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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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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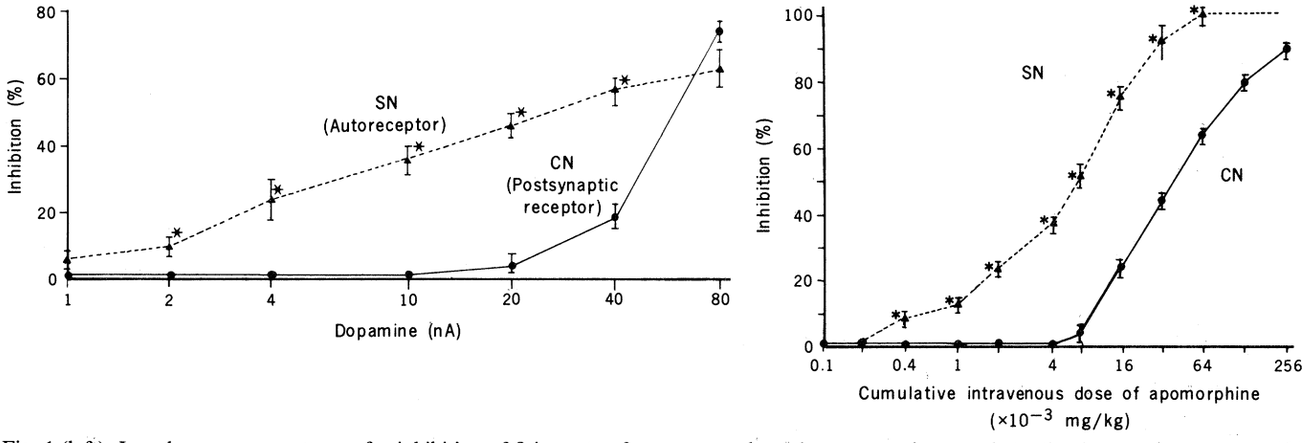

Fig. 1 (left). Log dose-response curves for inhibition of firing rate of spontaneously active neurons in the substantia nigra zona compacta (*SN*) (autoreceptor) and the head of the caudate nucleus (*CN*) (postsynaptic receptor) in response to iontophoretically applied DA (0.1*M*, *p*H 4). Each point on the curve represents the mean inhibition ($N = 10$) obtained at a given ejection current of DA. The vertical bars represent the standard error of the mean. Asterisks indicate significant differences from control ($P < .001$, Student's *t*-test). Despite marked differences in the sensitivities of these two receptors to weak iontophoretic DA currents (10 to 40 nA), no difference was discernible at a current of 80 nA. This suggests that whenever one attempts to compare receptor sensitivities, it is important that dose-response curves be obtained. Fig. 2 (right). Cumulative log dose-response curves for inhibition of firing rate of spontaneously active neurons in the substantia nigra zona compacta (*SN*) and the head of the caudate nucleus (*CN*) in response to systemic APO. Each point on the curve represents the mean inhibition ($N = 10$) obtained at a given cumulative dose. Apomorphine was administered intravenously in increasing incremental doses. The vertical bars represent the standard error of the mean. Asterisks indicate significant differences from control ($P < .001$, Student's *t*-test).

gic cell bodies (*2*), where it may be involved in dendrodendritic synapses on dopaminergic or nondopaminergic neurons (*3*). Is this receptor more sensitive to dopamine agonists than the postsynaptic DA receptor? If it were more sensitive, one would predict that DA agonists in small doses might produce biochemical or behavioral effects which resemble those commonly seen with DA antagonists. Several studies have attempted to answer this question. For example, it has been found (*4*) that small doses of the direct-acting DA agonist apomorphine (APO) decrease locomotor activity (an effect not dissimilar to the decrease in motor activity after administration of DA receptor blockers such as neuroleptic medication), whereas larger doses produce the usual behavioral effect seen with DA agonists—increased locomotor activity. To explain these dose-dependent, opposite, behavioral effects of APO, it has been suggested that in small doses APO acts on autoreceptors to inhibit the activity of the dopaminergic neuron and decrease DA release, whereas in larger doses it stimulates postsynaptic receptors directly (*5*).

