

The Vasopressor Response to Centrally Administered Ouabain

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SUMMARY. Ouabain (80 $\mu\text{g/kg}$) injected into the lateral cerebroventricles (ICV) of rats produced a prompt and sustained increase in arterial blood pressure. A diastolic blood pressure increase of about 40 mm Hg began within 10 minutes of injection and lasted at least 1 hour. This dose of ouabain had no effect on arterial pressure when given intravenously. The vasopressor response to intracerebroventricularly administered ouabain was not blocked by prior intravenous administration of phentolamine (1 mg/kg) or hexamethonium (3 mg/kg). However, continuous intravenous infusion of saralasin (2 $\mu\text{g/kg}$ per min) prevented the pressor response to intracerebroventricularly administered ouabain. In addition, bilateral nephrectomy, adrenalectomy, pretreatment with intravenously administered propranolol (2 mg/kg) or captopril (10 mg/kg) abolished the increase in blood pressure evoked by intracerebroventricularly administered ouabain. Plasma renin and epinephrine levels at the peak of the pressor response to intracerebroventricularly administered ouabain were respectively, about 2.5- and 2-fold higher than in control rats. Our data indicate that ouabain administered into the central nervous system produces a hypertensive effect which does not primarily involve peripheral α -adrenergic receptors, but appears to be due to angiotensin II produced by renin of renal origin. These data suggest that digitalis agents can interact with sites in the central nervous system to induce a release of renin from the kidney; this release appears to involve activation of β -adrenergic receptors by catecholamines from the adrenal medulla, perhaps through a direct adrenal-kidney vascular network. (*Circ Res* 55: 773-779, 1985)

DIGITALIS is known to exert cardiac, visual, and gustatory effects through actions within the central nervous system (Batterman and Gunter, 1948; Lyon and DeGraff, 1963). Many of the cardiac toxic effects of peripherally administered digitalis, most forms of which readily cross the blood-brain barrier, are believed to be mediated through the central nervous system (Gillis et al., 1972), with resultant stimulation of cardiac sympathetic nerves. Intracerebroventricular (ICV) injections, as well as discrete microinjections of digitalis to the medulla oblongata in dogs and cats, have been noted to produce cardiac arrhythmias (Bircher et al., 1963; Basu-Ray et al., 1972; Saxena and Bhargava, 1975).

Recently, while determining whether a polar cardenolide with limited access to the central nervous system (CNS) has the capacity to cause cardiac arrhythmias in dogs, when given ICV, we found that tachycardia and arrhythmias were produced which could be prevented by prior iv administration of the ganglionic blocker, pentolinium. However, a prominent rise in blood pressure was also noted which was not prevented by either ganglionic or α -adrenergic blockers (Puryear et al., 1981). These data suggested that the vasopressor effect does not involve sympathetic innervation of the vasculature. Such a pressor phenomenon has been reported in anesthetized cats given ouabain ICV by Saxena and

Bhargava (1975), who noted the rise in arterial pressure which was not blocked by prior iv treatment with the sympathetic neuronal blocking agent, guanethidine.

The purpose of the present study was to determine the means by which a digitalis agent within the CNS increases arterial blood pressure. We examined the involvement of peripheral adrenergic and renin-angiotensin mechanisms in the peripheral pressor action of ouabain given into the lateral cerebroventricle of the rat.

Methods

Sprague-Dawley rats (Harlan) weighing between 200 and 250 g were used in all experiments. Under ether anesthesia, rats' heads were secured in a stereotaxic apparatus, the skull exposed, and a small hole drilled at the coordinates: lateral = 1 mm, posterior = 1 mm from bregma. The tip of a 14-mm-long, 23-gauge steel cannula was lowered to depth of 5 mm below the surface of the skull and secured with dental acrylic cement, and small screws were placed in the skull. The guide cannula thus placed in the lateral cerebroventricle was sealed with a wire obturator until later use.

After a 5- to 7-day recovery period, the rats were anesthetized with chloral hydrate (350 mg/kg, ip, supplemented as necessary) and fitted with polyethylene catheters in a carotid artery (PE 50) and jugular vein (PE 90) for the measurement of arterial pressure, administration

of drugs, and sampling of blood. The airway was kept patent by placing a short PE 250 tube in the trachea. A 30-gauge stainless steel injector was inserted into the guide cannula and protruded so that its tip was 0.5 mm below the tip of the guide cannula. The injector was connected to a 25- μ l Hamilton syringe filled with either ouabain solution (6 mg/ml in saline) or normal saline.

