The Role of Serotonergic Raphestriatal Neurons In Parkinson's Disease and Apomorphine-Induced Dyskinesia

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Introduction

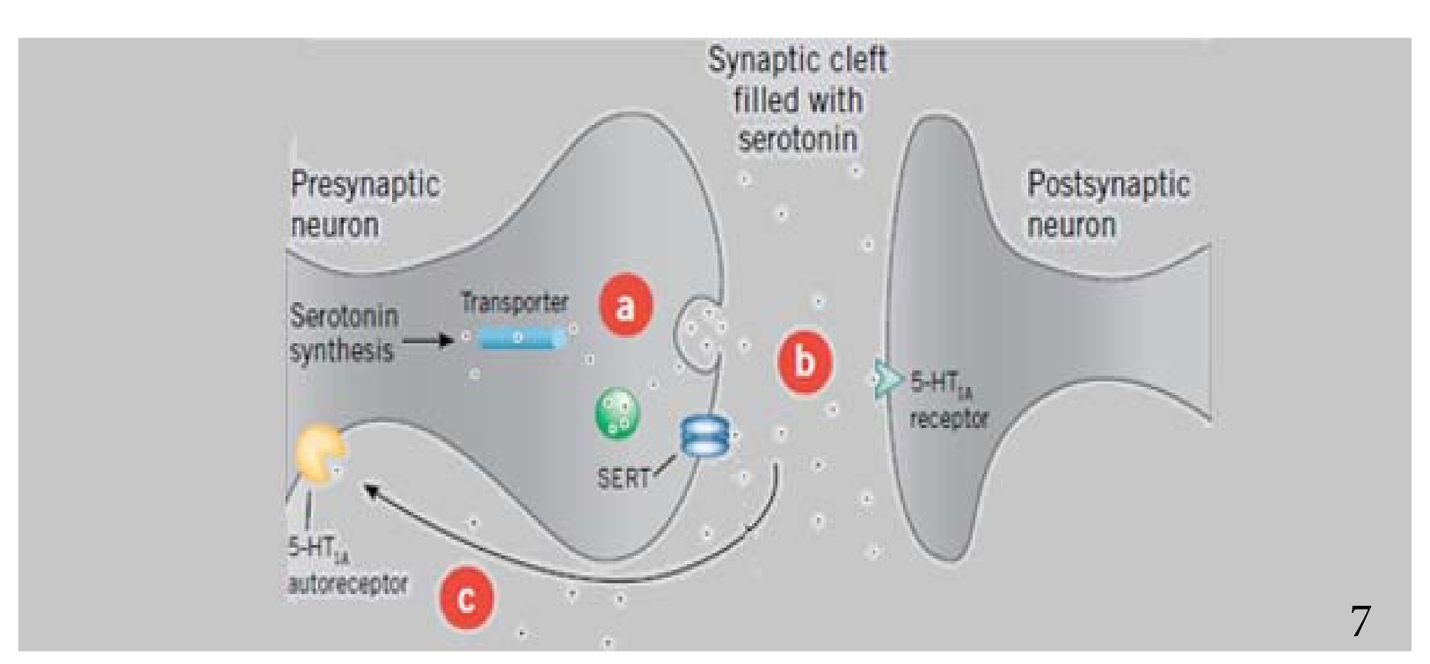
Parkinson's disease (PD) is a neurodegenerative disorder caused by denervation of dopaminergic neurons traveling from the substantia nigra to the striatum. After long-term treatment to increase dopamine (DA) using the precursor L-DOPA, increased involuntary movements called dyskinesia (LID) frequently appear, presumably by causing excess DA release. Although the symptoms of dyskinesia are opposite to those of PD, two classes of drugs, 5-HT1A agonists and glutamate NMDA antagonists, have been suggested to ameliorate both disorders.[1,2,3]

One hypothesis suggests that LID occurs because 5-HT raphestriatal neurons take up L-DOPA and convert it to DA thereby improving PD and causing LID when DA is released in excess[5]. This excess release further promotes dyskinesia as it results in sensitization of postsynaptic NMDA receptors[3]. 5-HT1A agonists are assumed to decrease LID by stimulating autoreceptors on these 5-HT neurons and decreasing DA release. Other hypotheses suggest that LID is due to changes in striatal post-synaptic 5-HT and glutamate receptors. One way of discriminating between these hypotheses is to induce dyskinesia (and reduce PD) by injections of the DA D2/D3 agonist apomorphine, which will not increase the amount of DA released by 5HT neurons and will, thus, eliminate their influence.

