ELSEVIER

European Journal of Pharmacology 272 (1995) 123–129

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# Systemic administration of the NMDA receptor antagonist MK-801 potentiates circling induced by intrastriatal microinjection of dopamine

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Received 22 July 1994; accepted 4 October 1994

**Abstract**

Systemic administration of the non-competitive antagonist of NMDA receptors MK-801 ((+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine) potentiates the circling response induced by direct stimulation of the striatal dopaminergic receptors through intracerebral application of dopamine. Microinjection of dopamine (1, 5, 25 or 50 $\mu$g/1.0 $\mu$l) induced a dose-dependent contralateral circling response, when injected directly into the lesioned side of unilaterally 6-hydroxydopamine-lesioned rats. Interestingly, intrastriatal application of dopamine (1, 5, 25 or 50 $\mu$g/1.0 $\mu$l) followed by a systemic administration of MK-801 (100 $\mu$g/kg i.p.) produced a potentiated contralateral circling response in unilaterally 6-hydroxydopamine (6-OHDA)-lesioned rats. This motor effect is reversed compared to the marked ipsilateral circling response produced by MK-801 when given alone. Moreover, the potentiated responses persist 4-fold longer compared to the circling induced by dopamine alone. The results suggest that the potentiation by NMDA receptor antagonists of motor activity induced by dopaminergic agonists in animal models of Parkinson's disease cannot be ascribed simply to increased release of dopamine. Other mechanisms including increased sensitivity of dopamine $D_1$ receptors or blockade or glutamatergic transmission in output structures must be considered.

*Keywords:* Dopamine; Microinjection; MK-801; Circling; Potentiation; Striatum, rat; 6-Hydroxydopamine

## 1. Introduction

Several studies have proposed that antagonists of excitatory amino acids may be beneficial for the treatment of Parkinson's disease (Klockgether and Turski, 1989; Carlsson and Carlsson, 1989a,b; Schmidt and Bubser, 1989; Olney et al., 1987). This new therapeutic approach is based in part on the belief that glutamate and dopamine are functionally opposite in the basal ganglia. In several models, dopamine receptor agonists and glutamate receptor antagonists, such as (+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (MK-801), a noncompetitive antagonist of the NMDA receptor/channel complex (Wong et al., 1986, 1988), have similar actions at both biochemical and behavioral levels. It appears that MK-801 produces behavioral responses partly mediated by the release of dopamine (Clineschmidt et al., 1982; Hiramatsu et al., 1989; Lösher et al., 1991; Rao et al., 1990), and partly by a catecholamine-independent process (Carlsson and Carlsson, 1990).

In fact, antagonism of excitatory amino acid neurotransmission by MK-801 administered systemically induces a marked ipsilateral circling response in 6-hydroxydopamine (6-OHDA) unilaterally lesioned rats (Clineschmidt et al., 1982; St-Pierre et al., 1991). However, this compound produces a pronounced locomotor stimulation in catecholamine-depleted mice (Carlsson and Carlsson, 1989a) and rats (Klockgether and Turski, 1990), suggesting a catecholamine-independent mechanism. Moreover, an interesting property has been revealed about the noncompetitive NMDA receptor antagonists MK-801 and phencyclidine as well as the competitive NMDA receptor antagonists CPP (3-((±)-

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*SSDI* 0014-2999(94)00612-1

2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid) and SDZ EAA494 (D-CPPene) of the NMDA receptor. When combined in low doses either with the α-adrenoreceptor agonist clonidine or subthreshold doses of the dopamine receptor agonists apomorphine or L-dopa, which per se did not produce motor stimulation, these NMDA receptor antagonists induced a remarkable potentiation of the antiparkinsonian action in monoamine-depleted mice (Carlsson and Carlsson, 1989b; Carlsson and Svensson, 1990) and rats (Klockgether and Turski, 1990).