After a period of approximately 30 minutes for stabilization of blood pressure and heart rate, the rats were given either ouabain solution (80 μ g/kg) in a volume of about 5 μ l, or that volume of saline via the ICV cannula. Arterial blood pressure was monitored on a Grass polygraph 30 minutes before and 80 minutes after injection.

A 80 μ g/kg dose of ouabain for ICV injection was chosen because it produced a prompt blood pressure elevation of about 40 mm Hg. Smaller doses caused lesser rises.

Experimental Groups

No Pretreatment

Eleven rats received only the ICV injection of ouabain; nine rats received only ICV saline.

α -Adrenergic Blockade

Two groups of rats were pretreated iv with either phenolamine (1 mg/kg, $n = 7$) or prazosin (0.1 mg/kg, $n = 7$) 10 minutes prior to ICV injection of ouabain. Some of these rats were tested for degree of blockade using iv norepinephrine.

Ganglionic (Nicotinic) Blockade

Seven rats were given 3 mg/kg, iv, of hexamethonium 10 minutes before ouabain injection. Some of these rats were also tested for blockade using the ganglionic stimulant, DMPP (1,1-dimethyl-5-phenyl-piperazinium iodide).

Angiotensin II Antagonist

Seven rats were administered a continuous iv infusion of saralasin (2 μ g/kg per min) for 20 minutes before and 80 minutes after ICV injection of ouabain.

Converting Enzyme Inhibitor

Six rats were pretreated with captopril (10 mg/kg, iv) 10 minutes before ICV injection of ouabain.

β -Adrenergic Blockade or Nephrectomy

Seven rats received propranolol (1 mg/kg, iv) 10 minutes before ICV injection. Eight rats underwent bilateral nephrectomy under chloral hydrate anesthesia (as above) about 24 hours before ICV injection of ouabain; food was withheld during this recovery period.

Adrenalectomy

Seven rats underwent bilateral adrenalectomy under chloral hydrate anesthesia 1–1½ hours before ICV injection of ouabain.

Combined Muscarinic and Ganglionic (Nicotinic) Blockade

Five rats were pretreated iv with both atropine methylnitrate (1 mg/kg), a polar muscarinic agonist with limited access to CNS, and hexamethonium (3 mg/kg) 10 minutes before ICV injection of ouabain.

Plasma Renin Determinations

One-half milliliter samples of venous blood were slowly taken over 30 seconds from each of seven rats given ICV ouabain at the peak of pressor response ($\approx +5$ minutes). Samples of the same volume were also taken from 11 rats at 5 minutes after ICV injection of 5 μ l of saline.

Plasma renin was measured by radioimmunoassay of the angiotensin I generated during incubation for 1 hour at 37°C at pH 6.5 of the plasma specimen (10 μ l) with pooled plasma from 48-hour nephrectomized rats (1.0 ml). The incubation was carried out in the presence of disodium ethylenediaminetetraacetate (5 mM), 2,3-dimercapto-1-propanol (5 mM) and phenylmethylsulfonyl fluoride (1.5 mM) to inhibit angiotensinases and converting enzyme (Barr et al., 1980). The enzyme activity is expressed as nanograms of angiotensin I generated per milliliter of plasma per hour of incubation (ng/ml per hr). Intra-assay variability was 3.1%.

Plasma Epinephrine (E) Determinations

Blood samples (8 ml) were collected following decapitation of anesthetized rats 5 minutes after ICV injection of ouabain or saline in chilled heparinized syringes (Sartstedt Inc.) containing 18 mg of ethylene glycol bis(β -aminoethyl ether) N,N' -tetraacetic acid and 12 mg of glutathione. Samples were centrifuged (2000 rpm) at 4°C for 10 minutes, and the plasma was stored at -70°C . Content of E in plasma samples was measured within 30 days of blood collection with an amperometric detector after catecholamine separation by high-pressure liquid chromatography (Bioanalytical Systems LC-304B). E was extracted from plasma by alumina adsorption. One milliliter of plasma was transferred to 5-ml conical vials containing 50 mg of acid-washed alumina. After addition of 1 ml of 1.5 M Tris buffer (pH 8.7) containing 2% EDTA, the vials were vortexed and placed on a reciprocal shaker for 5 minutes. The alumina was allowed to settle in the vial, washed twice with 1.5 ml of glass-distilled H_2O , transferred to a microfilter tube, (0.2- μ m filter), and spun dry in a microfiltration centrifuge (Bioanalytical Systems). E was eluted from the alumina by two rinses with the same 100- μ l volume of 0.1 M perchloric acid. Twenty microliters of the filtered extract were injected onto the high-performance liquid chromatograph column. The amount of E in the injection volume was calculated from the height of the peak, which had the same retention time as standard E, on the basis of both internal and external calibration methods. The calibration curves were determined before and after injection of 10 samples. The recovery of E from plasma or phosphate buffer by alumina extraction averaged $60 \pm 6.3\%$. The precision of the assay was determined from a pooled plasma sample assayed in replicate and the interassay coefficient of variation was less than 5%.

