Commentary

A new mouse model to study compensatory mechanisms that support normal motor function in Parkinson’s disease


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Introduction

Many studies have shown that compensatory mechanisms are an important aspect of disease progression in both experimental Parkinson’s disease (PD) models as well as in PD patients, including compensation by dopaminergic [1-3] and nondopaminergic pathways such as acetylcholinergic [4], GABAergic [4], and glutamatergic [5] systems. For example, when dopamine levels decrease, synthesis of dopamine is increased promptly by rapid upregulation of tyrosine hydroxylase (TH) activity [2]. After this initial response, slower compensatory mechanisms take effect. These mechanisms include increased TH expression as well as increased sensitivity of striatal neurons to dopamine, the latter is caused by augmented sensitivity or by increased expression of postsynaptic dopamine receptors [1, 3]. In addition, Bezard and Gross [6] postulated that a correlation exists between defined stages of PD and specific compensatory mechanisms. Development of strategies that build upon these compensatory effects, particularly at early stages of the disease, can help maintain or possibly regain normal motor function in PD patients by enabling the survival of remaining dopaminergic neurons. These strategies may be crucial for disease treatment. A recently published study in the Journal of Neuroscience by Golden et al. [7] reported that congenital loss of dopaminergic neurons induces a remarkable adaption of the nigrostriatal system, which allows a limited amount of striatal dopamine to maintain normal motor function. This study highlights the potential for the activation of compensatory systems as promising therapies that would help PD patients adapt to the loss of dopamine, alleviating their motor symptoms.

Golden et al. [7] established a mouse model which expresses diphtheria toxin (DTA) in dopamine transporter (DAT)-positive neurons to create a model of developmental damage specific to dopaminergic neurons (DAT-DTA mice). DAT-DTA mice exhibited up to a 90% loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) and ventral tegmental area (VTA, Fig. 1D), a significant reduction of dopaminergic fibers in the striatum (Fig. 6), and a concomitant depletion of striatal dopamine (Fig. 7). These pathological features mimic those observed in PD patients. Motor and sensorimotor function in these animals was evaluated by conducting a broad spectrum of behavioral tests including locomotor activity (Fig. 4A-C), rotarod (Fig. 4D-H), pole climbing (Fig. 5A,B), movement-initiation (Fig. 5C), inverted screen test (Fig. 5D), and gait analysis (Fig.5E,F). Surprisingly, almost no motor behavior deficits were detected in DAT-DTA mice. When treated with haloperidol, a dopamine receptor antagonist, performance of DAT-DTA mice in the open-field test and the movement...
initiation test was impaired to the same degree as control mice (Fig. 8A), indicating that the remaining striatal dopamine (3% of control; Fig. 7A) is sufficient to sustain normal motor function in DAT-DTA mice. To further investigate how small amounts of striatal dopamine sustain normal motor function in DAT-DTA mice, their sensitivity to L-DOPA was measured. A dose of L-DOPA that did not affect control mice in the open-field test significantly increased locomotor activity of DAT-DTA mice (Fig. 8B). These results suggest that striatal dopamine receptors are highly sensitized in DAT-DTA mice, providing a plausible explanation for the observed preservation of motor behavior by very small amounts of dopamine.

The studies by Golden et al. [7] have significantly advanced our knowledge and have uncovered new, important avenues of research. Non-motor symptoms including olfaction impairment, autonomic nervous system failure, cognitive dysfunction, and mood disorders precede motor symptoms in PD [8]. Thus, it would be important to determine whether the DAT-DTA mice exhibit non-motor symptoms. For example, dopamine levels are positively associated with learning and memory [9, 10], the severe depletion of dopamine in the DAT-DTA mice could conceivably affect cognitive function. Furthermore, VTA dopaminergic neurons project to prefrontal cortex. Ascertaining whether loss of VTA dopaminergic neurons (Fig. 1D) leads to a decrease in dopamine levels in prefrontal cortex would provide key information related to non-motor function in DAT-DTA mice, as prefrontal dopamine signaling regulates cognitive and executive function. Moreover, the DAT-DTA model may be useful to study vulnerability to PD risk factors such as aging, and exposure to neurotoxins (e.g. rotenone, paraquat, 6-hydroxydopamine or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). The study of Golden et al. (2013) may also provide key insights into the mechanisms that permit the more efficient utilization of remaining dopaminergic neurons after their depletion in PD.

