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# Stress and Its Timing: Critical Factors in Determining the Consequences of Dopaminergic Agents

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ANTELMAN, S. *Stress and its timing: Critical factors in determining the consequences of dopaminergic agents.* PHARMAC. BIOCHEM. BEHAV. **17:** Suppl. 1, 21–23, 1982.—Dopaminergic agonists and antagonists can have opposite effects, depending on the state of the organism involved. The importance of prior state in determining the consequences of treatment with dopaminergic agents is illustrated in Serra's recent experiments. Although repeated treatment with DA antagonists enhanced the hypokinetic effects of 10 μg/kg of apomorphine, they obviated the influence of 25 μg/kg. In the former case, chronic DA-receptor blockade induced supersensitivity of DA autoreceptors; in the latter it resulted in subsensitivity. Since autoreceptor subsensitivity typically occurs after repeated treatment with DA agonists these experiments illustrate that neuroleptics can behave like DA agonists. We discuss these and similar studies, emphasizing the role of stress and time in determining the consequences of dopaminergic agents.

Stress Timing Dopaminergic agents

IT IS axiomatic, although often forgotten (especially by researchers), that the effects of drugs depend on the history of the organism [11]. This is no less true for agents acting on dopaminergic systems than on other neuronal systems. In fact, in many respects the distinction between dopamine (DA) agonists and antagonists is of limited value since the same agent may have precisely opposite effects, depending on the history and present state of the organism. For instance, although amphetamine (AM) typically exacerbates schizophrenia it may also have a therapeutic effect in some individuals [15].

The importance of prior state in determining the functional consequences of treatment with dopaminergic agents is particularly well illustrated in recent experiments of Serra and his colleagues [14]. Although these investigators found that repeated treatment with the DA antagonists, haloperidol and chlorpromazine, greatly enhanced the hypokinetic effects of 10 μg/kg of apomorphine, they completely obviated the influence of 25 μg/kg of this DA agonist. In other words, in the former case chronic blockade of DA receptors induced supersensitivity of DA autoreceptors, while in the latter it resulted in subsensitivity. Since autoreceptor subsensitivity typically occurs after repeated treatment with DA agonists, these experiments illustrate that under some conditions neuroleptics behave like DA agonists.

In this article I will emphasize the importance of stress and its timing as factors in determining the effects of dopaminergic agents. I shall begin my discussion by considering the influence of stress on the effects of haloperidol. In a series of experiments designed to test our hypothesis of a stress-related interaction between norepinephrine (NE) and DA, we examined the effect of DA receptor blockade in the presence or absence of additional pharmacological treatments designed to interfere with NE during stressful and "unstressful" conditions. Thus, haloperidol's effects on tail-pressure-induced eating (stress condition) and catalepsy (quiescent condition) were observed in the presence of inhibitors of NE synthesis (FLA–63 and methimazole), postsynaptic alpha- and beta-receptor blockers (phenoxybenzamine, propranolol, and alprenolol), and the alpha$_2$ agonist, clonidine. In each case, interfering with NE function (by whatever means) counteracted the suppressive behavioral influence of DA receptor blockade during the stressful condition. In stark contrast, precisely the same doses of NE-inhibiting agents (except for the beta blockers) given according to the same schedule as in the stress condition failed to produce even a tendency toward reversing the effects of haloperidol in the "nonstress" (i.e., catalepsy) situation [2]. In these experiments the functional effects of haloperidol were clearly dependent on whether mild stress was present.