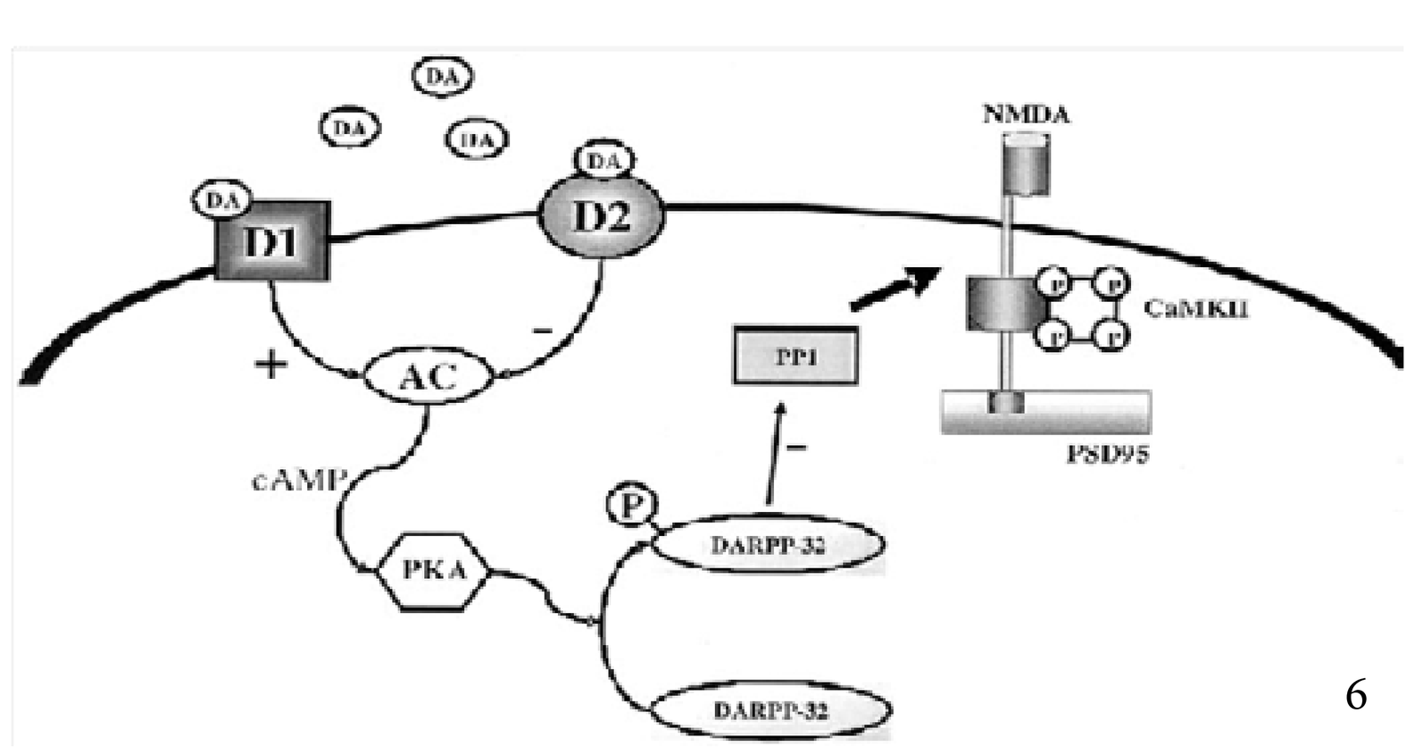
Objectives:
1) Determine if 8-OH-DPAT, a 5-HT1A agonist is effective in treating PD in the absence of dyskinesia.
2) Determine if 8-OH-DPAT and MK-801 will reduce PD and dyskinesia in rats made dyskinetic by injections of apomorphine.