Statistical Analyses

Results are expressed as means \pm SE. Data on diastolic blood pressure were analyzed by two-way analysis of variance and Newman-Keuls tests. Data for plasma renin and epinephrine were analyzed by the unpaired Student's t -test.

Results

No Prior Treatment (Fig. 1)

Diastolic blood pressure in rats given 80 μ g/kg of ouabain rose promptly by about 40 mm Hg and was

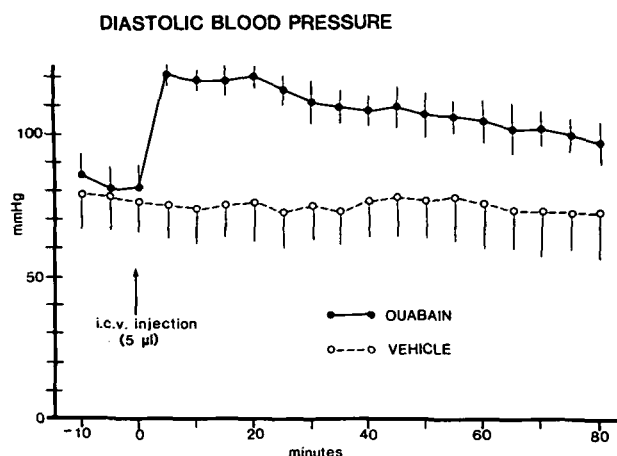


FIGURE 1. Diastolic blood pressure of rats after ICV injection of ouabain (80 μ g/kg, $n = 16$) or vehicle (saline, $n = 7$).

sustained for about an hour with no alteration in heart rate except for a brief bradycardia (approximately 30 beats/min) and hypotension (about 15 mm Hg) lasting for about 30 seconds occurring within 2 minutes after the ICV injection of ouabain (not shown). Rats given only vehicle did not demonstrate cardiovascular changes.

Pretreatment with α -Adrenergic or Ganglionic (Nicotinic) Blockade (Fig. 2)

To determine if this pressor response was of the same character which we noted earlier in dogs (Puryear et al., 1981), we pretreated groups of rats with either the α -adrenergic antagonist, phentolamine (1 mg/kg) or the ganglionic blocker, hexamethonium bromide (referred to in this paper as hexamethonium) (3 mg/kg). Although both pretreatments decreased baseline blood pressure, neither prevented

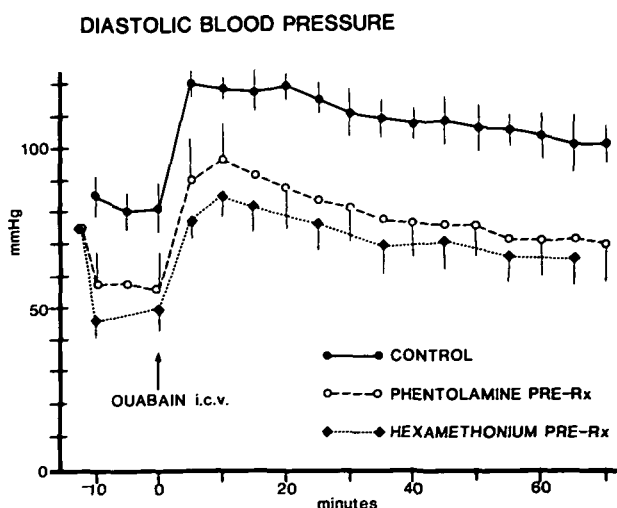


FIGURE 2. Diastolic blood pressure after ICV injection of ouabain (80 μ g/kg) in rats given no pretreatment (control), or iv phentolamine (1 mg/kg, $n = 5$), or hexamethonium (3 mg/kg, $n = 7$) 10 minutes before ICV ouabain.

the rise in blood pressure caused by ICV ouabain; the pressor responses were of a magnitude similar to that noted in control rats.