Not only does the nature of the interaction between NE and DA vary with stress, so too does the interaction between serotonin and DA. In single-unit electrophysiological experiments we recorded both basal firing and stressor-induced changes in the activity of type A and B DA neurons in the substantia nigra following destruction or electrical stimulation of dorsal raphe serotonin neurons ([2] and Chiodo, L. A., unpublished doctoral dissertation, 1981). While destruction of serotonin neurons increased basal discharge of type B DA neurons, it completely prevented the change in DA firing

usually observed in response to the stressors, tail-pressure and light flash. Conversely, repetitive dorsal raphe stimulation suppressed the basal activity of DA cells while enhancing their response to tail pressure. These data strongly suggest that modification of serotonin activity affects the firing of nigral DA neurons in opposite ways during stressful and quiescent conditions. One could predict then that dopaminergic agents administered to organisms with compromised serotonin activity would have very different consequences under stressful conditions.

Not only are stress and other pharmacological agents important variables in determining consequences of dopaminergic drugs, but the timing of such stimuli relative to the administration of DA agonists or antagonists is also important. It is now well established that when AM, cocaine, or other stimulants are administered on a regular although intermittent basis, sensitization to many of their behavioral effects takes place [13]. Indeed, the gradual evolution and intensification of paranoid symptoms which often occurs following repeated abuse of these compounds is thought to reflect behavioral sensitization [10,12]. Sensitization is a fascinating phenomenon which, perhaps more than any other, points out the importance of considering prior state. Although it is typically demonstrated after regular drug administration, repeated treatment is not necessary. Rather, sensitization appears to depend on the passage of time. For example, two injections of AM or bupropion spaced at a three-week interval induce the same degree of sensitization as daily treatment with these agents ([5] and unpublished observations). This persistent time-dependent nature of behavioral sensitization may help to explain why previous AM abusers appear more likely to develop a paranoid psychosis after subsequent abuse than individuals who had not earlier abused the drug [1,7]. Given the variety of DA agonists that induce sensitization (e.g., AM, cocaine, L-DOPA, methylphenidate, bupropion, and apomorphine) and the fact that cross sensitization is seen among a number of them, it is not unlikely that all dopaminemimetic agents induce this phenomenon. Therefore, previous experience with any such drugs may alter subsequent responses to others. Even agents that were traditionally thought not to act on DA systems, such as tricyclic antidepressants, have been shown to exert a progressive time-dependent sensitization on these neurons. Using single-unit electrophysiological techniques, our group has demonstrated that brief treatment with tricyclics and, in fact, all major classes of antidepressants, induces a subsensitivity of autoreceptors on substantia nigra DA neurons (as indexed by noting the change in DA firing in response to apomorphine) which grows with the passage of time even in the absence of further treatment [4, 8, 9].

Since drugs presumably affect behavior and neuronal activity by mimicking the influence of naturally occurring events, it might be expected that an individual's non-drug history might similarly influence his or her sensitivity to dopaminergic treatments.

Experiments in our laboratory over the past several years have indicated that drugs such as AM appear to be interchangeable with a wide variety of stressors in their ability to induce behavioral sensitization. We have, for instance, shown that food deprivation, electric foot shock, immobilization, and even a single injection of isotonic saline are all able to sensitize a rat's response to AM when it is administered 2 to 3 weeks after stressor presentation has been terminated [3]. Brief stressors can not only induce a long-term enhancement of the organism's response to DA agonists but, as would be predicted, they also attenuate the functional effects of DA antagonists [3].

Knowing that stressors as well as a number of pharmacological agents have the capacity to induce long-term sensitization of brain DA systems and their associated behaviors may aid the clinician both in understanding the development of certain syndromes as well as devising novel means of treating others. For example, our work showing that stressors can sensitize the organism to AM has led us to suggest that vulnerability to or a prior history of stressful life events may explain the enigma of the extreme variability in susceptibility to AM (and cocaine) psychosis observed in naive users [3,6]. On the other hand, we have suggested that the time-dependent, sensitizing influence of antidepressants on DA autoreceptors may provide a model for the delayed therapeutic effects of such treatments and, therefore, that antidepressants may not need to be given on a daily basis for clinical efficacy [4, 8, 9].