In this report we describe experiments in which electrophysiological techniques were used to measure the sensitivity of DA auto- and postsynaptic receptors to DA agonists. We give evidence that DA autoreceptors on nigral dopaminergic cell bodies and dendrites are at least six to ten times more sensitive to the inhibitory effects of DA agonists than are postsynaptic DA receptors located on 86 percent of the spontaneously active cells in the caudate nucleus.

Experiments were performed in which single-unit recording and iontophoretic techniques (*6*) were used. A 3-mm burr hole was drilled at coordinates within the head of the caudate nucleus (anterior, 8380 μm and posterior, 3000 μm) in a group of Sprague-Dawley albino rats paralyzed with gallamine. In another group, a 3-mm burr hole was drilled in the center of the zona compacta of the substantia nigra [anterior, 1950 μm and lateral, 2200 μm, according to König and Klippel (*7*)]. Recordings were made from cells whose characteristics matched those of cells identified as dopaminergic in the zona compacta of the substantia nigra (*6*) and from spontaneously active caudate potentials (type I and type II) (*8*). Responses to increasing currents of iontophoretic DA were determined, and microiontophoretic warm-up effects were carefully controlled (*9*). Current artifact was checked by ejecting comparable currents of up to 100 nA from the balance channel containing 4*M* NaCl; in no case did this current affect the firing rate of the cell.

Cells in the zona compacta ($N = 10$) were more sensitive to DA at low iontophoretic currents than were the type I potentials in the caudate nucleus ($N = 10$). A 50 percent reduction in firing rate was measured in the zona compacta with DA currents of 20 nA; currents of 50 nA were necessary to cause a comparable reduction in caudate neuronal activity (Fig. 1). At the highest iontophoretic current (80 nA), there was no difference in the degree of response of the two receptors to DA; thus, both the autoreceptor and the postsynaptic receptor displayed a ceiling response to DA. It was not possible to totally inhibit the firing of nigral dopaminergic cells or the majority of caudate cells with currents of up to 100 nA.

In an effort to further compare the sensitivities of the pre- and postsynaptic receptors, we measured the effects of systemically administered APO. Figure 2 shows APO dose-response curve for dopaminergic cells ($N = 10$) and spontaneously active type I caudate potentials ($N = 10$). Dopaminergic cells were more sensitive than the caudate cells. A median effective dose (ED_{50}) for inhibition of nigral cells of 8 μg of APO per kilogram of body weight (intravenously) was found; this confirmed the findings of Guyenet and Aghajanian (*10*). In contrast, the ED_{50} for APO in the caudate nucleus was 50 μg/kg. In addition, three type I caudate cells failed to respond to APO at all.

Finally, the responses of spontaneously active type II potentials in the caudate nucleus were examined. This type of cell had a far more complex response to APO than either the type I potentials or the dopaminergic cells. Of the 14 type II cells examined, five showed a biphasic response to APO, increasing their firing rates with small doses of APO (2 to 4 μg/kg, intravenously) but reducing their firing rates by the time the dosage had been doubled or quadrupled. Thus, intrave-

nous doses as small as 8 μg/kg were effective in inhibiting the firing rate of type II cells by at least 50 percent. Six type II cells were inhibited by doses of APO comparable to those that affected type I cells (ED_{50} = 50 μg/kg, intravenously). Finally, three of the 14 cells did not respond at all to intravenous doses of APO as large as 400 μg/kg.

