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Effect of Levodopa on Arterial Blood Pressure in Unanesthetized and in Anesthetized Rats (39678)

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The use of levodopa in the treatment of parkinsonism has led to an increased interest in the physiological and pharmacological effects of this drug, as well as to an awareness that cardiovascular and, to a smaller degree, other derangements occur during levodopa therapy. For this reason the effects of levodopa on the cardiovascular system have been studied extensively. The results obtained are somewhat contradictory. For example, it has been reported that levodopa decreases (1-3) or increases (4-9) the arterial blood pressure. The difference in results might be due to the choice of the animal species or to the difference in administered doses of levodopa (16, 32). Anesthesia and surgical procedures may also be factors in variability of the obtained results. It has been shown that anesthesia and surgery profoundly change cardiac output, arterial blood pressure, and heart rate in experimental animals (10).

This main purpose of this work was to study the acute effects of levodopa on the arterial blood pressure in unanesthetized and anesthetized rats after chronic aortic cannulation. The mean arterial blood pressure was recorded before and after single administration of levodopa.

Materials and methods. Forty-two adult female Sprague-Dawley rats weighing 198 ± 7 (SD) g were used in the experiments. Each animal was housed in a separate cage and was given food and water *ad lib*. The aorta of each animal was cannulated under halothane (Fluothane, kindly supplied by Ayerst Laboratories) anesthesia with a fine polyethylene tubing (PE 10) via the left carotid artery 3-4 wk prior to the actual blood pressure measurement (11, 12). After full recovery from surgery and anesthesia, the animals continued to grow following the standard curve of growth for this species (12). In addition to the chronic aortic cannula, six rats were also carriers of a chronic right ventricular heart cannula (PE 10) permitting the iv administration of levodopa (12).

During blood pressure recording, each animal was placed in a plastic 4″ × 10″ × 4″ box. A 1/4-in. wide opening in the middle of the cover of the box permitted connection of the implanted cannula to the transducer and free movement within the box during voluntary locomotion of the rat. The implanted cannula of the animal was connected by a needle adapter to a pressure transducer (P23 De, Statham) and polygraph (Beckman). The pressure was recorded after the animal reached a complete resting state, 5-15 min after placement in the box. Each measurement after levodopa administration lasted one hour.

Levodopa (Hoffman La Roche) was dissolved in warm saline and administered intra-arterially through the chronically implanted aortic cannula. In six rats the levodopa was administered iv through the right ventricular heart cannula. The volume of administered fluid (saline as a solvent) never exceeded 0.5 ml. The arterial blood pressure measurements were made between 9 and 12 AM. Besides the mean arterial blood pressure, body weight, body temperature, and hematocrit ratio were monitored. Nembutal (sodium pentobarbital) was given ip, 40 mg/kg. Halothane was mixed with oxygen and introduced through a mask placed over the nose and the mouth of the rat. The flow rate of halothane and oxygen was maintained at a constant level. Depth of anesthesia was judged by breathing rate and corneal blink reflex. However, variations in the respiration rate and the duration of anesthesia probably have effects on the depth of anesthesia. Levodopa was administered 10 min after the animals reached the desired levels of anesthesia.

Statistical treatment consisted of single factor analysis of variance on repeated

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measures. Significance at the $P = 0.05$ level was determined from the least significant difference procedure for pairs of means.

Animal groups. All of the rats were randomly separated into six groups, each group consisting of six animals. The groups were:

Unanesthetized rats. 1. 10 mg/kg levodopa, i.a. injection. 2. 20 mg/kg levodopa, i.a. injection. 3. 10 mg/kg levodopa, iv injection.

Anesthetized rats. 4. 10 mg/kg levodopa, i.a. injection and nembutal anesthesia. 5. 20 mg/kg levodopa, i.a. injection and nembutal anesthesia. 6. 10 mg/kg levodopa, i.a. injection and halothane anesthesia.

Results. Mean arterial blood pressure after a single intravascular injection of 10 mg/kg of levodopa. Administration of nembutal or of halothane decreased the arterial blood pressure from 120 mmHg to 80–85 mm Hg. After administration of levodopa (10 mg/kg, ia), the arterial blood pressure increased in unanesthetized and in anesthetized rats (Fig. 1). The rise in arterial blood pressure reached a peak after 2–5 min in all groups. The increase of the arterial blood pressure in unanesthetized rats 2–5 min after i.a. levodopa administration was between 35 and 50 mmHg (Fig. 2). Fifteen minutes after levodopa administration, the arterial blood pressure of the unanesthetized rats was close to the control preadministration level, where it stayed during the next 45 min. The return to control values was somewhat slower in anesthetized rats. Intravenous administration of levodopa caused a larger increase of the arterial blood pressure in unanesthetized rats than the intra-arterial injection of the same dose.

