to the past experience and present state of the organism.

It has been proposed that these endogenous patterns of neural activity may reflect previous experiences and are in that sense released from memory rather than evoked (*8*). We have observed changes in visual evoked potentials to a positive discriminative stimulus during sensory conditioning and extinction (*6*). These changes suggested that in addition to the neuronal activity evoked by the flash, the wave shape of the evoked potential reflects the release of neuronal activity which is related to the past experience of the organism. Additional support for this approach comes from studies which show that when an expected event does not occur, a brain potential appears at a latency similar to that of potentials usually evoked by the expected stimulus. These brain events, called "emitted potentials," have been interpreted as reflecting memory processes corresponding to past stimuli (*9*). A possible implication of our observation is that the experience of a specific stimulus image is dependent on the establishment of those neurophysiological processes originally involved in the registration and coding of the stimulus.

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Tremor and Involuntary Movements in Monkeys: Effect of L-Dopa and of a Dopamine Receptor Stimulating Agent

Abstract. *Either L-dopa, in combination with 1-α-methyldopa hydrazine (MK-486), or 1-(2″-pyrimidyl)-4-piperonylpiperazine, an agent that stimulates dopamine receptors, relieves surgically induced tremor in monkeys and concomitantly evokes involuntary movements. These results indicate that tremor and involuntary movements are associated with a common mechanism and that the activity of the dopamine receptors is involved in the regulation of these dysfunctions.*

Abnormal involuntary movements have emerged as one of the most limiting side effects in achieving optimum therapeutic results with L-dopa (*1*). A model for studies of involuntary movements (IM) in animals could provide some insights on the mechanisms involved in the production of dyskinesias. In this report we describe the effects of L-dopa and of 1-(2″-pyrimidyl)-4-piperonylpiperazine (Trivastal), an agent that stimulates dopamine receptors (*2*), on the relief of tremor and on the production of IM in monkeys with ventromedial tegmental lesions. These studies show that the stimulation of dopamine receptors is associated in monkeys with the relief of tremor and the development of involuntary movements.

Green monkeys (*Cercopithecus sabaeus*) were used, and unilateral radiofrequency lesions were induced in the ventromedial tegmental region of the brainstem as previously described (*3*). Hypokinesia of the contralateral extremities appeared immediately afterward. In some monkeys a resting tremor (4 to 6 cycle/sec) developed 5 to 7 days later. The lesions were induced at least 1 month before the start of the experiments. Recordings of tremors were obtained by means of a transducer attached to the extremities

Table 1. Types of abnormal movements.

Type 1
Increased aggressiveness and threatening posture
Restlessness, chattering, irritability, hypersensitivity
Increased water intake
Type 2
Repetitive stereotyped movements of the mouth, tongue, and face, with (i) lip smacking, (ii) chewing, (iii) tongue rolling, (iv) cheek pouch manipulation, (v) biting
Striking hyperkinesia with apparent highly vigilant orienting behavior
Increased grooming activity, including prolonged repetitive grooming of the same body area
Monotonous side-to-side swaying of body
Repetitive hand movements, sometimes without visible purpose
Chorea-like movements
Unusual sitting or walking postures

Table 2. The effect of L-dopa or Trivastal (Servier, France) on tremor and on the development of IM in normal monkeys with ventromedial tegmental lesions (VMT). L-Dopa and MK-486 (Merck) were given intraperitoneally, MK-486 60 minutes before L-dopa. These drugs were given for 5 consecutive days to three normal monkeys and to three monkeys with lesions. The development of IM was usually observed in normal monkeys after 2 or 3 days of treatment; in monkeys with lesions, the disappearance of the tremor and the development of IM were usually observed 1 or 2 days after treatment. Trivastal was given intravenously to three normal monkeys and to three monkeys with lesions. The drug was tested six times in each monkey, once every fourth day. In all experiments, the disappearance of the tremor was observed 20 to 40 minutes before IM developed.

Surgical lesion	Drug	Motor impairment	Involuntary movements	
			Type	Duration (hours)
None	MK-486 (10 mg/kg) + L-dopa (100 mg/kg)	None	1	1 to 2
None	Trivastal (3 mg/kg)	None	1	1
VMT	None	Hypokinesia and tremor	None	1 to 2
VMT	MK-486 (10 mg/kg) + L-dopa (100 mg/kg)	Tremor stopped for 60 minutes	1, 2	3
VMT	Trivastal (3 mg/kg)	Tremor stopped for 3 to 4 hours	2	1 to 2

and were recorded on an electroencephalograph. The effects of drugs acting on the central nervous system were investigated in control monkeys and in monkeys in which ventromedial tegmental lesions had resulted in spontaneous resting tremors of the contralateral extremities. The involuntary movements were observed visually for a period of at least 6 hours after each experiment, and some experiments were recorded cinematographically.

