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*Letters to the editors***Conditional tolerance to haloperidol-induced catalepsy: striatal dopamine receptor supersensitivity is a possible explanation**

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We wish to comment on the conclusions presented by de Graaf and Korf (1986) in their recent article entitled, "Conditional tolerance to haloperidol-induced catalepsy is not caused by striatal dopamine receptor supersensitivity" (Psychopharmacology 90:54–57). In their study, for 28 days rats received daily injections of both haloperidol (0.5 mg/kg) and saline in two distinctive environments. Tolerance to the drug's effects on catalepsy and biochemical markers for striatal dopamine (DA) function were subsequently assessed. Half of the haloperidol-treated rats were tested for catalepsy in the haloperidol-associated environment while the remaining half were assessed in the saline-associated environment. The biochemical measures were determined immediately after the catalepsy test. Behavioral tolerance occurred in rats tested in the haloperidol-paired environment but was significantly attenuated in rats tested in the saline environment. In contrast, biochemical tolerance occurred in both groups. The authors concluded that the development of DA supersensitivity in the striatum, a proposed mechanism accounting for biochemical tolerance, cannot sufficiently explain the development of behavioral tolerance to haloperidol-induced catalepsy.

We suggest that the evidence does not unequivocally support this conclusion; indeed, we propose an alternative interpretation that DA supersensitivity may be the biochemical mechanism of behavioral tolerance.

In explaining their results, de Graaf and Korf made the implicit assumption that following chronic haloperidol treatment, supersensitivity occurred at *all* dopaminergic synapses in the striatum. Because animals tested in the saline environment showed biochemical tolerance but not behavioral tolerance, this assumption forced the authors to conclude that "conditional tolerance to haloperidol-induced catalepsy is not caused by striatal dopamine receptor supersensitivity" (p. 54). This conclusion, however, is not necessary if one adopts the alternative assumption that supersensitivity develops only at *some* dopaminergic synapses in the striatum. According to this assumption, the development of supersensitivity may depend on simultaneous blockade of dopaminergic synapses and activity at other striatal synapses that is the result of particular sensory events. Adopting this assumption avoids the complexity of postulating a different pharmacological or anatomical mechanism to account for behavioral tolerance.

Some aspects of the structural organization of the striatum support this proposal. Thus, the striatum can be understood as a stimulus-response interface. It receives sensory input from all major sensory areas of cerebral cortex and sends its efferents to motor nuclei, such as the globus pallidus and the substantia nigra (see Garcia-Rill 1986). Furthermore, study of the internal organization of the striatum suggests that DA afferents (which have extensive arborizations), cortical afferents, and striatal neurons connect with common cells, which may be striatal motor efferents (Bolam 1984). Thus, within the striatum, incoming sensory information influences motor output, and diffuse dopaminergic afferents may have some influence on these synaptic connections (Beninger 1983).

Perhaps, when an animal encounters particular environmental stimuli, only a subset of sensory neurons projecting to the striatum is active. When haloperidol is administered, the influence DA has on these synaptic connections is temporarily blocked and the behavioral manifestation is catalepsy. However, when haloperidol is chronically administered in the presence of a particular set of stimuli, one might postulate that repeated activation of this subpopulation of sensory neurons may contribute to the alteration of DA function at some postsynaptic cells. That is, enhanced DA function (biochemical tolerance) may occur only at this subset of dopaminergic synapses resulting in behavioral tolerance only when an animal is tested in the appropriate environment.

This model explains the results of de Graaf and Korf. Behavioral tolerance only occurred in the environment where haloperidol was repeatedly administered. It did not occur to the same extent in the saline environment, perhaps because the subset of striatal neurons associated with those environmental stimuli was never active in the presence of haloperidol blockade and thus supersensitivity failed to occur at the related dopaminergic synapses. On the other hand, biochemical tolerance was apparent to the same degree in both groups. However, it may have been limited to a subset of dopaminergic synapses, those that were active in association with other cells activated by sensory stimuli in the haloperidol environment. It is important to remember that because the entire striatum was homogenized, it is impossible to know whether some or all of the dopaminergic synapses developed supersensitivity.

Thus, de Graaf and Korf overlooked the possibility of selective biochemical effects in the striatum and as a result

had difficulty explaining the observation that animals showed biochemical tolerance but not behavioral tolerance. The present model can explain the apparent incongruent results and maintains the assertion that striatal DA supersensitivity is responsible for mediating tolerance to haloperidol-induced catalepsy. Clearly, this explanation is speculative and future research will address its validity.

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