Pharmacologic Aspects of Synthetic Angiotonin

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The synthetic octapeptide angiotonin evoked systolic and diastolic pressure responses in anesthetized and unanesthetized dogs identical with those due to a natural, largely decapeptide, angiotonin, and responses to both angiotonins were modified in the same manner by a variety of procedures. Infusion of synthetic angiotonin caused hypertension sustained for the durations of the infusions and tachyphylaxis was not observed. Induced tachyphylaxis to a crude renin preparation was accompanied by loss of response to both synthetic and natural angiotonin but not to norepinephrine.

With the synthesis of the octapeptide angiotonin by Bumpus, Schwarz and Page, it is now possible to compare its pharmacologic properties with those of naturally occurring angiotonin. It is our purpose to examine certain aspects of the cardiovascular effects of synthetic angiotonin and to establish whether there exists any significant difference between the actions of the synthetic octapeptide and a natural, largely decapeptide, angiotonin. Arterial pressure responses to both preparations were measured in anesthetized and unanesthetized dogs and in dogs and cats after a variety of procedures known to modify the action of natural angiotonin.

Methods

Unanesthetized or anesthetized adult mongrel dogs or anesthetized cats were used. The anesthetic agent was sodium pentobarbital (30 mg./Kg.). Mean femoral arterial pressure was recorded on a smoked drum from a mercury manometer; systolic and diastolic pressures were measured with a strain gage manometer connected to appropriate amplifying and recording equipment.

The angiotonin employed was the active octapeptide preparation synthesized by Bumpus, Schwarz and Page. Dosage is given in arbitrarily selected units, 5 units producing a pressor response averaging 20 mm. Hg. in dogs anesthetized with sodium pentobarbital (30 mg./Kg.). Mean femoral arterial pressure was recorded on a smoked drum from a mercury manometer; systolic and diastolic pressures were measured with a strain gage manometer connected to appropriate amplifying and recording equipment.

The angiotonin employed was the active octapeptide preparation synthesized by Bumpus, Schwarz and Page. Dosage is given in arbitrarily selected units, 5 units producing a pressor response averaging 20 mm. Hg. in dogs anesthetized with sodium pentobarbital. The natural angiotonin employed was a partially purified preparation composed mainly of the decapeptide but the oxytocic/pressor ratio (Bumpus, Schwarz and Page) indicated a small amount of octapeptide also present. Vasovactive drugs were given by injection or infusion through a catheter in one femoral vein.

Results

Effect of Single Injections before and after Anesthesia. Intravenous injection of 5 units of synthetic octapeptide angiotonin into unanesthetized dogs caused initial sharp rise in mean arterial pressure followed by a compensatory fall and then by a sustained pressor response, arterial pressure returning gradually to the control level after from 4 to 6 min. There was no late depressor phase of the response. Cardiac slowing during the pressure rise was slight compared with that accompanying the response to norepinephrine. In all these respects, response to synthetic angiotonin was identical with that to natural angiotonin and the form of the pressor responses were alike. Synthetic angiotonin increased both systolic and diastolic pressures, pulse pressure tending to increase slightly during the sustained portion of the response. Again, responses to synthetic and to natural angiotonin were apparently identical (fig. 1).

Induction of anesthesia with pentobarbital caused sharp lowering of arterial pressure and reduction of systolic and diastolic pressure response both to synthetic angiotonin and to norepinephrine. As arterial pressure recovered within 15 to 30 min., pressor responses increased but usually remained smaller than values before anesthesia, and the initial compensatory response remained dampened.

Effect of Infusion before and after Anesthesia. Infusion of synthetic angiotonin gave essentially the same results before and after anesthesia except that, as with quick injections, responses were somewhat dampened after administration.
of pentobarbital. The average response before anesthesia was 40/30 mm Hg and was maintained for as long as the infusion was continued (68 and 55 min. in two instances). It was usually difficult or impossible, however, to provoke a more prominent rise in arterial pressure in intact animals. One unit/Kg./min. was ordinarily sufficient to elicit the usual maximum or near maximum response of 40/30 mm Hg; doubling or trebling this dosage caused but slight, if any, further rise in pressure. This contrasted with responses to quick injections of angiotonin: progressive increase in dosage elicited rises in pressure to severely hypertensive levels, even though the dose-response relationship was not a linear one. Too, single injections would elicit pressor responses of magnitude out of proportion to those obtainable by giving much larger dosage by infusion. Inability to obtain more severe hypertension was not due to tachyphylaxis since responses to single injections of angiotonin immediately after the infusion were identical with those before the infusion. As expected, nervous compensatory mechanisms were active in opposing the pressure rise due to infusion of angiotonin: TEAC (5 mg./Kg.) caused further rise in pressure during the infusion and fall in pressure after.

Renin Tachyphylaxis. Infusion of highly purified natural angiotonin has been shown previously not to cause tachyphylaxis (Page\textsuperscript{3}) and, as mentioned, there was no evidence of tachyphylaxis during sustained pressor responses to infusion of large amounts of synthetic angiotonin.

Page and Helmer\textsuperscript{4} showed that injection of large doses of impure renin reduces and finally abolishes the pressor response to natural angiotonin. Response to synthetic angiotonin was found to be similarly abolished, both in anesthetized and unanesthetized dogs. Large doses of a crude renin preparation were given repetitively, each after pressure had returned to the control level, until it no longer produced a response, or produced one that was much diminished. Usually, three or four or more doses were required. When response to renin was thus reduced, that to synthetic angiotonin was lost, while responses to norepinephrine and serotonin were unchanged (fig. 2).

