# Hypotensive Effect Induced by a Cyclic Dopamine Analog, *trans*-4-Methyl-7,8-dihydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline

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**Abstract** □ The antihypertensive effects of *trans*-4-methyl-7,8-dihydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline, a dopamine agonist, were investigated in dogs and spontaneous hypertensive rats. Intravenous administration of low doses of this cyclic analog of dopamine (0.25–1.00 μg/kg) consistently reduced blood pressure and heart rate, concurrently recorded in the dog. This effect was antagonized by haloperidol, a specific dopamine antagonist. The dopamine analog also reduced systolic blood pressure of spontaneous hypertensive rats. This study confirmed the possibility that the decrease in blood pressure and heart rate elicited by the dopamine analog is attributable to an effect on specific dopaminergic receptors.

**Keyphrases** □ *trans*-4-Methyl-7,8-dihydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline—hypotensive activity evaluated in dogs and spontaneous hypertensive rats □ Benzo[*f*]quinoline, substituted—hypotensive activity evaluated in dogs and spontaneous hypertensive rats □ Hypotensive activity—substituted benzo[*f*]quinoline evaluated in dogs and spontaneous hypertensive rats □ Dopamine analogs, cyclic—hypotensive activity evaluated in dogs and spontaneous hypertensive rats

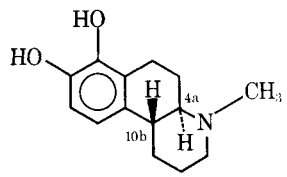
Dopamine acts on α- or β-adrenergic and dopaminergic receptors (1–9). It has received considerable attention as a potential therapeutic agent because of its ability to dilate renal and sphanchnic vasculature in experimental animals (2, 3, 6, 7, 10–13). Previously, depressor responses were elicited with small doses of dopamine, biphasic responses with intermediate doses, and pressor responses with large doses in dogs and cats. Dopamine in rabbits induced only a fall in blood pressure at all doses (1, 9, 14–19).

The depressor effect of dopamine and other dopaminergic agonists is assumed to be achieved through an action on specific dopaminergic receptors (12, 20–23). *trans*-4-Methyl-7,8-dihydroxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline (I) is a potent inhibitor of adrenergic nerve terminals in cats (24, 25). The present investigation was undertaken to determine if I would affect blood pressure of dogs and rats in the same manner as dopamine by acting on dopaminergic receptors.

## EXPERIMENTAL

**Dog Arterial Blood Pressure and Heart Rate**—Mongrel dogs (14–18 kg) were anesthetized with pentobarbital sodium (30 mg/kg iv). The animals were intubated and artificially ventilated with a respiration pump. Blood pressure was measured using a recorder and pressure transducer connected to a catheter inserted in the right femoral artery. Heart rate was monitored using a cardiotachometer. Drugs were injected through a catheter inserted in the left femoral vein.

**Systolic Blood Pressure of Spontaneous Hypertensive Rats**—The systolic blood pressures of conscious spontaneous hypertensive rats were determined by tail-cuff plethysmography. The rats were prewarmed by placing them in a glass-doored incubator at 30° for 20 min. The tail cuff was then applied while the rat was loosely restrained, and five consecutive readings of systolic blood pressure were obtained. The procedure was similar to that described by Friedman and Freed (26) in which occlusion cuff pressure was monitored visually while systolic pulses, detected by a pulse transducer, were monitored with an audiosignal.




I

Consistent readings were obtained by following a fixed routine and ensuring that the same person performed the measurements at the same time on each occasion. It was important that the tail cuff was placed on the same part of the tail and that extraneous noise was kept to a minimum. The rats were trained for 2 weeks before injection of the compound.

The hydrobromide salt of I was synthesized[1]. The data were analyzed statistically by the paired *t* test (27). A *p* value <0.05 was regarded as significant. Relative potencies of I before and after haloperidol were obtained from a split plot design six-point bioassay (28).

## RESULTS

**Effect of I on Arterial Blood Pressure and Heart Rate**—The resting mean arterial blood pressure and heart rate of the anesthetized dogs were 120 ± 4 mm Hg and 182 ± 6 beats/min, respectively. Intravenous injections of I were given in dosage increments from 0.25 to 1.00 μg/kg. These doses elicited a depressor effect associated with a decrease in heart rate; both the depressor effect and decrease in heart rate were dose dependent. The effects persisted 15–30 min, depending on the doses used, showing that I possessed a short duration of action.

