

## A Clinically Relevant Unilateral Rat Model of Parkinsonian Akinesia

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In transplantation research on Parkinson's disease, behavioral evidence of graft-specific improved function is as necessary as anatomical or chemical data in evaluating the success of the procedure. The circling model of Ungerstedt has been widely adopted to provide such evidence, in part because it is so convenient and (relative to primate models) inexpensive. In this model 6-hydroxydopamine (6-OHDA) is used to deplete nigrostriatal dopamine (DA) unilaterally. A reduction of the contraversive circling induced by the DA receptor agonist apomorphine or of the ipsiversive circling induced by amphetamine has been useful as a screen to test the integrity of grafts. However, it would be more compelling if the model included akinesia, one of the most disruptive symptoms of the disease. In addition, the model should reflect the clinical finding that akinesia becomes increasingly resistant to DAergic agonists, particularly in the severe later stages of parkinsonism. In the unilateral 6-OHDA rat, DA-agonist induced circling is actually more vigorous when the depletion of DA is more severe. Moreover, during circling behavior all limbs make stepping movements, even the limbs contralateral to the DA depletion in an undrugged animal (thus, there is no obvious akinesia). In this study, we describe a method of examining behavior in unilateral 6-OHDA rats which addresses these concerns.

When stepping behavior in the contralateral forelimb of unilateral 6-OHDA-treated rats was tested in isolation, severe and chronic akinesia was found in that limb. That is, when the hind-quarters and ipsilateral forelimb were raised off the ground so that the contralateral forelimb alone supported the weight of the animal, the contralateral forelimb failed to step. Occasional trembling could be observed in the limb, but no

more than a few small steps were ever initiated. In contrast, the isolated ipsilateral forelimb stepped normally (about 20 steps/min, which was similar to that of sham-operated animals when either limb was tested in isolation).

After D-amphetamine (3 mg/kg, i.p.), which caused ipsiversive circling in a standard rotation test, the number of steps taken by the isolated ipsilateral limb in the 6-OHDA rats increased to a mean of 48 steps/min, which was similar to that of amphetamine-treated sham control rats in this test. However, amphetamine did not significantly increase the number of steps taken by the isolated contralateral limb, which remained akinetic.

After apomorphine (0.5 mg/kg, s.c.), which caused contraversive circling in a standard rotation test, the number of steps taken by the isolated ipsilateral limb in the 6-OHDA rats increased to a mean of 45 steps/min, which was not significantly greater than that of apomorphine-treated sham control rats. Surprisingly, like amphetamine above, apomorphine did not significantly increase the number of steps taken by the isolated contralateral limb. Instead the limb remained akinetic, with intermittent bursts of dyskinetic, in-place movements.

How is it that both limbs step equally during standard rotation tests? Further examination of circling behavior indicated that the ipsilateral (unimpaired) forelimb shifted the weight of the animal to a new location in space, whereas the contralateral forelimb made only catch-up steps designed to re-establish support of the body's weight. The catch-up step in the contralateral limb appears not to require DA because non-lesioned animals treated with high doses of a DA antagonist (e.g., 3 mg/kg haloperidol) can readily step with either limb if the experimenter slowly

forces the animal forward or laterally in either direction. In the unilateral 6-OHDA animal, the ipsilateral limb provided both the stepping and the direction of stepping. After apomorphine the ipsilateral limb stepped almost continuously in the contraversive direction. In the standard circling test, the ipsilateral limb crossed over the contralateral limb, which in turn was simply picked up and placed under the newly shifted center of gravity. The well-known tight circling observed after apomorphine may be explained by this crossover pattern. After amphetamine the ipsilateral limb was less directionally biased than after apomorphine, but was generally ipsiversive, thus leading to the wide turns typically observed in rotation tests.

The data suggest that in the severely depleted unilateral 6-OHDA rat, movements typical of the ipsilateral forelimb but *not* of the contra-

lateral forelimb are DA-related. The ipsilateral forelimb is capable of initiating stepping movements that have major weight shifting consequences whereas the contralateral forelimb almost exclusively makes reactive steps to regain support of a displaced center of gravity, a behavior that does not require DA. The apomorphine-related dyskinesias and failure to alleviate reliably the akinesia in the contralateral forelimb are reminiscent of the unreliability of DA agonists in end-stage Parkinson's disease. Improvement in the capacity of the isolated contralateral limb to initiate normal stepping movements that substantially shift the center of gravity may be a more useful target for potential therapies than attenuation of circling behavior, which does not adequately mirror one of the most debilitating characteristics of Parkinson's disease: akinesia.