Vasopressin Tachyphylaxis. Since vasopressin is also an octapeptide the question was studied whether tachyphylaxis to this agent modified response to synthetic angiotonin. Loss of pressor response to vasopressin was pro-
duced by giving it repeatedly in progressively larger doses. In 3 dogs, there was no accompanying change in response to either natural or synthetic angiotonin or to norepinephrine.

Effect of Hydralazine. It has been asserted that hydralazine blocks the pressor action of natural angiotonin; we have not been able to confirm this finding. The experiment was repeated here using synthetic angiotonin. One-half or 1.5 mg./Kg. of hydralazine was given intravenously to anesthetized dogs and, after from 10 to 30 min. when arterial pressure had stabilized at a moderately lower level, angiotonin was given again. Response to small dosages of angiotonin was slightly enhanced; maximum responses were slightly dampened.

Effect of Spinal Pithing. A period of approximately 1 hour was allowed for stabilization of blood pressure and reactivity after pithing of the cat's spinal cord. Responses to natural and synthetic angiotonin were affected similarly, both increasing roughly fourfold. Augmentation of response to norepinephrine was greater than that to angiotonin.

Effect of Ganglion Blocking Agents. Ganglion blocking agents such as tetraethylammonium chloride (TEAC) have been shown previously to augment the pressor action of natural angiotonin. Response to the synthetic material was found here to be affected in the same manner and to the same degree. TEAC was given repetitively by injection (5 to 10 mg./Kg.) to anesthetized dogs and cats until response reversed from depressor to pressor, usually after total dosage of from 20 to 50 mg./Kg. At completion of this treatment, resting arterial pressures were not greatly changed from control values and there was marked augmentation of response both to natural and to synthetic angiotonin and to norepinephrine. As an example of the extent of the change, response to synthetic angiotonin increased from 21 to 84 mm. Hg and that to norepinephrine from 36 to 108 mm. Hg.

Effect of Cutting Buffer Nerves after TEAC. Section of the carotid sinus and aortic buffer nerves after treatment with TEAC has been shown previously to cause marked further increase of response to natural angiotonin while not affecting, or diminishing, response to norepinephrine. This procedure was found here to have the same effect on response to synthetic as to natural angiotonin, pressor responses being increased by 2 to 3 times.

Effect of Nephrectomy. Mean arterial pressure responses to synthetic angiotonin were measured in anesthetized dogs before and then two days after bilateral nephrectomy. Responses were found to be enhanced in the same manner and to the same degree as were those to natural angiotonin in a previous investigation.

Summary

Synthetic octapeptide angiotonin and natural angiotonin elicited identical systolic and diastolic pressor responses when given by intravenous injection in anesthetized and unanesthetized dogs. Given by infusion, synthetic angiotonin raised arterial pressure an average of 40/30 mm. Hg and the response was maintained without the appearance of tachyphylaxis for the 1 hour or longer periods of infusion. It was ordinarily difficult, or impossible, to provoke a more prominent rise in pressure in either intact anesthetized or unanesthetized dogs by increasing the rate of infusion, contrasting with the effect of increasing dosage of angiotonin given by quick injection. Response to a ganglion blocking agent during the infusion was a rise rather than a fall in pressure.

While tachyphylaxis to synthetic angiotonin was not observed, that to a crude renin preparation was produced readily, and there was an accompanying loss of response to both synthetic and natural angiotonin while response to norepinephrine and serotonin was unchanged. Production of tachyphylaxis to another octapeptide, vasopressin, did not modify response to synthetic angiotonin. The administration of hydralazine did not block response to synthetic or natural angiotonin.

Responses to natural and synthetic angiotonin were modified in identical manners by spinal pithing, by nephrectomy, by administration of a ganglion blocking agent, and by section of the buffer nerves after administration of a ganglion blocking agent.
**Summary in Interlingua**

Le synthetic octapeptido angiotonina e angiotonina natural, administrate per injection intravenose a canes anesthetisate e non anesthetisate, evocava identic responsas de pression systolic e diastolic. In administration per infusion, angiotonina synthetic augmentava le pression arterial per un addendo medie de 40/30 mm Hg, e iste responsa eseva manutenite durante periodos de infusion de 1 hora o plus sin manifestation de tachyphylaxe. Ordinarimente il eseva difficile o mesmo impossibile evocar un plus prominent augumento del pression in intacte canes anesthetisate o non anesthetisate per accelerar le infusion, per contrasto con le effecto de augmentate doses de angiotonina administrate per injectiones rapide. Le responsa al administration de un agente de blocage ganglionic durante le infusion eseva un augmento plus tosto que un reduc- tion del pression.

Durante que nulle tachyphylaxe eseva notate con angiotonina synthetic, tachyphylaxe a un preparato de renina crude se produceva promptemente. Isto eseva accompaniante per un perdita de responsa a angiotonina natural e a angiotonina synthetic, sed le responsa a norepinephrina e a serotoninax remaneva inalterate. Le production de tachyphylaxe a un altere octapeptido, vasopressina, non modificava le responsa a angiotonina natural.

Le responsas a angiotonina natural e synthetica eseva modificatte de maniera identic per destruer le medulla spina, per nephrectomia, per le administration de un agente de blocage ganglionic, e per le section del nervos tamponator post le administration de un agente de blocage ganglionic.

**References**

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