Pretreatment with the antagonists caused a marked antagonism of the pressor responses to either the α -agonist, norepinephrine (by phentolamine), or the nicotinic-ganglionic stimulant, DMPP (by hexamethonium) administered iv; 50-fold and 35-fold shifts 1.0 in the dose-response curves to norepinephrine and DMPP, respectively, were observed.

In a separate group of rats given a prior iv dose of the selective α_1 -adrenergic antagonist, prazosin (0.1 mg/kg), ICV injection of ouabain also produced a prominent pressor response which was similar to that of control rats (38 ± 2 mm Hg).

Interruptions of the Renin-Angiotensin System (Fig. 3)

Prior and simultaneous treatment with the angiotensin II antagonist saralasin, at a dose-rate of 2 μ g/kg per min, prevented any blood pressure response to ICV ouabain. This dose-rate of saralasin produced an approximate 10-fold antagonism of the pressor responses to iv angiotensin II. Furthermore, heavy pretreatment with the converting enzyme inhibitor, captopril (10 mg/kg, iv), prevented the rise in pressure to ouabain.

Nephrectomy and β -Adrenergic Blockade (Fig. 4)

Rats with both kidneys removed did not exhibit any increase in diastolic blood pressure when given ouabain ICV. Basal diastolic blood pressure was low in this group, 46 ± 3 mm Hg at time 0.

Prior pretreatment with propranolol (2 mg/kg, iv) also prevented any significant rise in pressure to ouabain injection. Basal diastolic blood pressure was lowered by administration of propranolol.

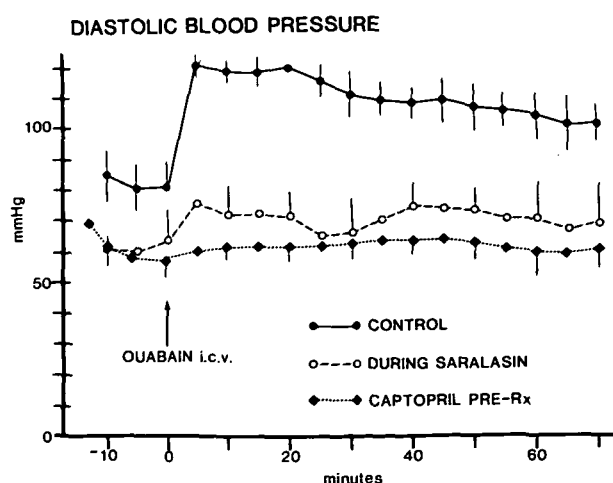


FIGURE 3. Diastolic blood pressure after ICV injection of ouabain (80 μ g/kg) in rats given pretreatment (control), iv infusion of saralasin (2 μ g/kg per min from -10 to +70 min, $n = 7$), or iv injection of captopril (10 mg/kg, $n = 7$) 10 minutes before ICV ouabain.

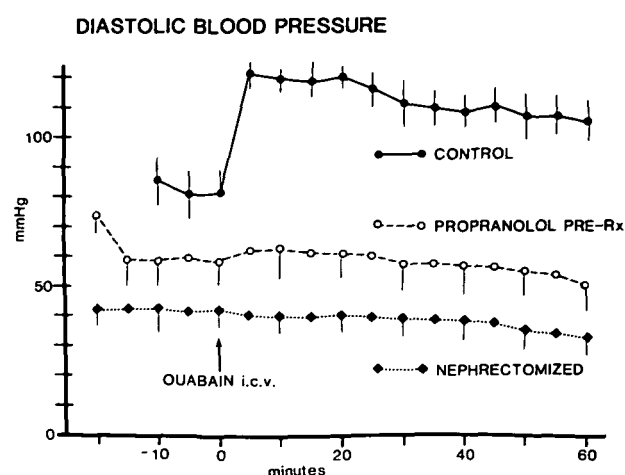


FIGURE 4. Diastolic blood pressure of rats after ICV injection of ouabain (80 μ g/kg) with no pretreatment (control), prior nephrectomy ($n = 6$), or *iv* propranolol (2 mg/kg, $n = 6$) given 10 minutes before ICV ouabain injection.

Adrenalectomy, and Muscarinic and Nicotinic Blockade (Fig. 5)

Rats with both adrenal glands removed 1–1½ hours prior to injection failed to show any significant increase in blood pressure to ICV ouabain. Rats in this group tended to have lower baseline pressures than the control group rats.