Raphestriatal Involvement in Dyskinesia

1. Serotonin:
- Non-physiological release of DA.
- $5HT_{1A}$ agonists reduce release by targeting autoreceptors.[5]



2. Glutamate:
- Phosphorylation of postsynaptic NMDA receptors increasing sensitization
- NMDA antagonists reduce stimulation of these sensitized receptors.[6]



Method

Nigrostriatal lesions were performed using 6-OHDA.
Experiment 1: Rats were injected with saline, 0.2 mg/kg 8-OH-DPAT, or 8 mg/kg L-DOPA. Forepaw stepping was tested 30 min later.
Experiment 2: 0.05 mg/kg apomorphine was administered for 10 days to induce dyskinesia. Rats then were given either saline, 0.1 or 0.2 mg/kg MK-801, 0.2 or 0.3 mg/kg 8-OH-DPAT, or a combination of the two drugs. After 20 min, 0.05 mg/kg apomorphine was administered. AIMs were tested at 30 and 45 min, forepaw stepping at 32 min.

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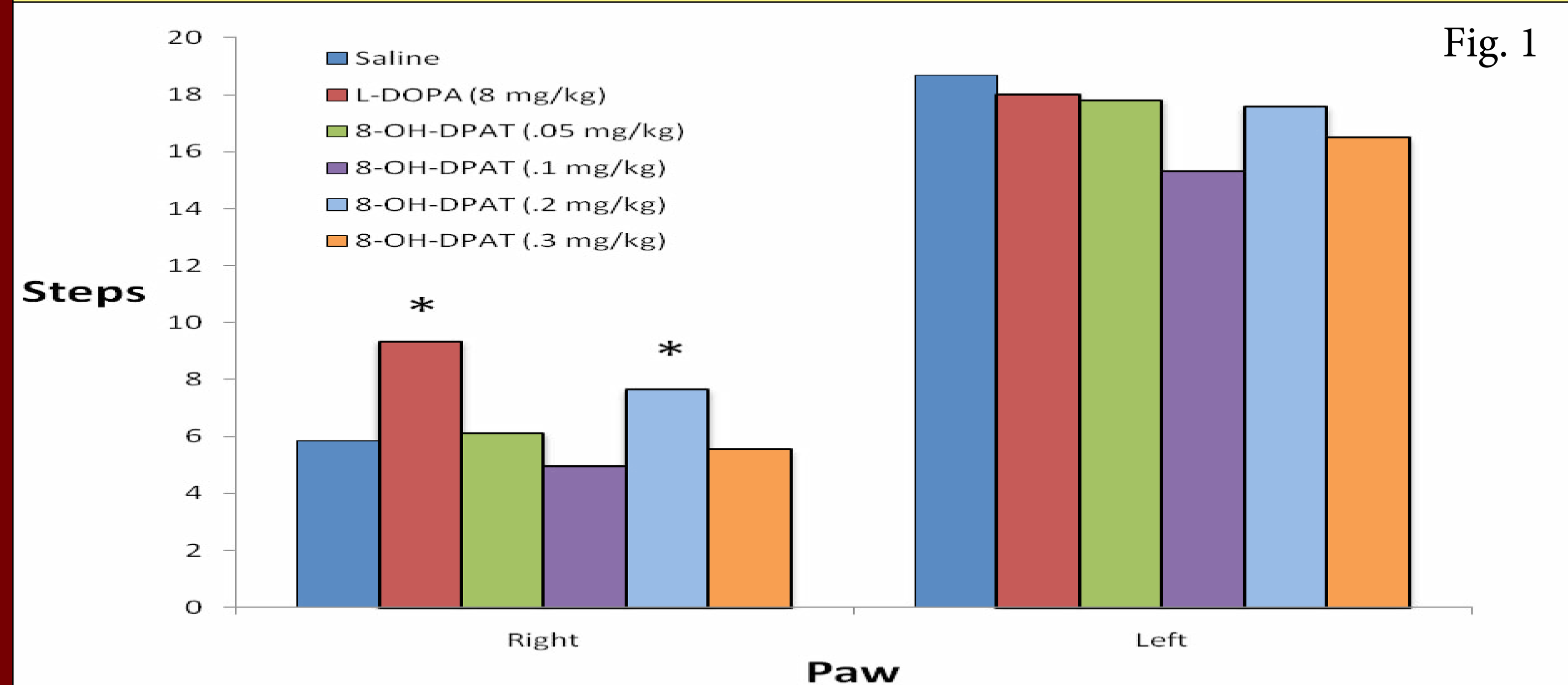
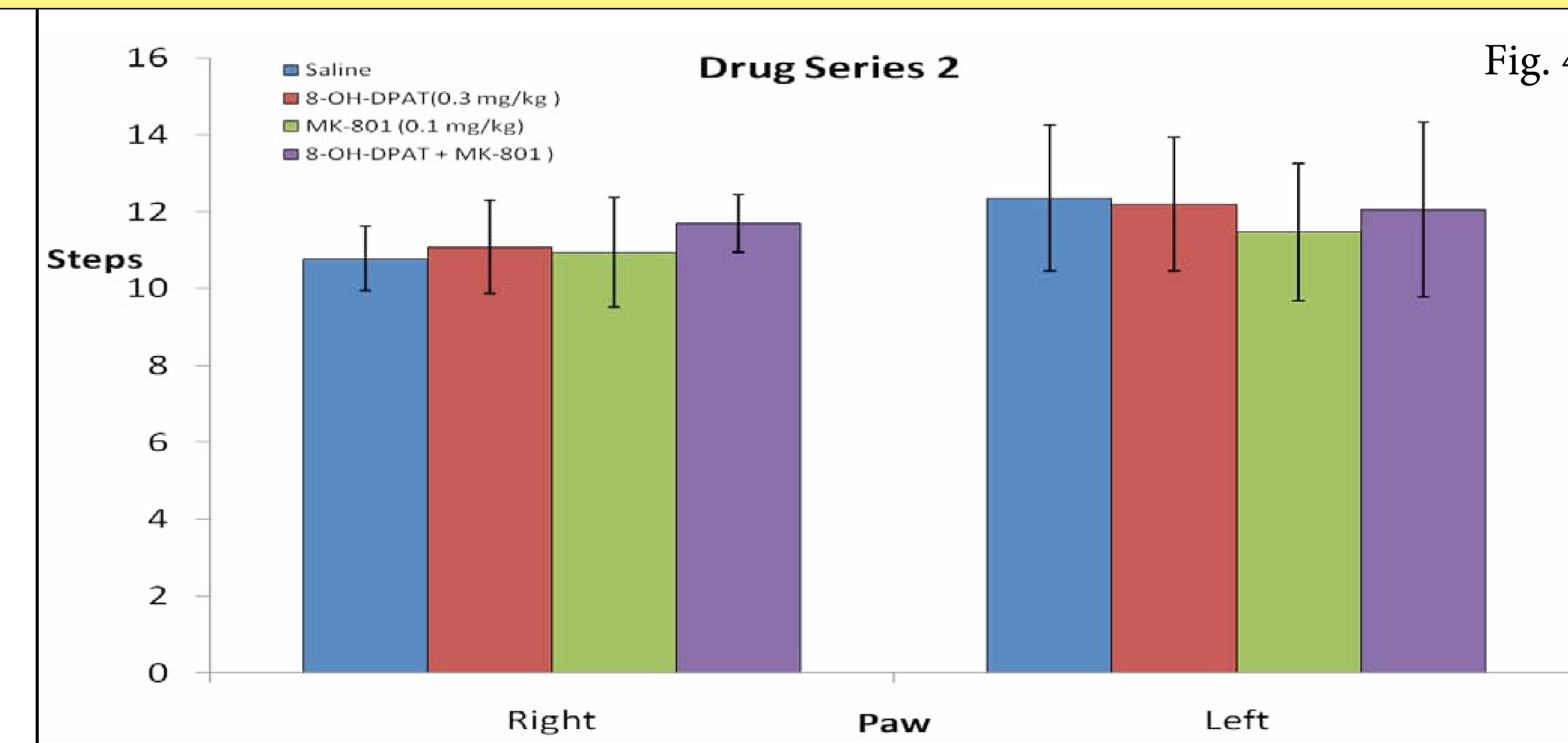
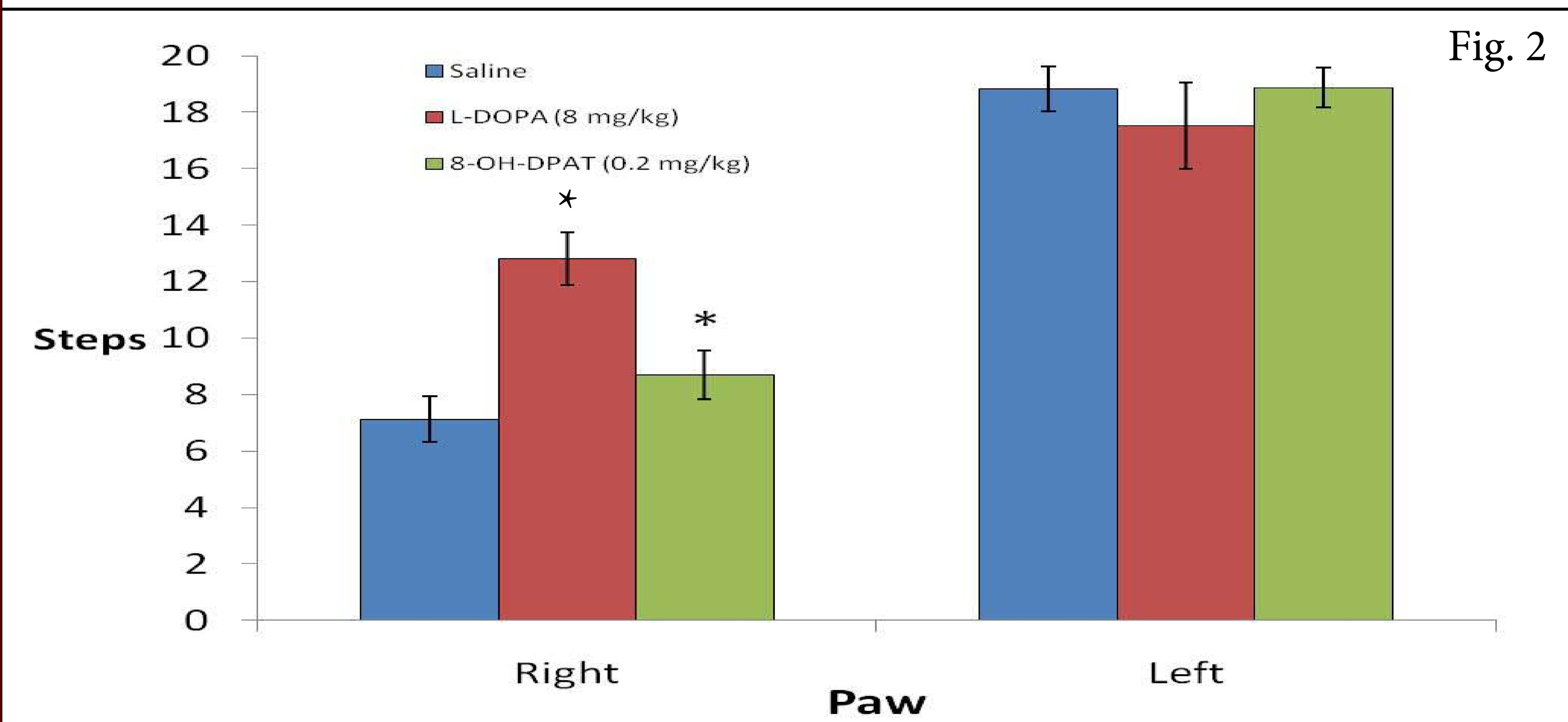
Results