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## REFERENCES

1. Angrist, B. and S. Gershon. The phenomenology of experimentally induced amphetamine psychosis. Preliminary observations. *Biol. Psychiat.* **1:** 95–107, 1970.
2. Antelman, S. M. and L. A. Chiodo. Stress: its effect on interactions among biogenic amines and role in the induction and treatment of disease. In: Handbook of Psychopharmacology, Vol. 18, edited by L. L. Iversen, S. D. Iversen and S. H. Snyder. New York: Plenum Press, 1982.
3. Antelman, S. M. and L. A. Chiodo. Amphetamine as a stressor. In: *Stimulants: Neurochemical, Behavioral, and Clinical Perspectives*, edited by I. Creese. New York: Raven Press, 1982.
4. Antelman, S. M., L. A. Chiodo and L. A. DeGiovanni. Antidepressant and dopamine autoreceptors: implications for both a novel means of treating depression and understanding bipolar illness. In: *Typical and Atypical Antidepressants: Molecular Mechanisms*, edited by E. Costa and G. Racagni. New York: Raven Press, 1982, pp. 121–132.
5. Antelman, S. M. and A. J. Eichler. Persistent effects of stress on dopamine-related behaviors: clinical implications. In: *Catecholamines: Basic and Clinical Frontiers*, edited by E. Usdin, I. J. Kopin and J. Barchas. New York: Pergamon Press, 1979, pp. 1759–1761.
6. Antelman, S. M., A. J. Eichler, C. A. Black and D. Kocan. Interchangeability of stress and amphetamine sensitization. *Science* **207:** 329–331, 1980.
7. Bell, D. S. The experimental reproduction of amphetamine psychosis. *Archs gen. Psychiat.* **29:** 35, 1973.
8. Chiodo, L. A. and S. M. Antelman. Repeated tricyclics induce a progressive dopamine autoreceptor subsensitivity independent of daily drug treatment. *Nature* **287:** 451–454, 1980.
9. Chiodo, L. A. and S. M. Antelman. Electroconvulsive shock: progressive dopamine autoreceptor subsensitivity independent of repeated treatment. *Science* **210:** 799–801, 1980.

10. Ellinwood, E. H. and M. M. Kilbey. Chronic stimulant intoxication models of psychosis. In: *Animal Models in Psychiatry and Neurology, I*, edited by I. Hanin and E. Usdin. New York: Pergamon Press, 1977, pp. 61–74.
11. Freedman, D. X. Introduction. In: *Depression Biology, Psychodynamics, and Treatment*, edited by J. O. Cole, A. F. Schatzberg and S. H. Frazier. New York: Plenum Press, 1978, pp 1–12.
12. Post, R. M. Cocaine psychosis: a continuum model. *Am. J. Psychiat.* **132:** 225, 1975.
13. Post, R. M. and J. C. Ballenger. Kindling models for the progressive development of psychopathology: sensitization to electrical, pharmacological, and psychological stimuli. In: *Handbook of Biological Psychiatry*, edited by H. M. van Praag, M. H. Lader, O. J. Rafaelsen and E. J. Sachar. New York: Marcel Dekker, 1981, pp. 609–649.
14. Serra, G., A. Argiolas and G. L. Gessa. Opposite changes in DA autoreceptors sensitivity induced by chronic antidepressants and neuroleptics. In: *Apomorphine and Other Dopaminomimetics, Vol. 1*, edited by G. L. Gessa and G. U. Corsini. New York: Raven Press, 1981, pp. 133–142.
15. van Kammen, D. P., W. E. Bunney, Jr., J. P. Docherty, D. C. Jimerson, R. M. Post, S. Siris, M. Ebert and J. C. Gillin. Amphetamine-induced catecholamine activation in schizophrenia and depression: behavioral and physiological effects. In: *Nonstriatal Dopaminergic Neurons*, edited by E. Costa and G. L. Gessa. New York: Raven Press, 1977, pp. 655–659.