on that of BRODIE and VALITSKI[8] was employed. Male rats (180–200 g) were starved for 24 h; drugs were injected immediately before the restraint. The rats were restrained by placing each in a prone position and taping the paws and head to the board. The animals were then placed in a cold room (4–7 °C) for 2 h.

AY-22,469 (15–hydroxy–15–methyl–9–oxoprostanoic acid) was prepared by Dr. J. F. BAGLI of Ayerst Laboratories; imipramine (Tofranil) was a gift from Geigy Ltd.

Results and discussion. AY-22,469 administered in the range of 30–3 mg/kg, p.o., immediately following the ligation caused essentially complete prevention of pylorus ligation-induced ulcer formation (Table I). Imipramine, a known inhibitor when administered parenterally[9,11], was relatively ineffective at 10–40 mg/kg, p.o.

In contrast to lacking activity when given after the pylorus ligation, imipramine (40–10 mg/kg, p.o.) was effective when given 30 min before the pylorus ligation; the ED_{50} was 16 mg/kg (Table I). Thus, the time of peroral administration of imipramine was of importance.

AY-22,469, when given perorally after the pylorus ligation, inhibited the ulcer formation exhibiting an ED_{50} of 1 mg/kg (Table II). Imipramine, administered i.p. at this time, exhibited an ED_{50} of 25 mg/kg, while not showing appreciable activity even at 40 mg/kg when given perorally. With AY-22,469 similar activity was also obtained when the vehicle employed was carboxymethyl cellulose. AY-22,469 is thus relatively a very potent inhibitor of this type of induced-ulcer when given perorally.

AY-22,469 (10–30 mg/kg, p.o.) did not prevent the gastric lesion formation produced by reserpine (Table III). Imipramine exhibited an ED_{50} of 20 mg/kg. Therefore, in contrast to imipramine, AY-22,469 is ineffective in preventing the formation of this type of gastric lesion under the conditions examined.

AY-22,469 (p.o.), like imipramine, antagonized the ulcer formation caused by cold-restraint (Table III). The level of activity of AY-22,469 was, however, much less than that of imipramine as a dose of 30 mg/kg of AY-22,469 caused a 47% decrease in the number of animals exhibiting ulcers while at 5 mg/kg imipramine caused 63%.

The present findings demonstrate that the synthetic PGE analogue AY-22,469 administered perorally inhibits ulcer formation. As AY-22,469 is a racemate with four possible optical isomers, the activities of the isomers are of interest. In the present studies AY-22,469 has been compared to imipramine, which given parenterally, inhibits ulcer formation caused by pylorus ligation[12], reserpine administration[13,14] and restraint and cold-restraint[12,15]. Imipramine has been shown to be of interest in humans in this respect, as it reduces gastric acidity and relieves pain in ulcer patients[16].

In addition to being an orally active, anti-ulcer agent AY-22,469 also exhibits oral antigastric acid secretory activity[4]. These findings are of interest in relation to the activities of the natural prostaglandins in humans. Parenterally, PGA_1 reduces histamine-induced gastric acid secretion[17]. PGE_1 inhibits basal[18] and pentagastrin stimulated[19] gastric acid secretion. However, perorally PGE_1 is ineffective in inhibiting gastric acid secretion induced by pentagastrin in doses exhibiting effects on gastrointenstinal motility[20].

Résumé. AY-22,469, un analogue synthétique de la prostaglandine, inhibe les différents types d'ulcère développé chez le rat lorsqu'il est administré par voie orale.

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Effect of Chemical Sympathectomy on Pressor Responses to Norepinephrine, Angiotensin and Tyramine[1]

6-Hydroxy dopamine (6-OH DA) is a catecholamine analogue which produces anatomic and functional sympathetic denervation[2–5]. The hearts of animals pretreated with 6-OH DA demonstrate enhanced responsiveness to infused norepinephrine and nearly absent responses to sympathetic nerve stimulation or tyramine comparable to the changes seen with surgical sympathetic denervation[4,5]. In the cat 6-OH DA treatment is followed by enhanced arterial pressure responses to norepinephrine and reduced responses to tyramine[4], suggesting a role for sympathetic nerves in inactivating circulating norepinephrine throughout the systemic circulation. However, 6-OH DA administration reduces vasoconstrictor responses to norepinephrine in rat mesenteric arteries[6].