Rats pretreated with both the muscarinic antagonist, atropine, and the nicotinic blocking agent, hexamethonium, did not exhibit an arterial pressor response to ICV ouabain.

Plasma Renin (Table 1)

The level of plasma renin in rats given ICV ouabain at the height of the pressor response was significantly higher than the level in rats receiving only

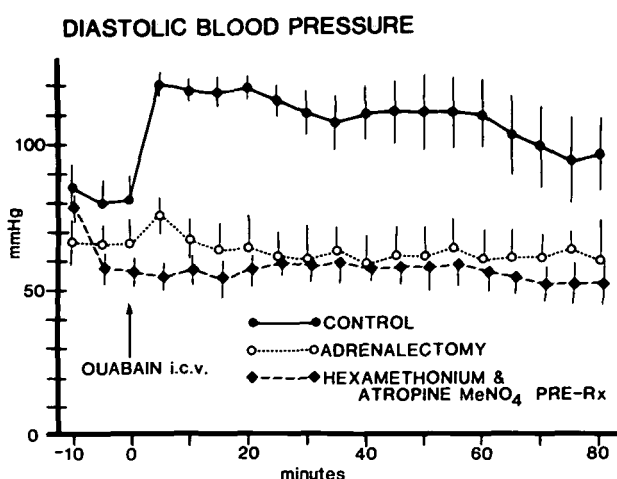


FIGURE 5. Diastolic blood pressure of rats after ICV injection of ouabain (80 μ g/kg). Control rats received no pretreatment ($n = 10$); seven rats underwent bilateral adrenalectomy 1.5 hours before ouabain injection ($n = 7$). Five rats were given *iv* injections of both atropine methylnitrate (1 mg/kg) and hexamethonium (3 mg/kg) 10 minutes before ICV ouabain ($n = 5$).

TABLE 1
Plasma Renin and Plasma Epinephrine Determinations

Group	Plasma renin (ng AI/ml per hr)
Control (+5 min after ICV saline, $n = 10$)	97.4 \pm 11.7
Ouabain ICV—80 μ g/kg (+5 min after injection, $n = 8$)	265.5 \pm 34.2*
Group	Plasma epinephrine (pg/ml)
Control (+5 min after ICV saline, $n = 5$)	256 \pm 38
Ouabain ICV—80 μ g/kg (+5 min after injection, $n = 6$)	434 \pm 56*

* $P < 0.05$ compared to values for control.

vehicle. Values in the treated group were approximately 2.5 times higher than those observed in the group given saline.

Plasma Epinephrine Levels (Table 1)

The concentration of epinephrine within plasma of rats 5 minutes after ICV injection of ouabain was slightly less than 2-fold higher than rats given only saline ICV.

Discussion

Cardiovascular actions due to digitalis administered into the central nervous system, particularly arrhythmias, tachycardia and hypertension, have been reported (Haley and Weinberg, 1955; Basu-Ray et al., 1972; Saxena and Bhargava, 1975). Indeed, most digitalis agents enter into various CNS structures readily after peripheral administration and create a portion of their total cardiovascular action through a CNS interaction (Pace and Gillis, 1976). Tachycardia and arrhythmias in response to a centrally administered digitalis agent can readily be prevented by prior administration of a ganglionic blocking agent or a sympathetic neuronal blocking agent, such as guanethidine (Saxena and Bhargava, 1975; Puryear et al., 1981). However, we previously observed that a pressor phenomenon in dogs to an aminocardenolide was not prevented by ganglionic blockade (Puryear et al., 1981). Similarly, in our present study with the rat, we found a pressor response to a centrally administered cardenolide which was not prevented by ganglionic or α -adrenergic blockade.

The fact that two α -adrenergic antagonists, given in amounts sufficient to antagonize the pressor responses to exogenously given norepinephrine by about 100-fold, failed to block or diminish the pressor response to ICV ouabain indicates that neither the sympathetic innervation of the vasculature nor a circulating α -adrenergic agonist are primarily in-

volved. It is quite probable that some portion of the pressor effect does result from activation of peripheral vascular α -adrenoceptors, since sympathetic nervous activation to centrally administered digitalis is well documented (Stickney and Lucchesi, 1969; Basu-Ray et al., 1972). However, any such contribution must be small, since the magnitude of the pressor response was not significantly altered by either of the α -adrenoceptor antagonists. This is in contrast to the mechanisms involved in the arterial pressor response induced by iv administration of digitalis, which is well documented to involve both neurally mediated actions upon vascular α -adrenergic receptors (Stark et al., 1972; Quest et al., 1976) and direct actions such as inhibition of the vascular Na pump (Fleming, 1980).

