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Splanchnic Vascular Effects of Pharmacologic Doses of Oxytocin in the Canine (41086)[1]

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Abstract. Effects of iv infusion of oxytocin in pharmacologic doses (0.95–7.6 U/min for 10 min) upon systemic arterial and portal venous pressures and on small intestinal and hepatic arterial resistances were observed in anesthetized male dogs. Arterial pressure underwent a biphasic response; transient decrease followed by an increase throughout the remainder of the infusion. With the largest dose pressure decreased 22% from 104 ± 10 to 81 ± 12 after 3 min, but returned to 108 ± 11 mm Hg after 10 min. One hour later, oxytocin infusion was repeated and no transient depressor response was seen, only a slight further 9% increase in pressure with 7.6 U/min. Small intestinal vasculature reflected a somewhat similar picture; a transient decrease in resistance, but followed by a rather prominent increase. During 7.6 U/min infusion it decreased 23%, from 3.5 ± 0.8 to 2.7 ± 0.8 after 3 min, but then increased 60% to 5.6 ± 0.9 mm Hg/ml·min·100 g after 10 min. No dilation but rather only a further 57% resistance increase was seen during the second infusion, from 5.1 ± 1.0 to 8.0 ± 2.0 after 10 min. Hepatic arterial resistance fell during the first infusion reaching a minimum after 3 min (30% decrease with 3.8 U/min). This was partially reversed, but not converted to an increase over initial level, even after 10 min at which time it was still 20% below control level. No increase was seen during the second infusion either; only a slight 7% decrease. The vasculature may contain both dilator and constrictor receptors for oxytocin. The dilator response is either overcome by the constrictor moiety or develops a tachyphylaxis to oxytocin challenge. The constrictor component is more prominent, and dilation more transient, in small intestinal than it is in hepatic arterial vasculature.

The primary physiological role of oxytocin, at least in the female, is to promote lactation by causing contraction of mammary myoepithelial cells and also to enhance the contraction of uterine smooth muscle late in pregnancy. Because of this latter property it is used in pharmacologic amounts in the practice of obstetrics and gynecology. Oxytocin has also been shown to have cardiovascular effects even in doses as low as 5 mU/kg (1). A recent report (2) expressed concern over cardiovascular-related deaths following single iv bolus pharmacologic doses given to patients postpartum. Alarming hypotensive responses have been seen when it was given to women undergoing first trimester abortion (3).

There are few data concerning the effects of oxytocin on specific vascular beds. In most cases observations on its effects have been limited to changes in systemic arterial pressure (4). The cardiovascular response to oxytocin seems to vary with species, sex, and reproductive status of the animal used (2–8). It is found in the male neurohypophysis and when administered to male rats has been shown to cause a significant increase in prostate, seminal vesicle and kidney blood flows without any change in cardiac output (9).

In the present study the effects of iv infusions of oxytocin in pharmacologic amounts on the small intestinal and hepatic arterial vasculatures were observed in male dogs. Mean systemic arterial and portal venous pressures were also recorded.

Material and Methods. Male mongrel dogs weighing about 18–25 kg were anesthetized with sodium pentobarbital at an initial dose of 30 mg/kg. In experiments using isolated autoperfused small intestine segments the abdomen was opened by a midline incision and the cecum and ileum were exposed. Lymph nodes in the region

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of the major mesenteric vessels were dissected away and a segment of distal small intestine served by a single artery and vein was surgically isolated. Short plastic tubes were securely tied into its open ends. The artery of the segment was ligated, cannulated, and perfused with blood from a femoral artery by an extracorporeal circuit which contained an electromagnetic flow transducer and a lateral connection for measurement of arterial perfusion pressure. Perfusion was briefly stopped while the vein from the segment was ligated and cannulated. Venous outflow was drained into a plastic reservoir and returned by way of a cannula in a jugular vein. Venous outflow pressure was also recorded. Gut segments were kept moist by gauze soaked in saline and warmed by a heat lamp.

