+} it occurred to us that Cd^{2+}, a heavy metal widely distributed in the environment and now causing increasing concern clinically (*10*), might prove toxic to the retina. Accordingly, using $CdCl_2$ we performed two experiments on receptor potential amplitude (Fig. 2B). A 12.5 μM concentration of Cd^{2+} diminished the amplitude of the rod response by 50 percent, while leaving the cone response unaffected. Since in the second of these experiments 5.0 μM Cd^{2+}depressed the rod response 27 percent, it would seem that the effect of Cd^{2+} (like that of Pb^{2+}) is concentration-dependent. The effects of Cd^{2+} and Pb^{2+} were also similar with respect to both reversibility and the kinetics of onset of, and recovery from, the amplitude depression. Although it still did not affect the cones, Cd^{2+} appears to be two to three times more potent than Pb^{2+} in depressing the rod potential (Figs. 1A and 2B); in other systems Cd^{2+} was more toxic than either Pb^{2+} or Hg^{2+} (*9*). Perhaps, therefore, scotopic vision deficits may be found in clinical or experimental situations after Cd^{2+} exposure.

The mechanism of action of heavy metals on the rod photoreceptors is not yet clear. Divalency of cations in general apparently is not the main factor since barium increases the rod response amplitude (*11*). By itself, that the effect of Hg^{2+} is irreversible indicates that Hg^{2+} acts in a manner somewhat different from Pb^{2+} and Cd^{2+}. In addition, only with Hg^{2+} did we see an initial transient increase in rod response amplitude prior to the typical decrease in rod potential observed with all three heavy metals. This initial transiency may or may not be responsible for the delay in the depressive effect of Hg^{2+} as compared to Pb^{2+} and Cd^{2+}. It is possible that Hg^{2+} is actually causing a selective degeneration of the rods, a capability that has been demonstrated in retinal cell cultures under conditions similar to ours (*12*). The rapid onset of the depression of the rod response with Pb^{2+} and Cd^{2+} and, especially, the reversibility may rule out cell degeneration as a factor. Alternatively, heavy metals have been shown to bind to ligands such as sulfhydryls (*13*), to decrease the activity of the Na^+, K^+-adenosinetriphosphatase pump (*14*), to inhibit the activity of calcium pumps (*15*), and to alter the permeability of cell membranes to Na^+ and K^+ (*13, 16*)—phenomena that occur or are proposed to occur in retinal rods (*17–19*).

A major problem in proposing a mechanism of action of the heavy metals is providing an explanation for the lack of effect on the cone photoreceptors. Cones are not impervious to attack by divalent cations since barium causes a decrease in cone response amplitude (*11*).

Little biochemistry has been done on retinal cones but it is usually assumed that their characteristics would be similar to those of the rods. A known difference between rods and cones is the outer segment morphology (*20*). Rod outer segments contain saccules or disks, which are enclosed by the plasma membrane but isolated from that membrane; these may function in the generation of the rod receptor potential (*19*). Cones usually have no such disks and their lamellae, which are analogous to the rod disks, are continuous with the extracellular fluid (*20*). This morphological difference may somehow account for the fact that Pb^{2+}, Hg^{2+}, and Cd^{2+}, depress the rod receptor potential amplitude but leave the cones unaffected.

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22. We thank D. A. Bolnick and A. E. Walter for technical assistance, Dr. R. P. Scobey for criticism of the manuscript, and the IVAC Corp. of San Diego for their gift of the flow controller used in this study. Supported in part by grants ES05094 from NIEHS (D.A.F.) and EY01839 from NEI (A.J.S.).
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2 April 1979; revised 29 May 1979

Dopamine Auto- and Postsynaptic Receptors: Electrophysiological Evidence for Differential Sensitivity to Dopamine Agonists

Abstract. *The responses of dopamine cells in the substantia nigra to iontophoretically administered dopamine and intravenous apomorphine were compared to the responses of spontaneously active neurons in the caudate nucleus. Dopaminergic cells were six to ten times more sensitive to dopamine and intravenous apomorphine than 86 percent of the caudate cells tested. This differential sensitivity of dopamine auto- and postsynaptic receptors may explain the apparently paradoxical behavioral effects induced by small compared to large doses of some dopamine agonists and may provide a means of developing new types of drugs to antagonize dopaminergic influence in the central nervous system.*

Recent biochemical and electrophysiological studies have provided evidence for a new dopaminergic receptor whose function seems to be the regulation of dopamine (DA) influence on postsynaptic cells. This presynaptic receptor (autoreceptor) is present both on caudate dopaminergic nerve terminals, where it appears to regulate transmitter synthesis and release (*1*), and on nigral dopaminer-

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