This pressor phenomenon was also not prevented by the ganglionic (nicotinic) blocker, hexamethonium, given in a dose which markedly antagonized the pressor response of the ganglionic stimulant, DMPP. This is further evidence that the rise in blood pressure to ouabain occurs within major participation of the sympathetic innervation to the vasculature. Moreover, it indicates that the pressor mechanism is probably humoral in nature.

Of the humoral pressor mechanisms which could be responsible, the renin-angiotensin and vasopressin systems were considered. No other nonadrenergic humoral systems were deemed capable of producing such a prompt and marked pressor action. Pressor responses of this magnitude would require massive vasopressin release which would be expected to depress cardiac contractility, due to this hormone's potent coronary vasoconstricting action. However, arterial pulse pressure was not altered by ICV ouabain, indicating that vasopressin was not involved. A role for the renin-angiotensin system was supported by the finding that prior or concurrent peripheral treatment with the converting enzyme inhibitor, captopril, or angiotensin antagonist, saralasin, virtually abolished the pressor response to ICV ouabain. Moreover, plasma renin was elevated about 2.5-fold following ICV ouabain. These data strongly suggest that the vasopressor action was mediated through an increase in circulating levels of renin with a subsequent increase in angiotensin II. The control levels of plasma renin in the rats anesthetized with chloral hydrate in the present experiment were considerably higher than values reported for conscious rats (Carvalho, 1983); however, anesthesia and surgery are known to elevate plasma renin (Nasjletti and Masson, 1971).

The primary source of peripheral circulating angiotensin II is certainly through the action of renin of kidney origin upon plasma angiotensinogen. Moreover, one stimulus for kidney renin release is β -adrenergic stimulation of the juxtaglomerular cells (Ganong, 1972); the activation of these β -receptors occurs either through sympathetic humoral or neural means. Our experiments demonstrating that both pretreatment with the β -adrenergic antagonist, pro-

pranolol, and prior bilateral nephrectomy prevented the pressor effect to ICV ouabain strongly indicate that a renal β -adrenergic mechanism is an integral portion of the pressor phenomenon. However, since ganglionic blockade was incapable of preventing the pressor response it is very unlikely that an increase in sympathetic nerve activity to the kidney, with resultant β -adrenergic stimulation, is involved. Moreover, Meyer and Herrmann (1978) have suggested that neurally released norepinephrine has an inhibitory role in regulating plasma renin, presumably through α -adrenoceptors. Therefore, activation of the renal β -adrenergic receptors mediating renin release through an increase in circulating catecholamines, particularly epinephrine, is an attractive possibility.

The differential ability of circulating epinephrine to increase renal renin release through a β -adrenergic mechanism, in contrast to norepinephrine, has been well documented in the rat (Pettinger et al., 1976; Carvalho, 1983). Plasma renin concentration in conscious rats can be markedly elevated (2.5- to 3-fold) by small increases in circulating levels of epinephrine. Elevations in plasma renin activity after ICV ouabain may have been a consequence of adrenal epinephrine release, since adrenalectomy prevented the pressor response.

Neurally mediated adrenal catecholamine release has been shown to occur in the presence of ganglionic blockade by a nicotinic antagonist. Several investigators have demonstrated that action of acetylcholine on muscarinic receptors is a prominent mechanism for catecholamine release from the adrenal medulla (Lee and Trendelenburg, 1967; Kovacic and Robinson, 1970). Furthermore, studies by Tsuijimoto and Nishikawa (1975) indicate that with inactivation of nicotinic receptors within the adrenal medulla, release of catecholamines to muscarinic stimulation is enhanced. Our own experiments have demonstrated that pretreatment with high doses of both a peripherally active muscarinic and a ganglionic antagonist effectively blocked the pressor response to ICV ouabain. Therefore, the pressor effect we noted due to ICV ouabain after hexamethonium treatment could well have involved epinephrine release from the adrenal medulla. However, epinephrine concentration in blood was only slightly higher in rats 5 minutes after ICV injection of ouabain, compared to rats receiving only saline ICV. This difference in circulating plasma levels of epinephrine would not be expected to be of particular importance in increasing renin release or the level of blood pressure.