In the present study, we were particularly interested in determining whether the presence of striatal dopamine is really crucial in the ipsilateral circling (toward the denervation) response of 6-hydroxydopamine-lesioned rats induced by MK-801. If so, local application of dopamine on the denervated side should decrease or abolish the ipsiversive circling response to systemic administration of MK-801 by restoring the balance in stimulation of dopamine receptors. Moreover, it is well known that injection of the neurotoxin 6-hydroxydopamine into the medial forebrain bundle (MFB) of the rat causes degeneration of the ipsilateral nigrostriatal dopamine neurons and loss of dopamine from the ipsilateral striatum (Ungerstedt, 1968), and leads to supersensitivity of postsynaptic dopamine receptors. In this context, local administration of dopamine on these supersensitive receptors might even facilitate the motor response of the denervated striatum and induce contraversive circling in combination with systemic MK-801. A preliminary report of these results has been presented (St-Pierre et al., 1992).

## 2. Materials and methods

The experiments were carried out on 12 female adult Sprague-Dawley rats (Charles River, Canada) weighting 200–300 g at the beginning. The animals were housed in single cages on a 12 h light/dark schedule with free access to food and water. Monitoring of circling activity took place between 9 a.m. and 11 p.m. The measurements began a few minutes after intracerebral microinjection of drugs, and was continued for a period of up to 600 min. A period of 30 min was allowed for habituation prior to drug administration.

### 2.1. 6-Hydroxydopamine lesion

Unilateral lesions were performed in the left medial forebrain bundle at the following stereotaxic coordinates B −4.8, L + 1.4, V −8.5 (Paxinos et Watson, 1986). All lesions were done in ovariectomized rats under ketamine/xylazine (87 mg/kg, 13 mg/kg i.m.) anaesthesia. 6-Hydroxydopamine (8 mg/2 ml ascorbate (0.1%) saline (0.9%) (Sigma, St. Louis, MO, USA)), was delivered at a rate of 0.5 μl/min with a Harvard infusion pump. The stainless-steel injection cannula (30 gauge) was left in place an additional minute to allow diffusion of the neurotoxin.

### 2.2. Behavioral test

Fifteen days after the lesion, the rats were tested with apomorphine (0.25 mg/kg of body weight s.c.; Merck Frost). After systemic administration, the animals were placed in circling activity cages (rotometers). Each activity cage consists of a Plexiglas cylinder measuring 40 cm high and 30 cm wide. One by one, the rats were fitted with a harness and attached to the activity monitoring system. The circling response induced by the dopaminergic agonist was monitored during 30 min. Animals which circled more than 5 turns per minute were selected for further study.

### 2.3. Guide cannula implantation

All rats assigned to intracerebral microinjection experiments were anesthetized with intramuscularly administered ketamine/xylazine (87 mg/kg, 13 mg/kg). Two stainless-steel intracerebral guide cannulas (23 gauge) were stereotaxically implanted into the striatum at the following stereotaxic coordinates: B + 0.25, L ±2.7, V −5.6, according to Paxinos and Watson (1986). The guide cannulas were secured 2.0 mm above the injection site with dental cement and skull screws. Moreover, protection stylets (30 gauge) were inserted into guide cannulas between injections. Experiments were performed at least 3 days after implantation.

### 2.4. Combined injections

Prior to the intracerebral microinjection, the protection stylets were removed. A stainless-steel injection cannula (30 gauge) of appropriate length was connected to a 10 μl Hamilton syringe by polyethylene tubing and carefully lowered through the guide cannula. Microinjections were made by a Harvard infusion pump in conscious animals. The injected volume was 1.0 μl and the rate of injection was 1.0 μl/min. The injection cannula was left in place an additional minute to allow diffusion of the solution.

Intrastriatal microinjections were performed into the lesioned side of the unilaterally 6-OHDA-lesioned rats. Twelve animals received a dose of 1, 5, 25 and 50 μg of dopamine, in a random order. For experiments 1 and 3, dopamine (Sigma) (solubilized in Ringer solution containing NaCl 147 mM, $CaCl_2$ 2.3 mM, and KCl 4 mM) was followed by administration of a 0.9% NaCl solution. For experiment 2, microinjection of dopamine was followed by MK-801 (100 μg/kg of body weight:

RBI). Each microinjection of dopamine was repeated 3 times in the same animals and followed, 20 min later, by intraperitoneal administration of MK-801 or saline. One injection of saline preceded and the other followed the combination with MK-801 to ensure that responsiveness to dopamine was maintained. After the systemic injection, each animal was placed in the circling activity cage. Six animals were also tested with the same dose of MK-801 alone. The animals were allowed to rest 5–7 days between experiments.