In experiments in which hepatic artery blood flow was measured an incision was made below the right costal margin exposing the great vessels of the upper abdomen. A segment of common hepatic artery was carefully stripped of sheath and attached nerves. The gastroduodenal artery was doubly tied and sectioned beyond the most distal of the proper hepatic arteries such that all common hepatic artery blood flow went to the liver. The common hepatic artery was then perfused from a femoral artery by an extracorporeal circuit as described above for the gut segment. Inferior vena cava pressure at the level of the hepatic vein orifices was measured by a catheter inserted through a femoral vein and portal pressure at the hilum by one inserted through a pancreatic or splenic tributary.

Dogs were heparinized (500 U/kg) in either case before the first cannulation was done. Mean systemic arterial pressure was recorded from a catheter inserted by way of a femoral artery. Blood flows were expressed as ml/min·100 g of organ tissue. Gut segment vascular resistance was calculated as segment arterial perfusion pressure−outflow venous pressure/segment blood flow. Hepatic artery resistance was calculated as hepatic artery perfusion pressure−inferior vena cava pressure/hepatic artery blood flow. Resistance units were mm Hg/ml·min·100 g. Pure synthetic oxytocin (Calbiochem) freshly made up in saline was infused into a femoral vein using a Harvard syringe pump.

Results. Effects of 10-min iv infusions of oxytocin at four different dose rates (0.95, 1.9, 3.8, and 7.6 U/min) were studied in a series of 32 dog experiments. Only one dose was given to each dog, but after 60 min an infusion at the same dose rate was repeated in each case. The response of mean systemic arterial pressure is summarized in Table I. During the first infusion the lowest dose had little or no effect while during infusion at the three higher doses systemic pressure showed a dose-related transient decrease (9, 14, and 22%, respectively) which reached its minimum after about 3 min infusion and then subsequently returned to a value near its control level during the remainder of the infusion period. The transient decrease in pressure was not

TABLE I. EFFECT OF 10 min iv INFUSION OF OXYTOCIN ON MEAN SYSTEMIC ARTERIAL PRESSURE (mm Hg)[a]

Dose (U/min)	First infusion				Second infusion			
	0.95	1.9	3.8	7.6	0.95	1.9	3.8	7.6
N	8	8	8	8	8	8	8	8
Time								
0	127 ± 3	128 ± 4	114 ± 3	104 ± 10	132 ± 3	128 ± 4	113 ± 6	105 ± 12
3 min	128 ± 3	116 ± 6[b]	98 ± 6[b]	81 ± 12[b]	134 ± 3	129 ± 5[c]	114 ± 6[c]	109 ± 12[c]
10 min	129 ± 3	125 ± 5	110 ± 5	108 ± 11	135 ± 3	130 ± 5	118 ± 6	114 ± 12

[a] Mean ± SEM values after 3 and 10 min infusion.
[b] Value after 3 min infusion significantly (P = 0.05 or less) different from that existing at zero time.
[c] Relative change seen during second infusion significantly (P = 0.05 or less) different from that seen during first infusion.

seen during the second infusion, but rather a tendency to increase throughout the entire infusion period; however, even the 9% increase seen after 10 min at the highest dose did not prove to be statistically significant. The relative changes seen after 3 min infusion were significantly different from those seen during the first infusion.

Changes in arterial perfusion pressure, blood flow, and vascular resistance of isolated, autoperfused segments of small intestine during iv oxytocin infusion were also followed in these experiments. Gut segment arterial perfusion pressure behaved much in the same fashion as did mean systemic arterial pressure except that the changes were of a slightly greater magnitude. After 3 min of first infusion, perfusion pressure was significantly decreased 14, 17, and 25%, respectively, with the three higher doses. Subsequent increases seen during the remainder of the first infusion and throughout the entire second infusion again did not prove to be significant. The only significant difference in relative response between the first and second infusions were seen at the 3-min point with the three higher doses. These data are shown in Fig. 1.

Gut segment blood flow values varied considerably; from 20 to 32 at onset of first infusion and from 14 to 24 ml/min·100 g at onset of the second infusion. During the first infusion at the three lower doses it tended to show a transient rise (7, 15, and 3%, respectively) which peaked after 3 min, but then subsequently declined to values below initial levels. It decreased throughout the entire infusion at the highest dose. Flow was significantly decreased after 10 min infusion at the three higher doses; 19, 27, and 30%, respectively. It apparently showed little or no recovery during the 60 min between the infusions and continued to decline throughout the entire second infusion; showing no initial transient rise at any dose.