However, a direct vascular connection or rete between the adrenal and the kidney has been described in both the cat (Cow, 1914) and dog (Katholi et al., 1979). Such a network in the rat would provide a means by which adrenal catecholamines could specifically reach the kidney in a concentration considerably higher than that in peripheral venous blood. A much more prominent effect upon

kidney renin release could occur through direct delivery of epinephrine from the adrenal to the kidney via a connecting rete.

The prospect of activation of a discrete portion of the sympathetic nervous system has precedence. Nathan and Reis (1975) have reported a hypertension and tachycardia in cats with lesion irritation of the anterior hypothalamus which can be completely prevented by prior adrenalectomy or adrenal demedullation. That ouabain and other digitaloids within the brain might have the ability to stimulate adrenal medullary release of catecholamines selectively by such a discrete action is, of course, unproven, but is a very interesting speculation.

Equally intriguing questions need to be answered on the nature of the associated molecular events occurring within the brain following introduction of digitalis. Earlier work of Saxena and Bhargava (1975) indicates that this pressor phenomenon may be mediated through central adrenergic mechanisms. Our studies were not directed toward examining that proposal.

We would imagine that this pressor effect involves inhibition of Na^+, K^+ -ATPase activity at critical brain structures; specific inhibition of the cell membrane Na^+, K^+ -ATPase activity is widely accepted molecular action of digitalis (Schwartz et al., 1975; Caldwell and Nash, 1978). It is difficult, however, to decipher existing data on the involvement of the Na pump (viz. Na^+, K^+ -ATPase) within CNS neurons in this pressor phenomenon. Vanadium, another agent known to alter Na^+, K^+ -ATPase activity, has been reported to elevate blood pressure when given ICV. However, this effect appears to be through a mechanism separate from that for digitalis, since ganglionic blockade eliminated the pressor response to ICV vanadium (Hom et al., 1981). Confusion is added, since vanadium may potentially inhibit or stimulate Na^+, K^+ -ATPase activity, depending on its valance state (Cantley and Aisen, 1979; Werdan et al., 1982).

Recently, several laboratories have reported the existence of a "digitalis-like" substance in brain which specifically inhibits Na^+, K^+ -ATPase activity or binding of [^3H]digitalis to this enzyme (Fishman, 1978; Hauptert and Sancho, 1978; Lichstein and Samuelov, 1979; Whitmer et al., 1982). This described pressor mechanism in response to central application of digitalis may respond to endogenous "digitalis-like" ligands with an increase in peripheral blood pressure.