### 2.5. Histology

When the experiments were completed, the animals were perfused successively with 500 ml of a 0.9% NaCl solution and 500 ml of 10% formaline under ketamine/xylazine anesthesia. The brain was then excised carefully and coronal tissue sections were prepared frozen on a microtome. The sections were placed on chromalun microscope slides and stained with cresyl violet for verification of injection sites (Fig. 4).

### 2.6. Statistics

Measurements of the circling activity such as total counts and maximum rate were expressed as the mean and standard error of the mean (S.E.M.) for each dose of dopamine. Significant differences were evaluated using an analysis of variance (ANOVA) for repeated measures followed by Scheffe's a posteriori test with a level of $P < 0.05$ being considered significant.

## 3. Results

MK-801 (100 $\mu$g/kg i.p.) per se produced a marked ipsilateral circling activity as we had reported previously (Fig. 1). Microinjections of dopamine, in doses of 1, 5, 25 and 50 $\mu$g/1 $\mu$l in experiments 1 and 3, were used as controls. Intrastriatal injections of dopamine into the lesioned side induced a dose-dependent contralateral (referred to the injection site) circling response. Importantly, the circling activity produced by each dose of dopamine in experiment 1 was similar to the response observed in experiment 3 showing that there was no change in responsiveness to dopamine itself during the course of the experiment (Fig. 2). The duration and the total counts of the circling response for each dose of dopamine were virtually identical (Figs. 2 and 3A).

Furthermore, in the second experiment, systemic administration of MK-801 (100 $\mu$g/kg i.p.) combined with intrastriatal application of dopamine (1, 5, 25 and 50 $\mu$g/1 $\mu$l in the striatum) induced a potentiated contralateral circling response (Fig. 2). This reversed response to the combined drugs persisted with a duration 4-fold that of the circling response induced by dopamine alone (Fig. 2). The total counts of the poten-

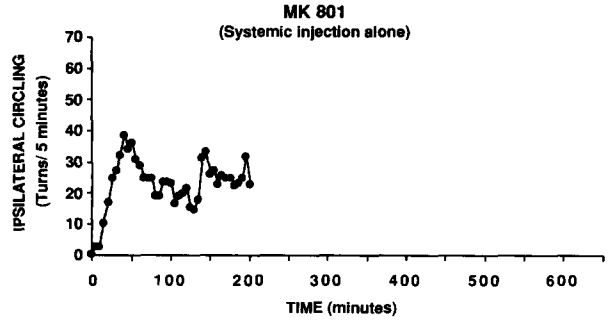


Fig. 1. Time course of action of an intraperitoneal injection of MK-801, 100 $\mu$g/kg, in unilaterally lesioned rats. Results are expressed as mean values ($n = 6$).