After initial resting blood pressure returned to normal, haloperidol, 100 μg/kg, was slowly infused over 15 min. It did not significantly alter blood pressure or heart rate. Compound I, in doses that previously produced inhibition of blood pressure and heart rate, was then administered after haloperidol infusion, and the degree of inhibition was determined. Compound I (0.25–2.00 μg/kg) hardly affected blood pressure and heart rate after haloperidol. The need for increasing the doses of I to 16.0 μg/kg to obtain maximal depressor response showed that haloperidol antagonized its inhibitory effect on blood pressure and heart rate (Fig. 1).

**Effect of Intraperitoneal Injection of I on Systolic Blood Pressure**—Measurements of systolic blood pressure were made before the injection of I and were considered as controls. Systolic blood pressure was measured 20 min after the injection of I. Low intraperitoneal doses of I reduced arterial systolic blood pressure of spontaneous hypertensive rats from 238 ± 8 to 218 ± 7 mm Hg. The 3.1-μg/kg dose elicited an 8.4% reduction of the initial resting blood pressure. A high dose of 25.0 μg/kg reduced arterial systolic blood pressure from 236 ± 7 to 206 ± 5 mm Hg, amounting to a 12.7% reduction of initial resting blood pressure.

All doses elicited a significant pressure decrease ($p < 0.01$) (Fig. 2). Higher doses of I tended to excite the rats, and measurements of systolic blood pressure became difficult. Saline injected intraperitoneally to spontaneous hypertensive rats in volumes similar to those used when injecting I produced no significant effect on blood pressure.

The blood pressure of seven spontaneous hypertensive rats (group mean systolic pressure of 240 ± 7 mm Hg) was reduced by a single dose of I (25.0 μg/kg ip). The nadir of the depressor effect occurred 20 min after I injection ($p < 0.01$), and the mean systolic blood pressure was reduced to 204 ± 2 mm Hg. Second measurements after 80 min showed a still-

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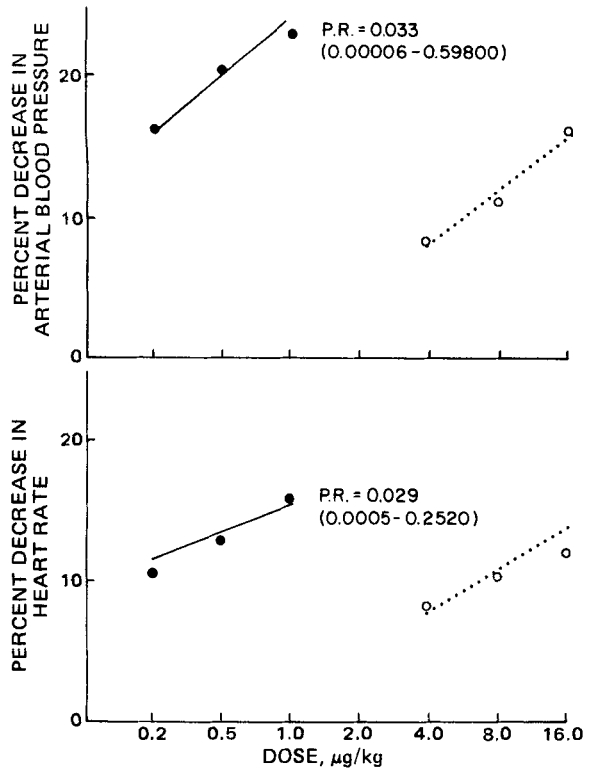


**Figure 1**—*Dose-response curves illustrating the effect of I on blood pressure and heart rate and the antagonism by haloperidol in anesthetized dogs. Each point represents the mean of seven experiments before (●) and after (○) haloperidol infusion (100 μg/kg over 15 min). The initial resting blood pressure and heart rate before intravenous administration of I were 120 ± 4 mm Hg and 182 ± 6 beats/min, respectively. The blood pressure and heart rate after the infusion of haloperidol (100 μg/kg) were 106 ± 7 mm Hg and 197 ± 13 beats/min, respectively. P.R. equals the relative potency as defined by Finney (28).*

significant decrease in systolic blood pressure ($p < 0.01$). The blood pressure returned to pretreatment level after 140 min (Fig. 3).