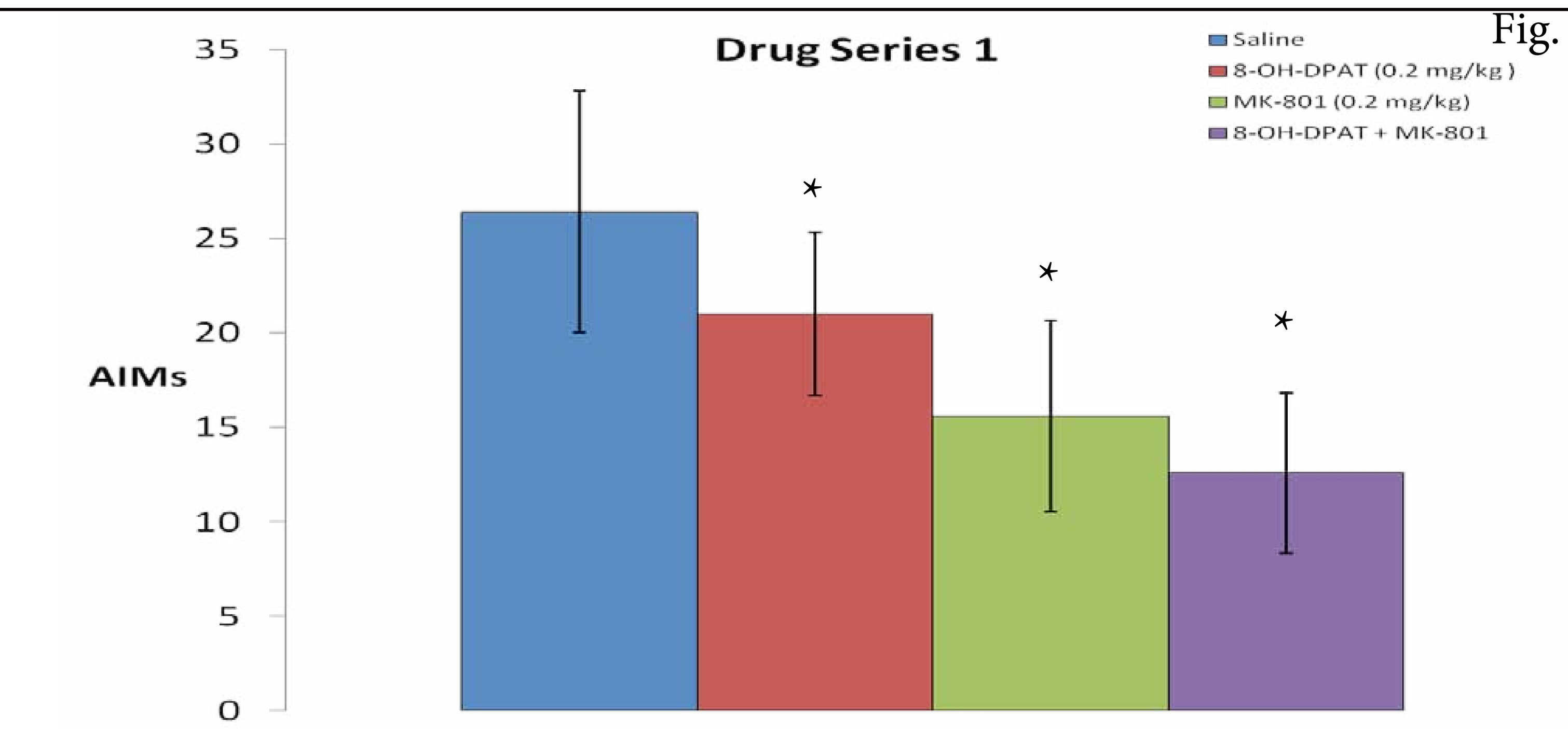
The unilateral 6-OH-DA lesion impaired stepping with the right paw, but not the left paw. Preliminary analyses indicated that 8 mg/kg L-DOPA and 0.2 mg/kg 8-OHDA improved right paw stepping with no effect on left paw stepping. In the next experiment, I increased subjects tested at these doses. *p <.05