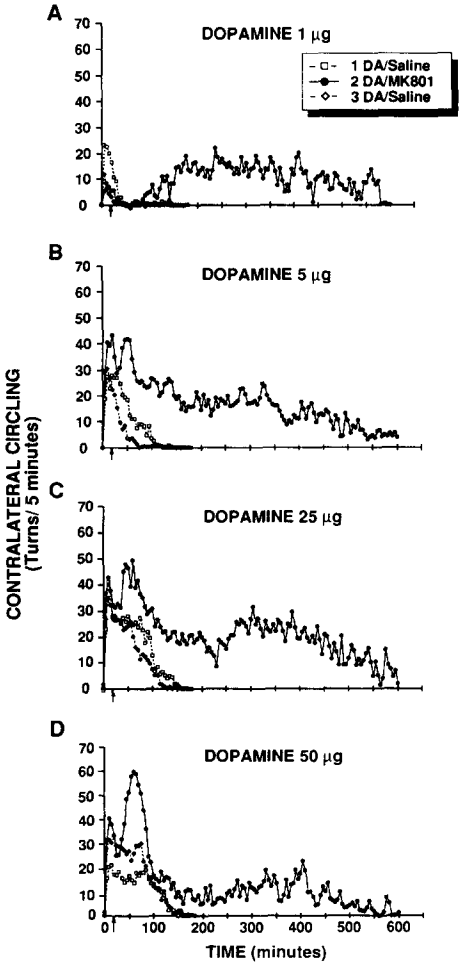


Fig. 2. Time course of action of intrastriatal microinjections of dopamine into the lesioned side at a dose of (A) 1, (B) 5, (C) 25, and (D) 50 $\mu$g in 1.0 $\mu$l followed by intraperitoneal administration (arrow) of either vehicle (□ ----- □, ◇- - - - -◇) or MK-801 (●———●), 100 $\mu$g/kg, on the circling response in unilaterally lesioned rats. Results are presented as mean values. Statistical evaluations of the curve parameters are shown in Figs. 3 and 4.

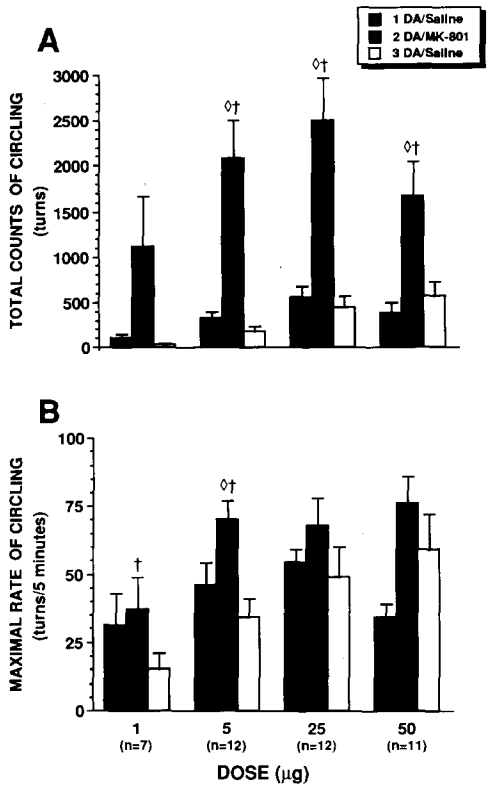


Fig. 3. Total counts (A) and maximum rate (B) of the circling response induced by intrastriatal microinjections of 1, 5, 25, and 50 $\mu$g/1.0 $\mu$l of dopamine (DA) into the lesioned side followed by vehicle or by MK-801, 100 $\mu$g/kg, administered intraperitoneally in unilaterally lesioned rats. The number of animals is given in parentheses. Results are presented as means ± S.E.M. ($^{\diamond}$ $P < 0.05$ vs. experiment 1 (DA/Saline), $^{\dagger}$ $P < 0.05$ vs. experiment 3 (DA/Saline), Scheffe's a posteriori test).

tiated circling reponse, for all doses of dopamine, were significantly different compared to the control experiments 1 and 3 except for the dose of 1 $\mu$g in which the group was smaller (Fig. 3A). However, the duration of each potentiated rotation activity was significantly different compared to the control experiments 1 and 3 for all doses of dopamine (Fig. 2). Curiously, the potentiated circling responses induced at all doses of dopamine had a biphasic curve for the total counts whereas the durations are equal (Figs. 2 and 3A). The maximum circling rate seems to be potentiated by MK-801 at all doses of dopamine but the difference reached statistical significance only at a dose of 5 $\mu$g of dopamine compared to control experiments 1 and 3 (Fig. 3B).

## 4. Discussion

This study demonstrates that systemic application of MK-801 potentiates the circling response induced by direct stimulation of the striatal dopaminergic receptors with intracerebrally administered dopamine. Moreover, microinjection of dopamine combined with MK-801 reverses the circling response in unilaterally 6-OHDA-lesioned rats compared to the marked ipsilateral circling response produced by MK-801 when given alone (Figs. 1 and 2). In fact, dopamine induced a contralateral circling response, when injected directly into the lesioned side. The response to dopamine appeared to increase with the dose up to 25 $\mu$g (Fig. 3A). Similarly, microinjection of dopamine into the lesioned side followed by systemic injection of MK-801 produced a contralateral circling response both in terms of duration and maximal rate (Figs. 2, 3A and B). Again the maximum effect was seen at 25 $\mu$g of dopamine. This circling response persisted with a duration 4-fold that of the circling response induced by dopamine alone (Fig. 2). Interestingly, the potentiated responses still continued in the contralateral direction long after dopamine-induced circling responses should have been terminated. We might have expected at the end of the normal effect of dopamine to see a progressive reversing of the contralateral to an ipsilateral circling response as seen when MK-801 is given alone. Since there should be only a minimal amount of dopaminergic fibers remaining reported on the lesioned side, the persisting MK-801-induced contralateral circling response seems to be related to the activation of postsynaptic dopaminergic receptors. It could also mean increased efficacy of the signal originating in the striatum at the level of output structures such as the substantia nigra pars reticulata.

