Behavioral and biochemical evaluation of the anti-dyskinetic potential of sarizotan, a 5-HT_{1A} agonist, in 6-OHDA lesioned rats.

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**Conclusion**

Chronic treatment with L-DOPA/sarizotan caused less dyskinetic behavior and a lower striatal neuronal IEGs response compared to chronic L-DOPA treatment.

In contrast, these treatments caused similar neuroadaptive changes in opioid peptides expression in the striatum.

Overall, it seems that evaluation of neuronal IEGs responses in striatum upon drug administration provides a tool for the preclinical characterization of the dyskinetic potential of a drug beyond behavioral tests.

**Methods**

Unilateral 6-OHDA lesion

Rats were anesthetized with ketamine/xylazine 50 mg/kg each, and 6-OHDA (in a 5mg/ml solution) was injected into the median forebrain bundle on the side contralateral to the lesion in a still position; (2) limb abnormal involuntary movements. According to their turning behavioral. According to their turning behavior, rats were divided into two main groups: (1) chronic treatment with L-DOPA and L-DOPA/sarizotan did not induce any change compared to the first day of treatment.

**BEHAVIORAL ANALYSIS**

![Turning behavior](image)

- Both L-DOPA and L-DOPA/sarizotan significantly increased arc and c-fos mRNA level in the lesioned side as compared to lesioned side of vehicle treated rats.
- mRNA level of both IEGs in L-DOPA/sarizotan treated rats was significantly lower compared to the L-DOPA-treated group.

**BIOCHEMICAL ANALYSIS**

- Dynorphin mRNA
- Enkephalin mRNA

**Efficacy of Unilateral 6-OHDA Lesion**

![Efficacy of Unilateral 6-OHDA Lesion](image)

- Measurement of contralateral turning after apomorphine and [^{3}H]RTI-55 autoradiography in striatum confirmed the efficacy of the 6-OHDA lesion

- 6-OHDA lesion caused a decrease in dynorphin and an increase in enkephalin mRNA level compared to the intact side

- Both treatments with L-DOPA and L-DOPA/sarizotan significantly increased dynorphin mRNA level in the lesioned side as compared to lesioned side of vehicle treated rats while they did not induce any change in enkephalin mRNA level

**Protocols**

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Turning AIMs</th>
<th>Turning AIMs</th>
<th>Turning AIMs</th>
<th>Turning AIMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-DOPA (10 mg/kg)</td>
<td>1</td>
<td>7</td>
<td>14</td>
<td>21</td>
</tr>
<tr>
<td>L-DOPA/sarizotan (10/2.5 mg/kg)</td>
<td>2</td>
<td>12</td>
<td>21</td>
<td>23</td>
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</tbody>
</table>

**ISH in striatum for IEGs**

- (Arc and c-fos) neuropeptides (dynorphin and enkephalin)

**[^{3}H]RTI-55** autoradiography in striatum

- Winner of the ECNP Travel Grant Award

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