## DISCUSSION

Intravenous administration of I resulted in a depressor effect similar to that reported for low doses of dopamine in the dog (1, 2, 9, 19, 21). Haloperidol caused a shift to the right in the dose–response curves of I.

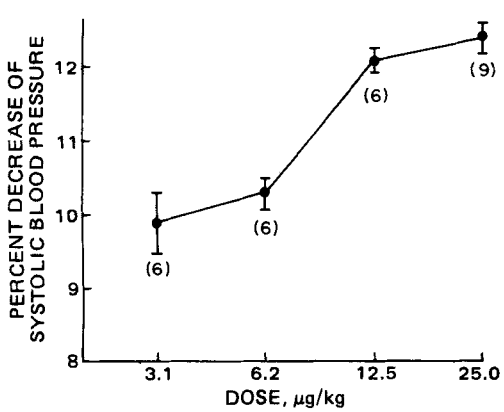


**Figure 2**—*Dose–response curve illustrating the effect of intraperitoneal I on systolic blood pressure of spontaneous hypertensive rats. Values within parentheses indicate the number of rats used at each dose. Each point is the mean ± SE. For the doses of 3.12, 6.25, 12.50, and 25.00 μg/kg, the control initial systolic blood pressure was 238 ± 8, 235 ± 10, 255 ± 8, and 236 ± 7 mm Hg, respectively.*

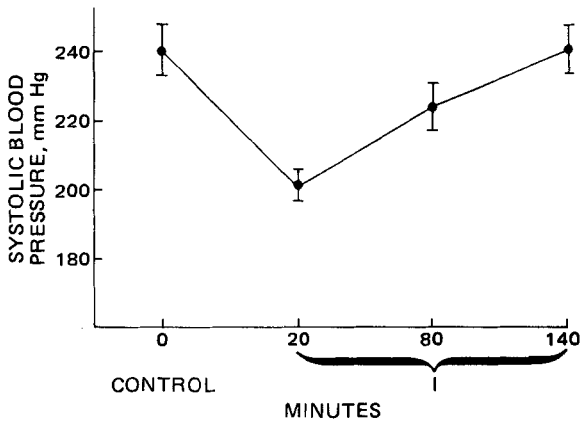


**Figure 3**—*Effect of I on systolic blood pressure of spontaneous hypertensive rats at different time intervals. Compound I was injected at a dose of 25 μg/kg ip, and systolic blood pressure was measured 20, 80, and 140 min after injection. Each value is the mean ± SE of seven rats.*

The fact that the before and after haloperidol curves do not deviate significantly from parallel suggests that haloperidol is a competitive antagonist. The results support the concept of specific dopaminergic receptors mediating a vasodilation, which is thus antagonized by haloperidol. Haloperidol is a known dopamine receptor blocker (6, 18, 29, 30). The vasodilation induced by dopamine in the different vascular beds is said to contribute to its depressor effect (6, 21, 31, 32).

Compound I has been postulated to be a potent dopaminergic agonist, impairing sympathetic transmission, an effect blocked by haloperidol (25). This inhibitory effect might involve dopaminergic receptors located on the nerve endings as well as on the autonomic ganglia. The resultant vascular dilatation would probably participate in the depressor effect of I. The decrease in heart rate could be attributed to the decrease of sympathetic discharges to the heart. The effect of dopamine on blood pressure was reported to differ from one species to another. Compound I lowered systolic blood pressure of spontaneous hypertensive rats in doses from 3.1 to 25.0 μg/kg. It was not possible to study the effect of higher doses of I in the rats since these doses produced excitement, probably because compulsive gnawing doses for these animals were approached.

Haloperidol affected the systolic blood pressure of spontaneous hypertensive rats; therefore, the antagonism of the depressor effect seen in the dog could not be demonstrated in the rat. The depressor effect of dopamine in anesthetized rats was antagonized by metoclopramide, another dopamine antagonist (22). The significance of the effect of I on blood pressure lies in the fact that I can be used to study some of the physiological properties of dopamine that are likely involved in regional circulatory beds where there are large numbers of dopaminergic receptors. With alterations of the chemical structure of dopamine, the intensity of its pharmacological actions can be changed. Compound I in the doses used in this study seems to be more potent as a hypotensive agent than dopamine since the reported doses of dopamine required to exert a similar hypotensive effect are greater. Since the duration of action of I on blood pressure is very short, it does not seem to be a promising hypotensive agent for clinical use.

