Introduction

Chorea in Huntington’s disease (HD) patients has been proposed to arise predominantly from indirect pathway (IP) dysfunction [1-4] and D2-expressing striatal medium spiny neurons (MSN) giving rise to IP projections appear more vulnerable to mutant huntingtin (mHtt) insult [4, 5]. Consistent with this, BACHD transgenic and Q175 knock in mouse models demonstrate age-dependent alterations in firing activity of downstream nuclei within the IP; namely an increase in mean firing rate of D2 MSN innervated globus pallidus (GP) neurons and a corresponding decrease in the mean firing rate of pallidal-innervated subthalamic nucleus (STN) neurons in vitro and in vivo (D.J Surmeier and J. Tepper, CHDI personal communication). We have tested this finding in a full length BAC transgenic Huntington’s disease rat model, by recording intrinsic firing rates from GP and STN nuclei in vivo at a behaviorally symptomatic age.

Material and Methods

Male BACHD rats and their WT littermate rats (8-10 months old) were anesthetized with Urthane (initial dose at 1.5 g/kg, i.p.) and surgically implanted with two catheters, one in the femoral vein and one in the femoral artery, for drug administration and blood sampling. The animal was mounted on a stereotactic apparatus (David Kopf instrument) in a flat skull position. Core temperature was maintained at 37°C by a heating pad. To gain access to the STN and GP recording sites, the micro-electrodes were advanced by a dual single axis in vivo micromanipulator system (Scientifica, United Kingdom) mounted on two koh stereotactic holders. Two burr holes were drilled on the skull. One with stereotaxic coordinate of AP -0.8 to 1.3 mm, Lateral 3-4.4 mm (GP recording, with a 10 degree angle) and the other at AP -3.2 to -3.9, Lateral 2.1-2.7 mm (STN recording). The recording electrodes were advanced to reach the target coordinates of the GP (5.5-5.7 mm below the brain surface) and STN (6.8 to 7.5 mm below the dorsal surface).

At the end of each experiment, the recording sites were marked by the microinjection of Pontamine Skyblue (20 µA, 15 min) into a cannula. Each rat was given an overdose of Urthane. The brain was immediately removed and fixed in 4% Paraformaldehyde for 4 hrs and placed in phosphate buffered saline (PBS) with 20% sucrose over night. The brains then were frozen and cut into 40 µM thick coronal sections. The sections were mounted on gelatin-coated slide and stained with Cresyl Violet in order to determine the location of the recording sites. The data were assessed using one-way ANOVA/two way ANOVA or paired Student T-test, when appropriate. All data are expressed as mean ± SEM or as percentage of the baseline firing rate. A P value less than 0.05 was deemed statistical significant.

Histology confirmation of the recording sites in Globus Pallidus (GP) and Subthalamic nucleus (STN)

In BACHD rats, mean firing rates showed a non-significant increase in GP and a significant decrease in STN

<table>
<thead>
<tr>
<th>Firing Rate (Hz)</th>
<th>GP WT</th>
<th>GP HD</th>
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<tbody>
<tr>
<td>WT</td>
<td>25.46 ± 2.816 N=13</td>
<td>20.26 ± 2.357 N=12</td>
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<tr>
<td>P</td>
<td>0.216</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Firing Rate (Hz)</th>
<th>STN WT</th>
<th>STN HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT</td>
<td>5.177 ± 1.854 N=12</td>
<td>10.87 ± 1.985 N=12</td>
</tr>
<tr>
<td>P</td>
<td>0.05</td>
<td></td>
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In HD rats, the overall firing pattern of GP neurons appears to become more regular with fewer burst-type cells. The firing pattern of STN neurons exhibits the opposite trend, with fewer regular firing cells and proportionally more burst-type cells.

Summary and Conclusion

• Our current findings provide evidence that mHtt affects firing properties of the pallidosubthalamic pathway in rodent HD models similar to those reported in clinically afflicted HD patients [1].
• The contribution of extrinsic versus intrinsic factors underlying these changes are being explored.
• Our dual recording approach in HD rodents may be a useful model for assessing compounds that revise abnormal activity of the indirect pathway.

References