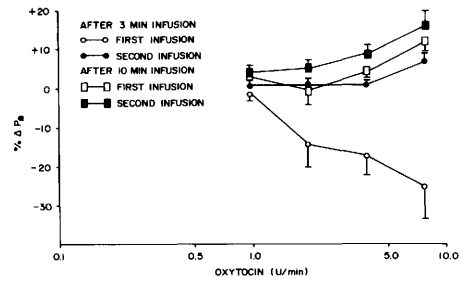

FIG. 1. Mean ± SEM percentage changes in arterial perfusion pressure ($\%\Delta P_A$) at 3 and 10 min during both the first and second iv oxytocin infusions at dose rates of 0.95, 1.9, 3.8, and 7.6 U/min. A recovery period of approximately 1 hr was allowed between the first and second infusions.

The response of gut segment vascular resistance to iv infusion of oxytocin was also biphasic in nature as is shown in Table II. During the first infusion there was an initial transient decrease in resistance. This decline was significant and amounted to about 25% at all three of the higher dose rates. Resistance was significantly increased during the remainder of the infusion period at all four doses in a somewhat dose-related fashion; by 14% at the lowest and 60% at the highest dose after 10 min. This is shown in Fig. 2. There was little or no recovery of resistance during the 60 min between infusions. No initial transient decrease was seen during the second infusion except for a slight indication at the lowest dose. It rose significantly throughout the second infusion at all four doses.

Response of the hepatic artery was followed during two successive 10-min iv infusions of oxytocin at 1.9 and 3.8 U/min in a series of 22 experiments. In general the response was vasodilator in nature, peaking after about 3 min during the first infusion. Starting at 20.4 ± 2.7 ml/min·100 g, hepatic artery flow rose to 25.2 ± 3.2, a significant 23% increase after 3 min infusion at 3.8 U/min. After 10 min infusion it was 24.3 ± 2.9 ml/min·100 g, still a significant 19% above its initial level. Flow decreased somewhat during the 60 min between infusions. It underwent a modest statistically nonsignificant increase throughout the entire second infusion. Starting at 19.0 ± 1.9 ml/min·100 g it rose to 20.4 ± 1.9 (a 7% increase) after 3 min and to 22.0 ± 2.1 (a 16% increase) after 10 min infusion at 3.8 U/min. The values for hepatic arterial vascular resistance, which are summarized in

TABLE II. EFFECT OF 10 min iv INFUSION OF OXYTOCIN ON GUT SEGMENT VASCULAR RESISTANCE (mm Hg/ml·min·100 g)[a]

Dose (U/min)	First infusion				Second infusion			
	0.95	1.9	3.8	7.6	0.95	1.9	3.8	7.6
N	8	8	8	8	8	8	8	8
Time								
0	3.6 ± 0.5	3.9 ± 0.5	2.7 ± 0.2	3.5 ± 0.8	4.3 ± 0.5	5.3 ± 0.8	3.6 ± 0.3	5.1 ± 1.0
3 min	3.3 ± 0.5	2.9 ± 0.6[b]	2.1 ± 0.2	2.7 ± 0.8[b]	4.2 ± 0.5	5.5 ± 0.8[c]	3.8 ± 0.4[c]	6.2 ± 1.0[b,c]
10 min	4.1 ± 0.4[b]	5.0 ± 0.8[b]	3.8 ± 0.3[b]	5.6 ± 0.9[b]	5.0 ± 0.5[b]	7.1 ± 1.0[b]	5.1 ± 0.7[b]	8.0 ± 2.0[b]

[a] Mean ± SEM values after 3 and 10 min infusion.
[b] Value after 3 or 10 min infusion significantly (P = 0.05 or less) different from that existing at zero time.
[c] Relative change seen during second infusion significantly (P = 0.05 or less) different from that seen during first infusion.