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References

- Barr JG, Diz D, Kauker ML, Nasjletti A (1980) Effect of the converting enzyme inhibitor SQ-20881 on urinary excretion of prostaglandin E_2 in the rat: Influence of pretreatment with deoxycorticosterone. *J Pharmacol Exp Ther* 215: 172-175
- Basu-Ray BN, Dutta SN, Pradhan SN (1972) Effects of microinjections of ouabain into medullary areas on cats. *J Pharmacol Exp Ther* 181: 357-361
- Batterman RC, Gunter LB (1948) Hitherto undescribed neurological manifestations of digitalis toxicity. *Am Heart J* 36: 582-586
- Bircher RP, Kanai T, Wang SC (1963) Mechanism of cardiac arrhythmias and blood pressure changes induced in dogs by pentylene-tetrazol, picrotoxin, and deslanoside. *J Pharmacol Exp Ther* 141: 6-14
- Caldwell RW, Nash CB (1978) Comparison of the effects of aminosugar cardiac glycosides with ouabain and digoxin on Na^+, K^+ -adenosine triphosphate and cardiac contractile forces. *J Pharmacol Exp Ther* 204: 144-148
- Cantley LC, Aisen P (1979) The fate of cytoplasmic vanadium. *J Biol Chem* 254: 1781-1784
- Carvalho JS (1983) Inhibitory effect of circulating norepinephrine on epinephrine-induced renin secretion. *J Cardiovasc Pharmacol* 5: 72-76
- Cow D (1914) The suprarenal bodies and diuresis. *J Physiol (Lond)* 48: 443-452
- Fishman MC (1979) Endogenous digitalis-like activity in mammalian brain. *Proc Natl Acad Sci USA* 76: 4661-4663
- Fleming WW (1980) The electrogenic Na^+, K^+ -pump in smooth muscle: Physiologic and pharmacologic significance. *Annu Rev Pharmacol Toxicol* 20: 129-149
- Ganong W (1972) Sympathetic effect of renin secretion: Mechanism and physiological role in control of renin secretion. *Adv Exp Med Biol* 17: 17-32
- Gillis RA, Raines A, Sohn YJ, Levitt B, Standaert FG (1972) Neuroexcitatory effects of digitalis and their role in the development of cardiac arrhythmias. *J Pharmacol Exp Ther* 183: 154-168
- Haley TJ, Weinberg SJ (1955) Comparison of strophanthidin-K and tryptamine-strophanthidin after intraventricular injection in unanesthetized dogs. *Proc Soc Exp Biol Med* 89: 345-349
- Hauptert GJ Jr, Sancho JM (1979) Sodium transport inhibitor from bovine hypothalamus. *Proc Natl Acad Sci USA* 76: 4658-4660
- Hom GJ, Chelly JE, Janhyala BS (1982) Evidence for centrally mediated effects of vanadate on the blood pressure and heart rate in anesthetized dogs. *Proc Soc Exp Biol Med* 169: 401-405
- Katholi RE, Oparil S, Urthaler F, James TN (1979) Mechanism of postarrhythmic renal vasoconstriction in the anesthetized dog. *J Clin Invest* 64: 17-31
- Kovacic B, Robinson RL (1970) Drug-induced secretion of catecholamines by the perfused adrenal gland of the dog during nicotine blockade. *J Pharmacol Exp Ther* 175: 178-182
- Lee FL, Trendelenburg (1967) Muscarinic transmission of preganglionic impulses to the adrenal medulla of the cat. *J Pharmacol Exp Ther* 158: 73-81
- Lichtstein D, Samuelov S (1980) Endogenous "Ouabain-like" activity in rat brain. *Biochem Biophys Res Commun* 96: 1518-1523
- Lyon AE, DeGraff AC (1963) The neurotoxic effects of digitalis. *Am Heart J* 65: 839-840
- Nasjletti A, Masson GMC (1971) A method for the measurement of plasma renin in the rat. *Proc Soc Exp Biol Med* 136: 344-348
- Meyer DK, Herrmann M (1978) Inhibitory effect of tyramine-induced release of catecholamines on renin secretion. *Naunyn Schmiedeberg Arch Pharmacol* 303: 139-144
- Nathan MA, Reis DJ (1975) Fulminating arterial hypertension with pulmonary edema from release of adrenomedullary catecholamines after lesions of the anterior hypothalamus in the rat. *Circ Res* 37: 226-235
- Pace DG, Gillis RA (1976) Neuroexcitatory effect of digoxin in the cat. *J Pharmacol Exp Ther* 199: 583-600

- Puryear SK, Nash CB, Caldwell RW (1981) Effect of cardiac β -adrenergic blockade or denervation on cardiotoxicity of digoxin and an aminosugar cardenolide. *J Cardiovasc Pharmacol* 3: 113-127
- Quest JA, Rowles HB, Bhat HB, Gillis RA (1976) Effect of hydro-ouabain on vascular tone of the perfused canine hindlimb. *J Pharmacol Exp Ther* 199: 255-261
- Saxena PR, Bhargava KP (1975) The importance of a central adrenergic mechanism in the cardiovascular responses to ouabain. *Eur J Pharmacol* 31: 332-346
- Schwartz A, Lindenmayer GE, Allen JC (1977) The sodium-potassium adenosine triphosphatase. *Pharmacol Rev* 27: 3-133
- Stickney JL, Lucchesi BR (1969) The effect of sympatholytic agents on the cardiovascular responses produced by the injection of acetylcholinesterase into the cerebral ventricles. *Eur J Pharmacol* 6: 1-7
- Stark JL, Sanders CA, Powell WJ (1972) Neurally mediated and direct effects of acetylcholinesterase on canine skeletal muscle vascular resistance. *Circ Res* 30: 274-282
- Tsujimoto A, Nishikawa T (1975) Further evidence for nicotinic and muscarinic receptors and their interaction in dog adrenal medulla. *Eur J Pharmacol* 34: 337-344
- Werdan K, Bauriedel G, Tishu B, Krawietz W, Erdmann E, Schmitz W, Scholz H (1982) Stimulatory and inhibitory action of vanadate on potassium uptake and cellular sodium and potassium in heart cells in culture. *Biochim Biophys Acta* 687: 79-93
- Whitmer KR, Wallick ET, Epps DE, Lane LK, Collins JH, Schwartz A (1982) Effects of extracts of rat brain on the digitalis receptor. *Life Sci* 30: 2261-2275

INDEX TERMS: Ouabain • CNS • Vasopressor • Angiotensin