In view of the increasing use of chemical sympathectomy with 6-OH DA as a tool for investigating arterial pressure

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in normal rats and various models of experimental hypertension[3,7-8], the pressor responses to infused norepinephrine, angiotensin II, and tyramine were evaluated in control and 6-OH DA treated rats. Cardiac catecholamine content was also measured as an assessment of cardiac sympathetic neuronal transmitter store.

Materials and methods. Sprague Dawley rats weighing between 200–250 g were used for these studies. 6-OH DA was kindly provided by Dr. W. E. SCOTT, Hoffman-La Roche Inc., Nutley, N.Y. 6-OH DA treated rats were given 100 mg/kg of hydrobromide salt[3] dissolved in isotonic saline containing 1 mg/ml sodium metabisulfite i.v. 24–72 h prior to the arterial pressure determinations. For the pressor assay rats were anesthetized with sodium pentobarbital, 50 mg/kg, intraperitoneally, given atropine sulfate, 0.4 mg/kg, s.c. and a tracheostomy was performed. Arterial pressure was measured via canulation of the carotid artery using a Statham P 23-Db transducer and a Physiograph DMP-4A recorder. Arterial pressure was recorded for 3 to 5 min; then pentolinium tartrate, 10 mg/kg, was given s.c. to achieve ganglionic blockade and the subsequent fall in pressure recorded. Pressor agents were infused through jugular vein catheters using Gilmont microsyringes. Norepinephrine, angiotensin II-amide (Hypertensin-Ciba) and tyramine were injected at various dose levels. All pressure responses were recorded in duplicate. The pressure responses were plotted versus the log of the dose injected so that the amount required to produce a 20 mm Hg rise in blood pressure could be determined by interpolation. Upon completion of the pressure assay the heart was excised and cardiac norepinephrine assayed by previously described fluorimetric methods[9].

Results. In Table I are shown the arterial pressures before and after ganglionic blockade and cardiac catecholamine concentrations of the 6-OH DA treated and control rats. It can be seen that prior to ganglionic blockade the 6-OH DA treated group had significantly lower arterial pressure than that of the controls. Following ganglionic blockade there was a greater fall in blood pressure observed in the control rats so that the arterial pressure of the two groups became identical. Cardiac norepinephrine concentration was markedly reduced in the hearts of the 6-OH DA treated rats to 6% of control levels.

Table I. Effect of chemical sympathectomy on arterial blood pressure and cardiac norepinephrine concentration

	Control (10)	6-OHDA (10)	*P*
B.P. Pre pentolinium (mm Hg)	110 ± 2.7	97 ± 3.6	<0.01
B.P. Post pentolinium (mm Hg)	62 ± 5.0	62 ± 3.5	NS
Cardiac norepinephrine (μg/g)	0.78 ± 0.04	0.05 ± 0.01	<0.001

Results are expressed as mean ± S.E.M. NS, not statistically significant at the 0.05 level. The number of animals studied is given in parenthesis.

Table II. Dose of norepinephrine, angiotensinII, or tyramine required to produce a 20 mm Hg rise in arterial pressure in control and 6-OHDA treated rats

	Control (10)	6-OHDA (10)	*P*
Norepinephrine (ng)	40.2 ± 3.1	14.9 ± 1.4	<0.001
Angiotensin II (ng)	13.4 ± 1.3	13.2 ± 2.3	NS
Tyramine (μg)	18.7 ± 1.7	217.0 ± 41.0	<0.001

Results are expressed as mean ± S.E.M. NS, not statistically significant at the 0.05 level.