Table III, reflect the same picture; significant dilation during the first infusion, peaking after 3 min, and a slight dilation throughout the second infusion.

Portal venous pressure was also recorded in this series of experiments. It was significantly decreased, generally to a greater extent during the second infusion than during the first. This reflects the continued vasoconstriction seen in the prehepatic splanchnic (small intestinal) vasculature throughout the second oxytocin infusion (see Table II).

Discussion. Oxytocin has been variously reported to increase, decrease, or have no effect on mean systemic arterial pressure in the dog (4). Pure synthetic oxytocin has usually been found to decrease systemic arterial pressure in human subjects (3, 4, 10, 11). Katz (11) found that in humans 10 U (ca. 140 mU/kg) of commercial synthetic oxytocin (Syntocinon) given iv produced a biphasic response in mean systemic arterial pressure. There was a transient 20–40 mm Hg fall in pressure 30–60 sec after injection, followed by a 5- to 15-mm Hg rise which lasted 2–5 min. In the present study systemic arterial pressure also showed a biphasic response during 10-min iv infusions of oxytocin. During infusion at the lowest rate (1.9 U/min) which caused any significant effect on systemic pressure, after 3 min about 285 mU/kg had been given and pressure reached a minimum level. It was decreased by about 12 mm Hg or 9%. At the end of the infusion when about 950 mU/kg had been given it was only 3 mm Hg below its initial value. This dose exceeds the maximum therapeutic doses of 30 U (ca. 420 mU/kg) which are given to humans. Much greater doses (7.6 U/min for 10 min or 3800 mU/kg), even though they produced a significant transient depressor response (−24%) failed to produce any significant secondary pressor response. The most significant observation was that after a 60-min interval when the oxytocin infusions were repeated no transient depressor response was seen, only a slight statistically nonsignificant rise in pressure. Thus pharmacologic doses of pure synthetic oxytocin in the canine produce only a modest and transient decrease in mean systemic arterial pressure which is followed by little or no tendency for systemic pressure to increase above its initial

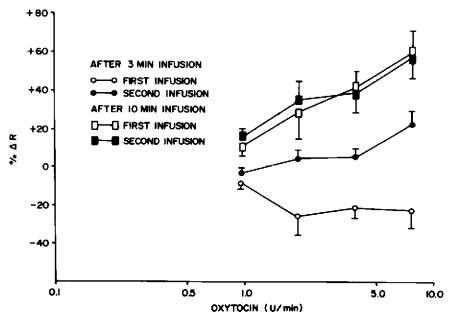

FIG. 2. Mean ± SEM percentage changes in gut segment resistance (%ΔR) after 3 and 10 min during both the first and second iv oxytocin infusions at dose rates of 0.95, 1.91, 3.8, and 7.6 U/min. The second infusion followed the first by approximately 1 hr.

TABLE III. EFFECT OF iv INFUSION OF OXYTOCIN ON HEPATIC ARTERY RESISTANCE (mmHg/ml·min·100g)[a]

	First infusion					Second infusion				
Dose (U/min)	0	3 min	%Δ	10 min	%Δ	0	3 min	%Δ	10 min	%Δ
1.9 $N = 9$	4.5 ± 0.7	3.6 ± 0.5[b]	−20 ± 3	4.1 ± 0.7	−9 ± 6	5.5 ± 0.6	5.4 ± 0.6	−2 ± 5[c]	5.1 ± 0.5	−7 ± 6[c]
3.8	5.2 ± 0.9	3.6 ± 0.6[b]	−30 ± 8	4.2 ± 0.7[b]	−20 ± 4	6.0 ± 0.8	5.7 ± 1.1	−6 ± 3[c]	5.6 ± 1.1	−7 ± 5[c]

[a] Mean ± SEM values after 3 and 10 min infusion.
[b] Value at 3 or 10 min significantly ($P = 0.05$ or less) different from value at zero time.
[c] Relative response seen during second infusion significantly ($P = 0.05$ or less) different from that seen during first infusion.

level even though additional oxytocin is administered. At the present we can offer no explanation as to why there is an apparent tachyphylaxis to the transient decrease in pressure. Weis and Peak (3) have reported a similar tachyphylaxis to oxytocin-induced hypotension in human subjects. Our findings in the dog support their suggestion that systemic hypotension can be reduced or avoided by utilizing slower rates of oxytocin administration.