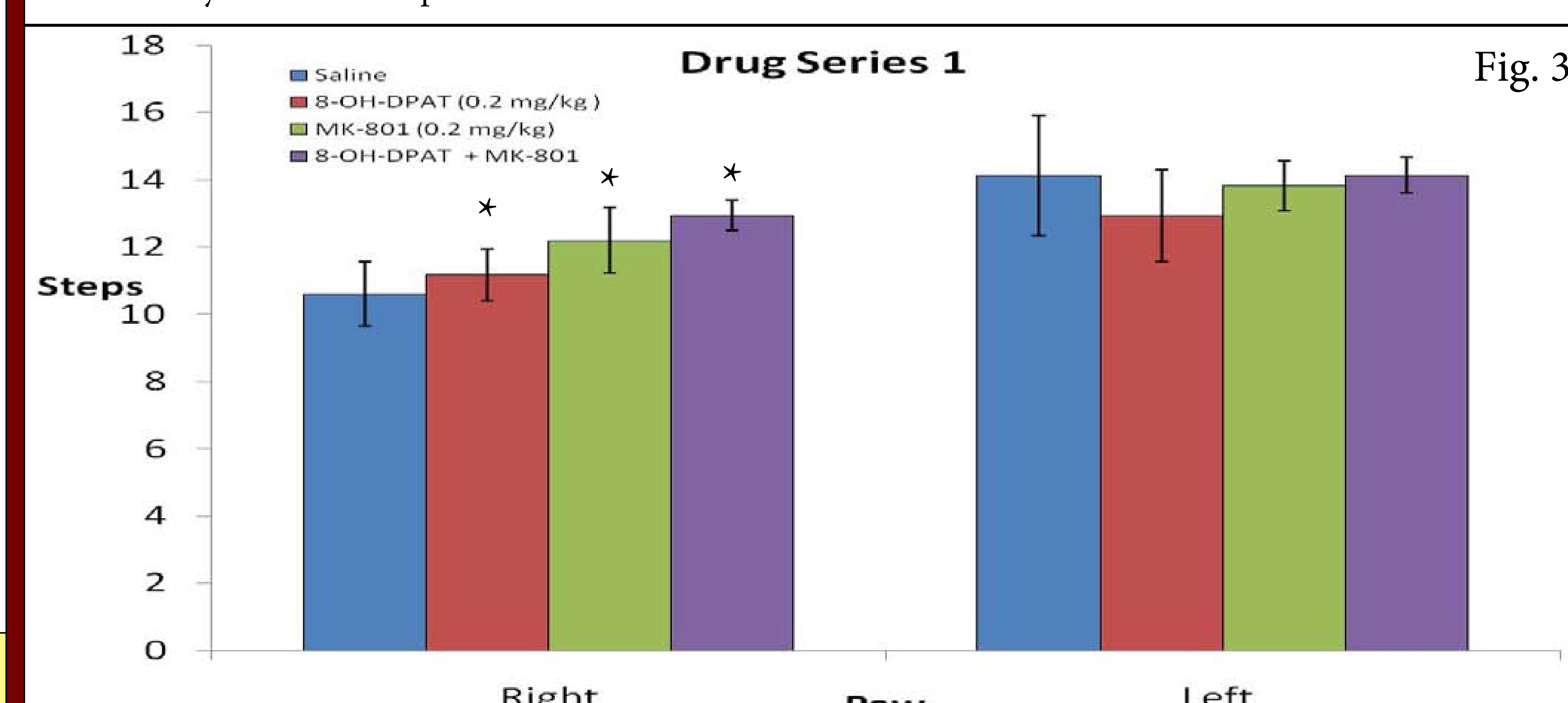
0.3 mg/kg 8-OH-DPAT and 0.1 mg/kg MK-801 had no effect on stepping in drug series 2, indicating boundaries of doses at which these drugs are effective. *p<.05