The amount of norepinephrine, angiotensin II, or tyramine required to produce an arterial pressure rise of 20 mm Hg in control and 6-OH DA treated rats is shown in Table II. It is readily apparent that there was increased sensitivity to norepinephrine in the 6-OH DA treated group, as the amount of norepinephrine required to produce a 20 mm Hg increase in arterial pressure was 37% of that required in controls. The sensitivity to angiotensin II, however, was nearly identical in the control and 6-OH DA treated rats. However, the response to tyramine was markedly reduced in the sympathectomized animals. In the Figure the arterial pressure responses in control and 6-OH DA treated rats to 3 dose levels of each pressor agent are shown. Linear dose – response relationships were observed with all 3 agents in both control and 6-OH DA treated groups. It should be noted that doses of norepinephrine, angiotensin II and tyramine were selected to give nearly equal pressure increases in the control animals. The marked supersensitivity to norepinephrine and subsensitivity to tyramine in the chemically sympathectomized animals is readily apparent. In contrast, chemical sympathectomy had no effect on the response to angiotensin II.

Discussion. Many actions of norepinephrine are enhanced by surgical sympathectomy. This is explained by the importance of neuronal uptake as a mechanism for inactivating the amine[10]. 6-OH DA administration produces marked reduction in tissue catecholamine content[11], disappearance of adrenergic nerve terminals by electron microscopy[1] and histochemical techniques[3]. After treatment with 6-OH, DA cardiac chronotropic and inotropic responses to norepinephrine are enhanced while responses to sympathetic nerve stimulation or tyramine are markedly reduced, a pattern identical to that seen after surgical sympathectomy[4,5]. The use of chemical sympathectomy with 6-OH DA has revealed the dual action of sympathomimetic agents such as dopamine which has both a direct effect and a tyramine like action on the isolated rat atrium[5]. In contrast to the heart, the isolated rat mesenteric artery preparation is less sensitive to norepinephrine after 6-OH DA administration although more sensitive after surgical denervation[6]. However, in the cat 6-OH DA treatment results in increased arterial pressure responses to infused norepinephrine and reduced responses to tyramine paralleling the cardiac response[4].

In the present study rats treated with 6-OH DA had a slight but significantly lower arterial pressure than controls prior to ganglionic blockade. Pentolinium, however, lowered blood pressure in 6-OH DA treated rats to levels identical to those observed in control rats. The pressure response to infused norepinephrine was markedly increased in sympathectomized animals. In view of the findings that adrenal catecholamine synthesis

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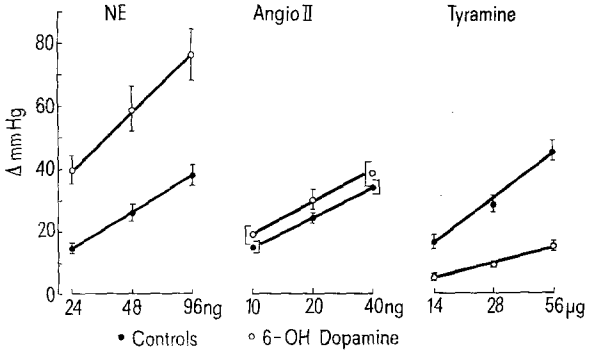
may be increased by this treatment[12] it is likely that increased adrenal catecholamine release in the 6-OH DA treated animals coupled with increased sensitivity to circulating norepinephrine accounts for the maintenance of arterial pressure at levels which are only slightly below normal. In contrast to the enhanced sensitivity to norepinephrine, the response to tyramine was markedly diminished in sympathectomized animals in agreement with prior studies [4,5] and illustrates the dependence of the tyramine response upon intact adrenergic innervation.