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# Determination of Flucytosine in Tablets by Differential Pulse Polarography

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Received November 9, 1976, from the **Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada M5S 1A1,* the ‡*Division of Clinical Pharmacology, Toronto Western Hospital, Toronto, Ontario, Canada,* and the ‡*Clinical Institute, Addiction Research Foundation, Toronto, Ontario, Canada.* Accepted for publication March 31, 1978.

**Abstract** □ A differential pulse polarographic assay was developed for determining flucytosine in tablets. The drug is extracted from the sample with water and hydrochloric acid and, after the pH is adjusted, an aliquot is added to the cell and the solution is polarographed at the dropping mercury electrode *versus* the saturated calomel electrode with 0.066 *M* Sørensen phosphate buffer (pH 5.6) as the supporting electrolyte. The polarographic peak height enables precise quantitative determination. The $E_p$ value for flucytosine is −1.54 v *versus* the saturated calomel electrode. The mean recovery of the drug is 101.5% ± 1.9 (*SD*). The method is simple, rapid, and precise.

**Keyphrases** □ Flucytosine—differential pulse polarographic analysis in dosage forms □ Polarography, differential pulse—analysis, flucytosine in dosage forms □ Antifungal agents—flucytosine, differential pulse polarographic analysis in dosage forms

Flucytosine, 5-fluorocytosine (I), is a fluorinated pyrimidine that has shown *in vitro* and *in vivo* antifungal activity. Microbiological (1), fluorometric (2, 3), and high-pressure liquid chromatographic (4) procedures were reported for the estimation of I in biological fluids. The USP (5) employs a spectrophotometric method for the estimation of I in capsules. The mechanism of polarographic reduction of pyrimidine derivatives was reported previously (6–8). This paper reports a simple, convenient, and rapid differential pulse polarographic analysis of I in tablets.

## EXPERIMENTAL

**Apparatus and Conditions**—Polarograms were obtained using a polarographic analyzer[1] equipped with a drop timer[2]; the differential pulse mode was used. A three-electrode cell (5–50 ml) was comprised of a dropping mercury electrode, a saturated calomel electrode (SCE), and a platinum wire auxiliary electrode. The drop time $t$, was 2 sec, the drop mass was 1.4 mg/sec, and the capillary characteristic was $m^{2/3}t^{1/6} = 1.3$, measured in 0.066 *M* Sørensen phosphate buffer (pH 5.6) with an open circuit and at a mercury column height of 95 cm. The current range was either 5 or 10 μamp for a peak response of full-scale deflection, the scan range was from −1.2 to −1.95 v, the peak potential was −1.54 v, the modulation amplitude was 25 mv, and the scan rate was 2 mv/sec. The polarogram was recorded on an $x$–$y$ recorder[3].

A pH meter[4], fitted with a combination glass–saturated calomel electrode electrode pair, was used to monitor the pH of all solutions.

**Reagents and Chemicals**—All chemicals were analytical reagent grade. The Sørensen buffer was prepared by mixing stock solutions A (9.073 g of monobasic potassium phosphate/liter) and B (11.87 g of dibasic sodium phosphate dihydrate/liter) in varying proportions to produce the desired pH (9). Flucytosine[5] was used as a standard.

**Calibration Curve**—An aqueous stock solution of I was prepared at $1 \times 10^{-2}$ *M*. A range of $1 \times 10^{-3}$–$1 \times 10^{-4}$ *M* was employed for the preparation of the diffusion current *versus* concentration calibration curve. All standard solutions were prepared by pipetting an aliquot of the aqueous stock solution and adding 13.0 ml of Sørensen phosphate buffer (pH 5.6) and sufficient distilled water to a final volume of 20 ml.

These solutions were transferred to the cell and deoxygenated with pure nitrogen for 10 min prior to obtaining the polarograms in quiescent solution. A layer of nitrogen was maintained over the solution surface during the electroreduction. Polarograms were obtained using the differential pulse polarographic mode.

[1] Princeton Applied Research (PAR) model 174A.
[2] Princeton Applied Research (PAR) model 172A.
[3] Houston Omnigraphic model 2000.
[4] Fisher, Accumet model 230 pH/ion meter.
[5] Hoffmann–La Roche lot I-898.

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