Oxytocin has also been variously reported to increase or decrease resistance in certain peripheral vascular beds. Weis (10) concluded from observations on pregnant women that it acts to decrease total peripheral resistance by stimulating beta receptors. Barnes (12) using the ^{85}Kr method in dogs reported a dose-dependent increase in renal blood flow when oxytocin was infused (1−100 mU/min) into the renal artery. Assali *et al.* (5) using chronically implanted electromagnetic flow transducers found that synthetic oxytocin had no effect on total renal blood flow in pregnant ewes. Davies and Withrington (13) found 0.5 U given by close ia injection caused an increase in vascular resistance in isolated blood perfused dog spleen. Nakano and Fisher (1) made some limited observations on the effect of 5 mU/kg infused ia in several pump-perfused vascular beds in anesthetized male, estrous female, and pregnant dogs. Resistance appeared to be decreased in the coronary, carotid, brachial, femoral, and superior mesenteric vasculatures. Human forearm blood flow has been reported to increase following iv oxytocin (14); however, it decreased if the forearm had first been subjected to local nerve block (15).

The present study utilized preservative-free pure synthetic oxytocin made up in saline. The test system used was isolated, autoperfused acutely denervated segments of dog intestine. Thus any observed effects on gut segment vascular resistance might be assumed to be direct effects of oxytocin on the intestinal vasculature. Resistance showed an initial transient decrease and then increased throughout the remainder of the 10-min infusion periods to reach levels above its preinfusion values. Vasodilation

did not appear to be dose related in nature but was about the same (ca. 25%) after 3 min infusion at any dose (1.9 U/min and above) which produced dilation to any significant extent. This would tend to support the idea that oxytocin exerts a direct vasodilator action on this vascular bed rather than the alternate conclusion that low doses dilate while higher doses constrict. Note (see Table II) that the dose lower than 1.9 U/min did not produce significant dilation but did produce a statistically significant secondary constriction. When the oxytocin infusions were repeated after a 60-min interval no transient dilation was seen and continued vasoconstriction was the prominent event. Thus constriction appears to be the major direct effect of oxytocin on the small intestine vasculature and it is clearly dose related in nature after 10 min during both the first and second infusions (see Fig. 2). At present we can offer no explanation for this biphasic response of the small intestinal vasculature to oxytocin infusion. Possibly oxytocin causes the release of something which is vasodilator in nature and its action is overcome by the direct vasoconstrictor effect of oxytocin. This is in contrast to what is seen during the iv infusion of vasopressin which causes a rapid, marked vasoconstriction of the small intestinal vasculature which is maintained throughout the infusion period (16).

The vasodilator response of the hepatic artery to 10-min iv infusions of oxytocin was much better sustained than that seen in the small intestine (see Table III). However, with the two dose rates used (1.9 and 3.8 U/min) it appeared to be dose related and most pronounced after 3 min and then subsequently waned throughout the remainder of the infusion. During the second infusion the response was still only vasodilation, but to an extent which did not prove to be statistically significant. Vasoconstriction may have supervened if the infusions had been carried on for a longer period of time. This is in contrast to the effect of iv vasopressin infusion on the hepatic artery where initial transient vasoconstriction is seen followed by vasodilation (16).

Another alternative explanation for these observations would be to postulate two types of oxytocin receptors in the vascular smooth muscle; one associated with dilation, and the other, more prominent in its effect, associated with vasoconstriction. The constrictor component was much more evident in the small intestinal than it was in the hepatic arterial vasculature. We have found that the constrictor responses of the canine superior mesenteric (17) and hepatic arterial (18) vessels during iv vasopressin infusion are inhibited by alpha-adrenergic blocking agents. These findings support the suggestion that part of the action of vasopressin involves alpha receptors, either directly, or by causing norepinephrine release. Any better understanding of the splanchnic vascular response to oxytocin awaits further investigation of a similar nature.

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