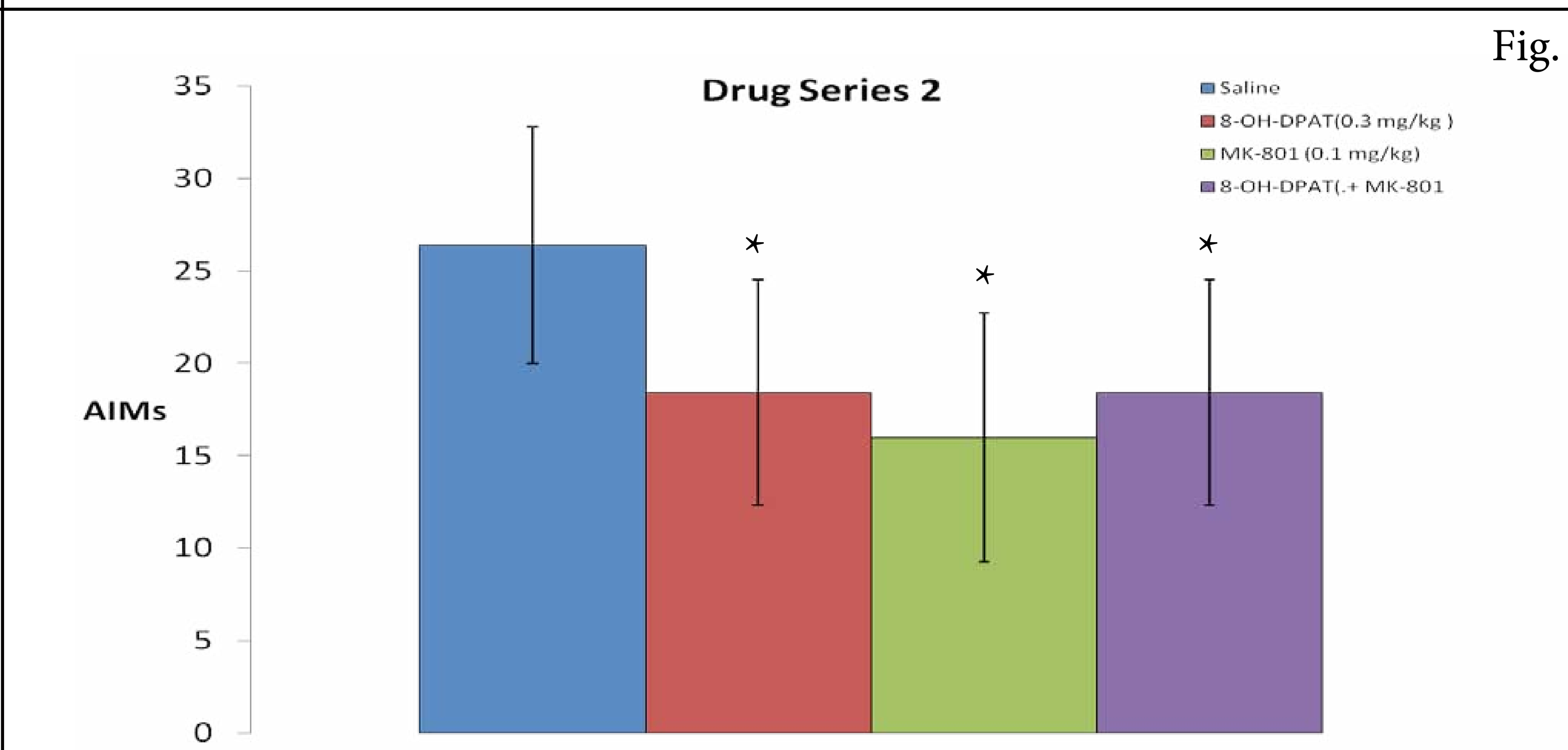
With a larger *n*, 8 mg/kg and 0.2 mg/kg 8-OH-DPAT increased right paw stepping. Although 8-OH-DPAT was not as effective as L-DOPA, this finding does indicate that 8-OH-DPAT can be effective in treatting PD in non-dyskinetic rats. *p <.05