There was no demonstrable alteration in the arterial pressure response to angiotensin II following chemical sympathectomy. Release of adrenal catecholamines by angiotensin II has been demonstrated during intravenous infusion of the peptide and in the isolated perfused adrenal gland[13]. If adrenal catecholamine release were a significant part of the pressor effect of angiotensin II it might be expected that increased pressor responses to this peptide would be observed in the chemically sympathectomized rat in view of the increased response to infused norepinephrine. Alternatively, if a significant portion of the pressor action of angiotensin II required intact sympathetic innervation via release of norepinephrine from nerve endings[14], chemical sympathectomy should be associated with reduced pressor responses to angiotensin II, similar to those observed with tyramine. The nearly identical pressor responses to angiotensin II, observed in control and 6-OH DA treated rats strongly suggests that the direct vasopressor action of angiotensin is unchanged by chemical sympathectomy, and that an indirect effect upon the peripheral sympathetic nervous system is of little consequence to the acute action of the peptide when nerve impulses are eliminated. This is in agreement with prior studies utilizing receptor blocking agent[15] or reserpine[16]. A possible central action of angiotensin II requiring ganglionic transmission[17] or an action dependent upon sympathetic nerve stimulation[18,19] could not be evaluated in this study.



The rise in arterial pressure produced by 3 levels of norepinephrine (NE), angiotensin II (angio II) and tyramine are shown for control and 6-OH DA treated rats. Data are presented as the mean ± S.E.M. The difference between control and 6-OH DA treated groups was significant ($P < 0.005$) at all dose levels for norepinephrine and tyramine. For angiotensin II, there was no significant difference ($p > 0.1$) at any dose level.

Résumé. L'action de la dopamine 6-OH (6-OH DA) sur les réponses de la tension artérielle à la norépinéphrine, la tyramine, et l'angiotensin II a été etudiée chez le rat. 24 h après l'injection i.v. de 6-OH DA (100 mg/kg), la différence de tension due à la norépinéphrine fut nettement plus marquée alors que celle à la tyramine avait presque disparu. L'ablation chimique du système sympathique n'a aucun effet sur la réponse de la tension à l'angiotensine II.

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Desoxyribonuclease I in Mäusenieren nach Ganzkörper-Röntgenbestrahlung oder Gabe von 2, 4, 6-Triäthylenimino-s-triazin unter dem Einfluss von Polyanionen

Biochemische Reaktionen mit unmittelbarem Bezug auf Nukleinsäuren lassen sich in vitro durch Polyanionen beeinflussen[1,2], wobei Hemm- und/oder Aktivierungseffekte auftreten können. Ersteren unterliegen RNA-Polymerase, Ribosomenfunktion und zellfreie Proteinsynthese[1-6], letzteren die DNA-Synthese[7-9], beiden u.a. der Abbau von DNA an Pankreas-DNase[10].

In vivo-Wirkungen von Polyanionen sind nicht zuletzt im Hinblick auf ihre gelegentlich beobachtete antimitotische Wirkung[11,12] von besonderem Interesse. Vorliegend wurde der Einfluss von Polyanionen (Polyvinylsulfat, Pentosanpolysulfat und heterologen Nukleinsäuren) auf die Induktion einer neutralen Desoxyribonuclease (DNase I, E.C. 3.1.4.5) in Mäusenieren nach Ganzkörper-Röntgenbestrahlung (GKB) oder Gabe von 2,4,6-Triäthylenimino-s-triazin (TEM)[13] untersucht.

Methodik. Für die Untersuchungen standen ca. 300 weibliche Mäuse (K.-Gew. 19–23 g) aus institutseigener, konventioneller Zucht zur Verfügung. Die Tiere wurden bei 22–24 °C in Versuchsgruppen von 4–6 gehalten und erhielten Futter (Altromin®) und Wasser ad libitum. Gruppen von jeweils 4–6 Tieren wurden zu Versuchsbeginn entweder röntgenbestrahlt (Kristalloflex 4 der Fa. Siemens und Halske, Röhrenspannung 60 kV, Stromstärke 30 mA, HWS 0,16 mm Cu, Filterung mit 0,16 mm Cu, Focus-Objekt-Abstand 24 cm, Oberflächendosisleistung 70 R/min, Oberflächendosis 420 R, entsprechend ca. 170 rad) oder erhielten TEM (Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York) i.v.. Den Testgruppen wurden unmittelbar anschliessend sowie 24 und 48 h später Polyvinylsulfat (PVS, K-salz, rein, Serva Nr. 33426), Pentosanpolysulfat (SP_{54}®, Na-salz,