While the studies by Golden et al. [7] have many merits listed above, there are some caveats that might affect their conclusions. For example, one caveat is that most experimental sample sizes are below 10 (n=2-13, Figs 4, 5, 8). In most behavioral studies using mouse models sample sizes of 10-20 are commonly needed to provide sufficient statistical power to detect moderate differences between groups [11]. Another weakness of the study is that male and female animals were pooled for all behavioral tests, but no evidence was provided whether there were any differences in outcomes between genders [11]. Although the authors reported marginal interindividual variance among animals in the various experimental groups, differences could have become apparent with larger sample sizes and/or by separating sexes.

Furthermore, body weight is a major confounding factor for many motor behavioral assays used in this study (e.g. rotarod, locomotor activity, pole test, inverted screen, and gait analysis) [12]. While DAT-DTA mice weighed significantly less than age-matched controls (females >3 months; males >10 months, Fig.1B, C), the influence of body weight was not parsed out in the data analysis. Thus, longer latency to fall on the inverted screen for DAT-DTA mice as compared to control mice (Fig. 5D) might be explained solely by their reduced body weight (Fig. 1B,C) [7].

Two more caveats should be considered regarding the progressive loss of dopaminergic neurons in SNc and VTA (Fig. 1D-F). First, the effect of age and genotype and the significance of differences in performance of control and DAT-DTA mice at each of the 4 time points examined would have been best determined using 2-way ANOVA or a mixed model instead of Student’s t-test. Second, because defects in rotarod performance become apparent at the age of 18- or 24 months old, studies using animals at those ages (older than 12 months) would be necessary to determine whether there is further loss of dopaminergic neurons. These studies would be very important because they would determine whether there is a threshold for the number of dopaminergic neurons needed before motor deficits are present in this model. Also, a progressive loss of dopaminergic neurons with advanced age could call into question some of the data that combine 18-24 (Fig. 4, 5A-D) and 12-24 months old (Fig. 7) animals [7]. Because of these potential confounds, it is possible that 24 month-old DAT-DTA mice might still be presymptomatic rather than asymptomatic.

Because there was no reported difference in motor function between DAT-DTA and control mice at the age tested (Figs. 4, 5), and behavioral data is highly variable, a vehicle-treated DAT-DTA group should have been included in the haloperidol and L-DOPA experiments to make the results more meaningful. This oversight in the experimental design compromised the conclusion that motor behavior in DAT-DTA mice is maintained by dopamine-dependent compensation.

Additionally, Golden et al. [7] did not discuss an important study previously published in Trends in Neuroscience, which reported that presymptomatic compensation in PD is not dopamine-mediated [13]. Bezard et al. [13] proposed three functional compensatory changes within and outside of the basal ganglia in the presymptomatic period of PD. In the first period, dopamine homeostatic compensatory mechanisms mask the disease. In the second period, after the breakdown of striatal dopamine homeostasis, a more powerful compensation takes place within the basal ganglia to increase the activity of the basal ganglia output structures (e.g. globus pallidus). In the third period, robust compensation within and outside (e.g. supplementary motor area) the basal ganglia takes place and plays a crucial role in leading to emergence of motor abnormalities. Thus, it is conceivable that DAT-DTA mice may represent a model of the second or third stages of the presymptomatic period as proposed by Bezard et al. Further
investigation of the activity of output structures within and outside basal ganglia should address these possibilities.

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References