Some studies have reported an increase of dopamine metabolism in several regions, including striatum, after systemic administrations of MK-801 (Hiramatsu et al., 1989; Lösher et al., 1991; Rao et al., 1990). It is possible that blockade of NMDA receptors causes activation of the dopamine release via an indirect influence on the dopaminergic nerve terminals. Inhibition of glutamatergic transmission in the striatum, a region with a high density of NMDA receptors (Albin et al., 1992), could lead to a decrease in the activity of the GABAergic striatonigral neurons resulting by suppressing the inhibitory feedback in an increase of the dopaminergic transmission in the striatum by the nigrostriatal neurons.

On the other hand, there is now considerable evidence that agonists of the glutamate receptors such as L-glutamate and *N*-methyl-D-aspartate (NMDA) can increase the synthesis (Arias-Montano et al., 1992) and release of striatal dopamine in vitro (Roberts and Anderson, 1979) and in vivo (Carter et al., 1988; Cheramy et al., 1986; Moghadam et al., 1990) by acting on excitatory amino acid receptors located on the dopaminergic terminals. Competitive and noncompetitive NMDA receptor antagonists can abolish the NMDA-evoked dopamine release without affecting the basal dopamine release in the striatum (Carter et al.,

1988). Moreover, electrophysiological studies have demonstrated that intrastriatal application of NMDA enhances firing rate of striatal cells in the rat (Overton and Clark, 1992). In addition, contraversive motor asymmetry and forelimb dyskinesias were observed when glutamate analogs were given unilarerally (Jenner et al., 1980; Toth and Lajtha, 1989), and increased motor activity when given bilaterally (Cools and Peeters, 1987).

Considering these results, the antagonist of the NMDA receptor might be expected to block dopamine release. In fact, microdialysis studies performed in vivo have shown that systemic application of MK-801 produced no increase of the extracellular level of dopamine indicating that MK-801 caused motor effects by a mechanism which does not involve release of striatal dopamine (Kashihara et al., 1990; Weihmuller et al., 1991). Considering the fact that dopaminergic nerve terminals are degenerated in the lesioned side in 6-hydroxydopamine animal models, it is conceivable that activation of the postsynaptic dopaminergic receptors would be responsible for the behavioral effects.

Recent molecular evidence shows that blockade of NMDA receptors could increase the effects of dopamine upon the dopamine $D_1$ receptors in the striatonigral neurons by preventing dephosphorylation of DARPP-32 (dopamine and cyclic AMP regulated phosphoprotein) (Halpain et al., 1990). In fact, a behavioral study performed in the 6-hydroxydopamine rat model has shown that SKF 38393, a dopamine $D_1$ receptor agonist or L-dopa, a pro-drug of dopamine, combined with MK-801 produce a potentiated contralateral circling response (Morelli and Di Chiara, 1990) while the opposite is true for the dopamine $D_2$ receptor agonist quinpirole.

It is known that the affinity of the dopamine $D_1$ receptors for dopamine is 10-fold higher than that of the dopamine $D_2$ receptors (Seeman et al., 1986). Then, it is possible that a certain degree of dopamine $D_1$ receptor stimulation is a prerequisite for facilitated DARPP-32 phosphorylation by NMDA antagonists and production of a potentiated response. In fact, in Fig. 2A, a very small dose of dopamine (1 $\mu$g) which by itself produces practically no motor response was followed about 40 min after MK-801 by a prolonged contralateral circling response. Probably, such as small amount of dopamine is sufficient at the cellular level to stimulate the dopaminergic receptors. As seen in Fig. 3A and B, the contralateral response to dopamine increases to a certain point with the dose in terms of peak circling rate and total circling counts. These two parameters were greatly magnified by the administration of systemic MK-801. The increase was parallel to that seen after dopamine alone. However, the duration of the response appears equal for all doses of dopamine suggesting that this potentiation is an all-or-none phenomenon which requires a minimal presence of dopamine at the post-synaptic receptors.