The IM in monkeys could be classified into two types (Table 1). Type 1 movements were evoked in normal monkeys by administration of L-dopa (100 mg per kilogram of body weight, intraperitoneally) in combination with 1-α-methyldopa hydrazine (MK-486) (10 mg/kg, intraperitoneally), a dopa decarboxylase inhibitor that acts peripherally. The same dosages of L-dopa and MK-486 given to monkeys with ventromedial tegmental lesions resulted in a transient disappearance of tremor with a concomitant development of IM of types 1 and 2 (Table 2). Lower doses of L-dopa (25 to 50 mg/kg) resulted in a transient relief of tremor (decreased amplitude for 1 hour), with a concomitant development of IM (type 1 movements for 15 to 45 minutes).

Trivastal had an effect similar to that of L-dopa (Table 2). In normal monkeys, Trivastal (3 mg/kg, intravenously) induced IM type 1; while in monkeys with ventromedial tegmental lesions, Trivastal at this dose relieved the tremor and induced IM of types 1 and 2. Trivastal at a lower dose (0.5 to 1 mg/kg) relieved the tremor for 1 to 2 hours and caused slight IM of type 1 for approximately 1 hour.

Table 3 shows the effects of Trivastal, in combination with other centrally acting drugs, on relief of tremor and on the development of IM. Haloperidol, an agent that blocks dopamine receptors, prevented the development of IM induced by Trivastal but decreased the effectiveness of the drug in reducing tremor. Trivastal in combination with haloperidol produced reduction of the tremor for 1 to 2 hours, but a tremor with higher than original intensity developed subsequently. Treatment of monkeys with 5-hydroxytryptophan diminished the Trivastal-induced IM of type 1, but had no effect on the IM of type 2 or on tremor reduction. The effectiveness of Trivastal in relieving tremor and in evoking IM was diminished by prior administration of α-methyl-*p*-tyrosine. Fusaric acid, which inhibits dopamine β-hydroxylase, had no effect on the tremor-relieving or IM-inducing activities of Trivastal.

Table 3. The effects of various centrally acting drugs on the Trivastal-induced involuntary movements. Trivastal and 5-hydroxytryptophan were given intravenously, haloperidol was given intramuscularly, and all other drugs were given intraperitoneally. All drugs were given 1 hour prior to the administration of Trivastal. Each drug was tested in three monkeys at least three times.

Drugs	Pharmacological response
None	Sustained hypokinesia and postural tremor
Trivastal (3 mg/kg)	Tremor absent for 3 to 4 hours, IM for 1 to 2 hours
Haloperidol (2 mg/kg) + Trivastal (3 mg/kg)	Tremor absent for 1 hour, then exaggerated tremor for 2 to 3 hours, IM absent
L-5 Hydroxytryptophan (30 mg/kg) + Trivastal (3 mg/kg)	IM of type 1 diminished
DL-α-Methyl-*p*-tyrosine (80 mg/kg) + Trivastal (3 mg/kg)	IM diminished
Fusaric acid (80 mg/kg) + Trivastal (3 mg/kg)	No effect on IM

The data presented here indicate that the activation of dopamine receptors—by administration either of L-dopa or of Trivastal, an agent that stimulates dopamine receptors—results in the relief of tremor in monkeys and in the development of IM. Trivastal given to monkeys relieves tremor at a much lower dose and for a longer period of time than does L-dopa. It is therefore conceivable that Trivastal might be more effective than L-dopa against tremor in Parkinsonian patients or in patients with other extrapyramidal disorders. The blockade of dopamine receptors with haloperidol abolishes the IM evoked by Trivastal but also diminishes the tremor-relieving activity of the drug. Thus the separation of the tremor relief from IM induction could perhaps be achieved by partial blockade of the dopamine receptors with neuroleptic agents.

Because α-methyl-*p*-tyrosine, an inhibitor of tyrosine hydroxylase, diminishes tremor-relieving and IM-inducing activities of Trivastal, we cannot exclude the possibility that some presynaptic events are partly involved in the mediation of activity of this drug. Inasmuch as it was postulated that norepinephrine formed from administered L-dopa is involved in the development of IM, it is noteworthy that fusaric acid, an inhibitor of norepinephrine biosynthesis, has no effect on either activity of Trivastal.

The data in this report indicate that tremor and IM in monkeys are associated with a common mechanism, and that dopamine receptors are involved in the regulation of these dysfunctions. Recent evidence indicates that a receptor-mediated feedback regulates the biosynthesis of dopamine (*4*), and that adenylate cyclase might be the receptor for dopamine in the brain (*5*). These results, in conjunction with those reported here, suggest that the biochemical aberrations in the development of tremor and of IM may involve changes in the generation of cyclic adenosine 3′,5′-monophosphate in postsynaptic neurons and in the rate of synthesis of dopamine in the presynaptic neurons.

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