0.2 mg/kg MK-801 and 0.2 mg/kg 8-OH-DPAT both decreased AIM scores in rats made dyskinetic with apomorphine. Because apomorphine does not increase DA release through raphestriatal neurons, these data indicate that these drugs target other mechanisms that DA release from 5-HT neurons*p <.05



Both 0.2 mg/kg MK-801 and 0.2 mg/kg 8-OH-DPAT significantly increased stepping in rats with apomorphine-induced dyskinesia. This demonstrates that effectiveness of these two drugs in treating PD is maintained in dyskinetic rats. Furthermore, there is an additive effect when these drugs are administered in combination *p <.05



8-OH-DPAT and MK-801 reduced AIMs somewhat less efficaciously in drug series 2, once again indicating boundaries of drug doses which result in maximal effects. *p <.05

Discussion

These data support previous findings that 8-OH-DPAT and MK-801 both are effective in reducing PD symptoms based on forepaw stepping. For 8-OH-DPAT, this is seen in both dyskinetic and non-dyskinetic rats, while for MK-801, all PD testing was conducted on dyskinetic rats.

The other major finding is that both drugs are effective in reducing dyskinesia produced by injections of the D2/D3 agonist apomorphine. Because apomorphine does not enable the raphestriatal 5-HT neurons to release excess DA, these results indicate that these drugs act at sites unaffected by this non-physiological release. For 5-HT1ARs, previous research indicates this extra raphe site may be located on corticostriatal glutamate neurons, either postsynaptically in the cortex, or as heteroreceptors in the striatum[5]. In upregulation/sensitization of NMDA receptors depends on unregulated release of DA from 5-HT neurons as postulated,[3] then perhaps the effectiveness of MK-801 in this paradigm reflects the ability of MK-801 to decrease the effects of excess glutamate release[1]. In any event, these data clearly indicate that these drugs can be effective in reducing both PD and dyskinesia in ways that do not require excess release of DA from 5-HT neurons. Further research is required to determine their precise sit and mechanism of action.