These data provide direct evidence that dopaminergic neurons are more sensitive than most caudate neurons to DA agonists (*11*). On the basis of these data, a biphasic response of caudate neurons to systemically administered APO would be expected; small doses would be expected to reduce dopaminergic neuron firing and thus increase caudate neuron activity, whereas larger doses would be expected to stimulate postsynaptic receptors directly and thus decrease caudate activity. Indirect evidence for such phenomena has been obtained in biochemical and behavioral studies (*1, 5*). Small intraperitoneal doses of APO (20 μg/kg) decrease motor and tyrosine hydroxylase activity, whereas large intraperitoneal doses (500 μg/kg) increase movement.

The autoreceptor response is of particular interest in light of possible mechanisms of regulation of nigral DA system activity. Our finding that the microiontophoretic administration of DA was unable to completely stop the firing of active cells in the zona compacta or the majority of cells in the caudate nucleus, whereas intravenous APO effectively shut off nigral cells, may provide evidence for a relative participation of pre- and postsynaptic systems in the regulation of neuronal DA. The importance of striatonigral feedback pathways for mediating drug-induced changes in dopaminergic activity is emphasized in these findings. It is of particular interest that the dose of APO that produced a 50 percent reduction in type I caudate potential activity was the same as the dose that caused an almost total inhibition of dopaminergic cell firing in the substantia nigra. Thus, small doses of APO preferentially affect the more sensitive autoreceptor whereas larger doses may "recruit" the postsynaptic inhibitory effects in the striatum, thereby producing, via striatonigral feedback pathways, a greater inhibition of dopaminergic cell activity. However, not even total destruction of the striatonigral pathways completely prevents intravenous APO from inhibiting nigral dopaminergic cells if the dose is large enough (for example, ~ 0.1 mg/kg) (*12*).

The greater sensitivity of the autoreceptor compared to the postsynaptic receptor is also suggested by our finding that five of 14 type II caudate potentials responded to very small intravenous doses of APO by increasing their rate of firing. Such an increase would be expected to occur if APO were specifically stimulating DA autoreceptors in the substantia nigra, inhibiting both dopaminergic cell activity and DA release and consequently removing caudate neurons from the inhibitory effects of DA. It is not known whether the somatic autoreceptor and the DA receptor on the nerve terminal are similar. Perhaps the terminal autoreceptor is also more sensitive to DA agonists than the postsynaptic receptor. If this is the case, similar effects would be expected if APO were decreasing DA release by stimulating the autoreceptor at the nerve terminal.

The mixed responses of the type II cell population in the caudate nucleus point out the complexity of the striatonigral system. Histological and biochemical studies (*13*) have shown that the striatum contains several types of cells and a variety of neurotransmitters which influence its function (*13*). The variety of responses of these cells to systemic APO suggests that the caudate nucleus is made up of subpopulations of cells whose innervation is heterogeneous.

Nevertheless, our data provide direct evidence that the sensitivity of dopaminergic cells to the inhibitory action of DA agonists is greater than at least 86 percent of spontaneously active caudate neurons. This has several clinical implications. Tardive dyskinesias are thought to be caused by the functioning of a striatal system that is made supersensitive to DA by long-term treatment with neuroleptic medication (*14*). Both the auto- and postsynaptic receptors have been shown (*8, 15*) to become supersensitive in response to such treatment (*8, 15*). If the difference in sensitivity between auto- and postsynaptic DA receptors still exists after supersensitivity develops, it should be possible to treat tardive dyskinesias with small doses of APO, thereby reducing DA release through the specific stimulation of DA autoreceptors. Such a hypothesis is supported by the clinical finding that treatment with APO in small doses has a beneficial effect on some tardive dyskinesia patients (*16*). Our data also point out the complex interactions that must be considered when trying to describe the mechanism by which a drug acts on the brain. A drug at one dose can act behaviorally and biochemically like a DA antagonist whereas in larger doses it can behave like a DA agonist—based solely on the anatomical site of its action. Finally, our data support the concept that it may be possible to develop new drugs that specifically stimulate the autoreceptor while having little effect on postsynaptic DA sites.

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