In the nembutal group the increase of the arterial blood pressure after 2–5 min was 90 mmHg, much greater ($P < 0.05$) than in other groups (Fig. 2 and Table I). After levodopa administration, the increase of the mean arterial blood pressure was smaller with halothane than with nembutal anesthesia (Figs. 1 and 2).

The composite analysis of the observed changes of the arterial blood pressure induced by 10 or 20 mg/kg of levodopa is given in Table I.

Mean arterial blood pressure after a single intra-arterial injection of levodopa (20 mg/kg). Levodopa (i.a.) caused hypertensive responses in unanesthetized and in anesthetized rats, with the peak response at 2–5 min postdrug administration (Fig. 3). The return to the control preadministration values was slower in anesthetized than in unanesthetized rats (Figs. 3 and 4). The increase of the arterial blood pressure was greater, 90 mmHg, in both nembutal anesthetized groups after levodopa (10 or 20 mg/kg, i.a.) administration than in unanesthetized animals (Fig. 4).

After intravascular administration of the same volume of saline (solvent for levodopa) to 12 animals, their arterial blood pressure stayed unchanged. Calculated on the 100% basis, before the saline administration, the values of the mean arterial blood pressure after saline injection were 100 ± 0.3% (SD).

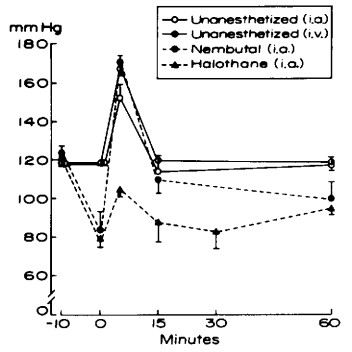

FIG. 1. Mean arterial blood pressure (±SE) of adult female rats after levodopa (10 mg/kg) administration (i.a., intra-arterial administration; iv, intravenous administration). Levodopa was administered at 0 min.

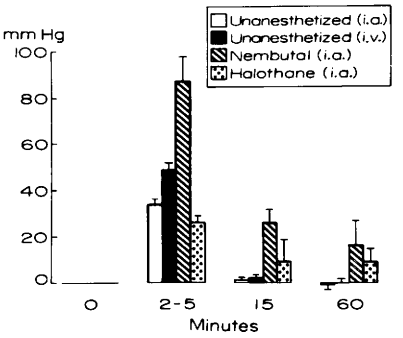

FIG. 2. Increases of the mean arterial blood pressure (±SE) of adult female rats after levodopa (10 mg/kg) administration (i.a., intra-arterial administration; *iv*, intravenous administration).

TABLE I. Composite Statistical Evaluations* of Mean Arterial Blood Pressure Changes 2–5 Min and 15 Min after Levodopa Administration to Unanesthetized and Anesthetized Rats.

Animal Group	Time, min					
Unanesthetized Levodopa, 10 mg/kg i.v.	2–5 15	NS NS				
Unanesthetized Levodopa, 20 mg/kg i.a.	2–5 15	<.05 NS	NS NS			
Halothane Levodopa, 10 mg/kg i.a.	2–5 15	NS NS	<.05 NS	<.05 NS		
Nembutal Levodopa, 10 mg/kg i.a.	2–5 15	<.05 <.05	<.05 <.05	<.05 <.05	<.05 <.05	
Nembutal Levodopa, 20 mg/kg i.a.	2–5 15	<.05 <.05	<.05 <.05	<.05 <.05	<.05 <.05	NS <.05
Animal Group	Time, min	Unanesthetized Levodopa, 10 mg/kg i.a.	Unanesthetized Levodopa, 10 mg/kg i.v.	Unanesthetized Levodopa, 20 mg/kg i.a.	Halothane Levodopa, 10 mg/kg i.a.	Nembutal Levodopa, 10 mg/kg i.a.

* Single factor analysis of variance on repeated measures. Significnce at the $P = 0.05$ level was determined from the least significant difference procedure for pairs of means. All P values $<.05$ are accepted as significant.

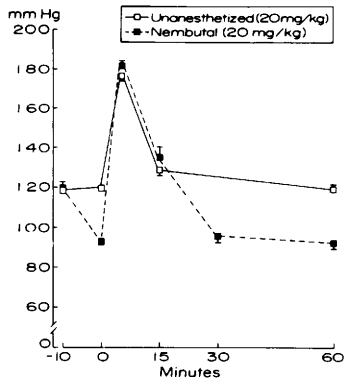

FIG. 3. Mean arterial blood pressure (±SE) of adult female rats after intraarterial levodopa (20 mg/kg) administration.

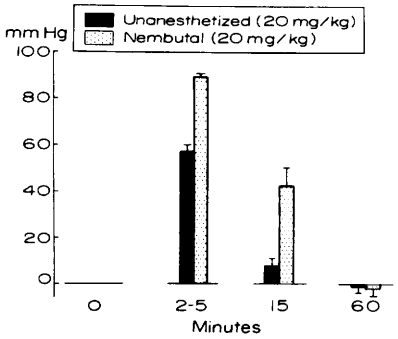

FIG. 4. Increases of the mean arterial blood pressure (±SE) of adult female rats after intra-arterial levodopa (20 mg/kg) administration.

