Technical Comment

# Controls for Lesions of the Nigrostriatal Dopamine System

Gerfen *et al.* (*1*) report that a unilateral 6-hydroxydopamine (6-OHDA) lesion of the nigrostriatal dopamine (DA) system in rat brain affects the expression of messenger RNAs (mRNAs) for $D_1$ and $D_2$ DA receptors, and for enkephalin and substance P, in the striatum ipsilateral to the lesion. They report that "dopamine deafferentation results in increases in both enkephalin and $D_2$ receptor mRNA expression in striatopallidal neurons, whereas there is a decrease in substance P and $D_1$ receptor mRNA in striatonigral neurons." On the basis of these observations they hypothesize how the apparent increases and decreases in mRNAs may influence striatal output.

Gerfen *et al.* may be correct in their interpretation, but to ascertain whether striatal DA denervation increases or decreases mRNAs, the signal in the striatum on the side of the lesion must be compared to that in some control tissue. The only control reported by Gerfen *et al.* was the amount of mRNA expression in the striatum *contralateral* to the 6-OHDA lesion. This would be appropriate if the striatum contralateral to a unilateral 6-OHDA lesion was not itself altered by the 6-OHDA lesion, but it may have been.

For example, after recovery from a large (>90%) unilateral 6-OHDA lesion of the substantia nigra, there was an increase in the extracellular concentration of DA in the *intact* striatum, contralateral to the lesion (*2*). The extracellular concentration of DA in the striatum *ipsilateral* to the lesion was maintained at normal or near normal levels until the lesion was essentially complete (*2, 3, 4*). In other words, after a partial unilateral 6-OHDA lesion was made, there was an asymmetry in the extracellular concentration of striatal DA, but this was largely caused by an increase in extracellular DA in the striatum on the "control" intact side of the brain, not by a decrease on the lesion side. In this case, if the extracellular concentration of DA on the side of the lesion was expressed relative to that on the intact side, there *appeared* to be a substantial lesion-induced decrease in extracellular DA; but this was illusory. Only by comparison with a neurologically intact control group was it possible to ascertain that the apparent decrease in extracellular DA on the side of the lesion was caused by an *increase* on the intact side (*2*). A complete 6-OHDA lesion produced a marked decrease in the extracellular concentration of DA on the side of the lesion, but in such animals extracellular DA in the contralateral striatum was still significantly elevated (*5*).

It has also been reported that single-unit activity in the striatum contralateral to a 6-OHDA lesion remains decreased (*6*) long after unit activity in the striatum ipsilateral to the lesion has returned to normal (*7*). Further, there was a long-lasting reduction in the sensitivity of the striatum opposite a 6-OHDA lesion to locally applied DA, which suggests that DA receptor had been down-regulated on that side (*8*). Soghomonian and Chesselet (*9*) found that a unilateral 6-OHDA lesion altered the expression of somatostatin (SOM) mRNA, but report that "the SOM labeling asymmetry in 6-OHDA treated rats was solely related to an increase of mRNA levels in the striatum on the contralateral side," not to changes on the side of the lesion.

It may be that a 6-OHDA lesion alters mRNAs for enkephalin and substance P on the side of the lesion. However, data on the effect of a unilateral 6-OHDA lesion on mRNAs in the contralateral, intact striatum are needed. This requires comparison of both sides of the brain in animals with a unilateral 6-OHDA lesion to both sides of the brains of neurologically intact control animals (*10*).

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*Response*: The crucial control group that Robinson suggests was included in a previous study (*1*) that appeared after our *Science* paper was published. In this study, we found that the amounts of enkephalin, substance P, and dynorphin mRNA in the striatum of control animals without lesions were not significantly different from those in the intact striatum of animals that received unilateral 6-OHDA lesions. The changes in peptide mRNA measured ipsilateral to the 6-OHDA lesion were the same regardless of whether they were compared to changes in the control animals without lesions or to changes contralateral to the lesion.

Before this study, we performed six pilot studies that compared control animals without lesions with animals that had unilateral 6-OHDA lesions. These unpublished studies showed that in the control animals without lesions, amounts of enkephalin, substance P, and dynorphin mRNA were not significantly different from those found contralateral to 6-OHDA lesions in experimental animals.

Because of these results, we felt justified, for practical reasons, in dropping the control group when we began studies that necessitated using large numbers of animals to test multiple drug treatments. Thus, although Robinson's questions about experimental design are relevant, they do not invalidate the findings of our *Science* report.

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