Taken together, our results suggest that the potentiation of dopamine effects seen in the present experi-

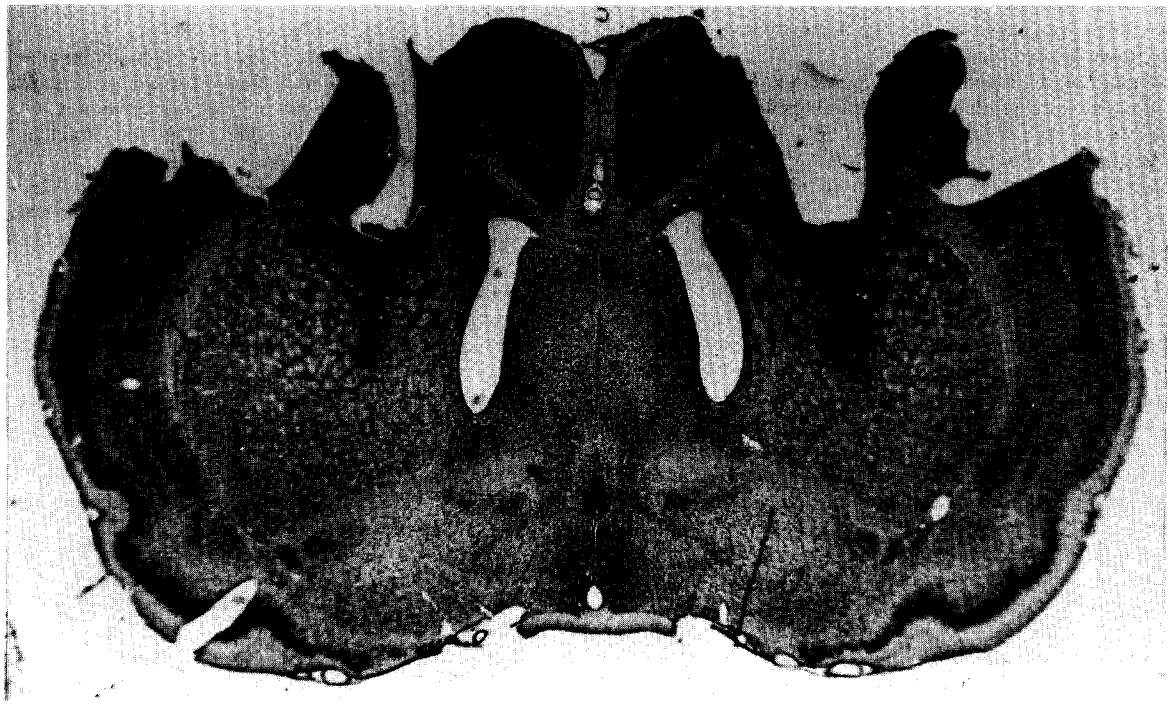

Fig. 4. Photomicrograph showing bilateral needle tracks with tips located in the striatum.

ment cannot be explained by increased release of dopamine due to MK-801. The interaction between these two agents could occur at the level of the striatum, but in the present experiment, we can only be certain that dopamine acted at this level. As for MK-801, it could act at multiple sites and in preliminary experiments (St-Pierre et al., 1991), we have observed a stronger effect of MK-801 on circling when injected directly in the substantia nigra pars reticulata than in the striatum. The combination of dopamine receptor activation (possibly $D_1$) and suppression of glutamatergic transmission leads to a new functional state of responsiveness to these agents which could be beneficial for instance in the treatment of Parkinson's disease.

## Acknowledgements

This work was supported by grants from the Medical Research Council (MRC) of Canada and the Fonds pour la Formation de Chercheurs et l'Aide à la Recherche (FCAR) from the province of Quebec. The authors wish to thank Mrs. Laurent Grégoire and François Tardif for technical assistance and Miss Monique Baron who helped prepare the manuscript.

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