No changes in body weight, body temperature and hematocrit ratio were observed after administration of levodopa.

Discussion. Levodopa therapy causes some derangements of the cardiovascular system (13). Long-term administration of oral levodopa to patients with Parkinson's disease induces orthostatic hypotension in about 30% of the cases (14, 15). The cardiovascular effects of levodopa are associated mainly with dopamine. It has been reported that dopamine stimulates myocardial β-adrenergic receptors (6) leading to increased cardiac contractile forces (16–20) and to an increased cardiac output (21). These effects were used beneficially in the treatment of cardiogenic and noncardiogenic shock (17, 20, 22–24). Dopamine causes hypertension largely by direct interaction with α-adrenergic receptors in vascular smooth muscle replacing (25) or releasing the stores of norepinephrine from sympathetic nerve fibers. Thus dopamine, naturally occurring catecholamine and the immediate precursor of norepinephrine, leads to both α- and β-adrenergic stimulation (26). After inhibition of dopa decarboxylase in peripheral tissues and inhibition or transformation of levodopa into dopamine, the administered levodopa induces hypotension probably due to the effects on the central nervous system (27, 28), presumably on the vasomotor center in the medulla (29). Large amounts of levodopa induce mesenteric, renal (22, 30) and cerebral vasodilation (31). Despite the proven effect of dopamine on alpha receptors, hypertension is rarely observed in patients following oral intake of levodopa. This might be due to the administration of drug in relatively small doses. However, in some patients treated with levodopa, anesthesia causes hypertensive and in others hypotensive responses (32).

Administration of levodopa or of dopamine causes hypertension in dogs (6, 9, 26) and rats (4, 7, 27, 28). The opposite effect, hypotension, is observed in cats (3), guinea pigs, and rabbits (1). These seemingly contradictory data indicate that vascular responses may depend on the animal species, on the administered doses (33), as well as on the route of administration.

Until now, the information about cardiovascular changes induced by levodopa administration was collected on anesthetized animals (several species) or in patients that were undergoing levodopa treatment. There is no information about the effect of levodopa on the circulation of chronically cannulated, unanesthetized, and unrestrained animals. In our work the effect of intra-arterially injected levodopa on arterial blood pressure was studied in unanesthetized, unrestrained, resting rats several weeks after chronic cannulation of the aorta. The levodopa was administered intravascularly in order to observe immediate circulatory effects of this drug unaltered by processes of absorption. It has been reported that orally administered levodopa might be degraded in the liver even before it enters the circulation (34). However, if intra-arterially injected, this drug passes through the blood brain barrier in 15 sec (35).

In our study all unanesthetized rats in-

creased mean arterial blood pressure after intra-arterial administration of levodopa. The increase was greater and appeared to last longer when the levodopa dose was doubled. For the dose of 10 mg/kg of levodopa, the increase of the arterial blood pressure was greater if levodopa was administered intravenously instead of intra-arterially. We believe that this might be associated with the direct action of levodopa on myocardium.

The results on unanesthetized animals were compared to the values obtained in the animals during nembutal or during halothane anesthesia. The later part of this work was done because it is known that anesthesia alters profoundly cardiovascular parameters (10). Furthermore, it was reported that halothane causes myocardial depression and that dopamine either decreases or leaves unchanged the total peripheral resistance in halothane anesthetized animals (24). The dopamine content of the brain is increased after anesthesia, as well as dopamine synthesis and turnover (37).

In our work on nembutal and on halothane anesthetized rats, we found an increased man arterial blood pressure after the injection (ia) of levodopa. The increase was much smaller in halothane anesthesia. This effect might be associated with the depressing action of this anesthetic on the heart and its profound effects on the CNS. The duration of the hypertensive response appeared to be longer in nembutal anesthetized animals that received a larger dose of levodopa. It is interesting to note that the peak value of the mean arterial blood pressure was not much different if 10 or 20 mg/kg of levodopa was given to nembutal anesthetized rats.

Summary. The arterial blood pressure responses in rats after intravascular levodopa administration were measured for the first time with direct methods in unanesthetized, unrestrained animals after full recovery from surgical stress due to the cannulation. The observed results were compared with results collected from anesthetized animals (nembutal or halothane). After levodopa administration, the mean arterial blood pressure of all rats was increased, reaching the peak value 2–5 min later. The animals in halothane anesthesia had a small rise of the mean arterial blood pressure. Doubling the dose of levodopa increased further the hypertensive responses in unanesthetized animals but not in nembutal anesthesia. Percentage-wise, levodopa caused a much greater increase of the mean arterial blood pressure in nembutal groups than in unanesthetized animals. However, the peak values were the same, around 170–180 mmHg, in all nembutal anesthetized animals as in unanesthetized animals that received a double dose of levodopa (20 mg/kg).

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