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Endogenous Vasopressin Supports Blood Pressure and Prevents Severe Hypotension during Epidural Anesthesia in Conscious Dogs

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To evaluate whether, and to what extent, release of endogenous vasopressin supports blood pressure when efferent sympathetic drive is blocked by epidural anesthesia, the authors studied the effects of high epidural anesthesia alone and when vasopressin was prevented from acting at its vascular (V_1)-receptor in six awake, trained, unsedated dogs. On different days, the same dose of 0.5% bupivacaine (8–13 ml) was injected epidurally in a randomized fashion either in the presence or absence of (V_1)-vasopressin receptor blockade, and the effects were evaluated on cardiovascular (arterial blood pressure, heart rate) and respiratory (blood gases, oxygen consumption) variables, and on plasma concentrations of vasopressin and renin. Results were also contrasted to those obtained after epidural injection of saline alone (placebo) in the same dogs. When endogenous vasopressin was prevented from acting by intravenous pretreatment with a specific V_1-receptor antagonist (β-mercapto-β, β-cyclopentamethylene-propionyl-O-Me-Tyr-Arg-Vasopressin), epidural anesthesia resulted in a rapid and sustained 35% decrease in mean arterial blood pressure from 92 mmHg ± 5 SE to 60 mmHg ± 4. In contrast, only a 14% decrease in mean blood pressure from 92 mmHg ± 5 to 79 mm Hg ± 6 was noted after epidural anesthesia alone. This difference between groups was statistically significant ($P = 0.0001$). The V_1-receptor blockade alone had no detectable effect. Vasopressin plasma concentrations significantly increased from 3.4 ± 0.3 pg·ml^{-1} to 16.2 ± 3.2 pg·ml^{-1} after epidural anesthesia but did not change after epidural saline. Renin activity did not change significantly in any group despite the marked hypotension observed after combined sympathetic and vasopressin blockade. Thus, in awake, unsedated dogs, blockade of most, if not all, efferent sympathetic drive by epidural anesthesia 1) is associated with hemodynamically effective increases in vasopressin concentrations, most likely to compensate for decreased cardiac filling or arterial pressure, and induces severe hypotension when endogenous vasopressin is prevented from acting at its V_1-receptor; and 2) suppresses the neurally mediated renin release known to occur in response to hypotension. The authors conclude that among the hormonal systems that can support arterial pressure, an intact vasopressin system plays an important role when spinal sympathetic outflow is selectively and markedly attenuated by high epidural anesthesia. (Key words: Anesthetic technique: epidural anesthesia. Complication: hypotension, arterial. Hormones, antidiuretic: renin; vasopressin. Sympathetic nervous system: sympathectomy.)

WE RECENTLY DEMONSTRATED[1] that plasma vasopressin concentrations markedly increase when arterial blood pressure is maintained during epidural anesthesia with widespread sympathetic blockade in conscious dogs. Presumably, this increase is a reflex response to diminished afferent input from cardiopulmonary or baroreceptor afferents. To investigate whether, and to what extent, release of endogenous vasopressin supports blood pressure when efferent sympathetic drive is attenuated by high epidural anesthesia, in the current study we evaluated the cardiovascular response to combined blockade of the peripheral sympathetic and vasopressin systems in awake dogs. Under the latter conditions, the renin system must receive particular attention because it may be deprived of its sympathetic control during epidural anesthesia.

Accordingly, in trained, conscious dogs, we studied the responses of blood pressure and renin activity to high epidural anesthesia while vasopressin concentrations were either allowed to increase or when vasopressin's action at its vascular receptor was prevented by pretreatment with a specific antagonist. Our results demonstrate that endogenous vasopressin supports arterial blood pressure and prevents severe hypotension during epidural anesthesia.

Methods

Experiments were performed on six trained mongrel dogs (weight, 22.7; range, 20.5–25 kg) housed in the local animal care facility and treated according to the Guidelines of the American Physiological Society. The study was approved by the Governmental Animal Protection Commission. The effects of epidural anesthesia alone (n = 6) and when combined with vasopressin (V_1)-receptor blockade (n = 6) on arterial pressure, heart rate, vasopressin (ADH) concentrations, and renin activity in plasma were evaluated in a randomized crossover fashion with each dog serving as its own control. Each experiment was performed on a different day with at least 2 days allowed to elapse between experiments. For further comparison, these data were also contrasted to those[1] obtained in the same six dogs several weeks previously after injection of

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epidural saline (placebo group). Thus, each dog was studied on three occasions. The dogs, which were acquainted with the laboratory setting and had been trained to lie unrestrained in the lateral position on a cushioned table, previously had been subjected repeatedly to epidural anesthesia.[1,2] For measurement of arterial blood pressure and blood sampling, five of the animals had had one or both carotid arteries exteriorized in skin loops several years earlier.

MEASUREMENTS

Electrocardiogram, heart rate (ECG-triggered cardiotachometer), whole body oxygen consumption, and arterial blood pressure (Statham 23 ID transducer) were measured continuously. The latter was done through a catheter inserted percutaneously into a carotid loop (5 dogs) or femoral artery (1 dog). Pressure was zeroed to atmospheric pressure and referenced to the level of the thoracic vertebral spinous processes. Heart rate was recorded both as mean heart rate, obtained by resetting a custom-built electronic counting circuit every 10 or 20 s, and as instantaneous (beat-to-beat) heart rate, performed to assess heart rate variability that correlates inversely with efferent vagal tone. Heart rate variability was defined as the average difference of maximum and minimum heart rate over consecutive 5-min periods.

Whole body oxygen consumption was measured with an open-circuit flow-through technique.[3] Briefly, the dog's head and upper trunk remained under a transparent plastic hood through which a constant flow of ambient air was sucked with a precision pump and from which the dogs breathed freely. Room air entered the hood at the edges of the hood, whereas the expired gas/air mixture was removed at the top of the hood. Oxygen consumption (standard temperature and pressure-dry [STPD]) was then derived from the air flow and the O_2 difference between in- and outflowing gas mixtures. (The apparatus has a time constant of 30 s.)

Arterial blood samples were collected in chilled tubes, placed immediately in crushed ice, processed further within 10 min, and stored at $-20°$ C until analysis. Arg^8-Vasopressin was measured in duplicate by radioimmunoassay (^{125}I Vasopressin, Euro-Diagnostics) using rabbit anti-vasopressin antiserum calibrated against the World Health Organization (WHO) standard and with a sensitivity of 0.8 $pg \cdot ml^{-1}$. Cross-reactivity with Lys^8-Vasopressin and oxytocin was 0.1%. Renin activity was measured and expressed as generated angiotensin I by radioimmunoassay (GammaCoat ^{125}I Plasma Renin Activity, Baxter, Cambridge, MA) at a *p*H of 6.0. Intra- and interassay variability was less than 10%. Arterial blood gas tensions (Pa_{O_2} and Pa_{CO_2}) and pH_a were determined using standard electrodes (Radiometer, Copenhagen, Denmark) at 37° C.

EPIDURAL ANESTHESIA

A radiopaque, wire-reinforced, flexible-tip epidural catheter was introduced percutaneously into the epidural space (usually between L-5 and L-6) through a 16-G Tuohy needle under sterile conditions during anesthesia with methohexital (4 mg/kg iv). Under fluoroscopy, the catheter was advanced rostrally into the epidural space (average catheter tip position, T10), sutured to the skin, and secured with plaster of Paris. The catheter was used subsequently for epidural injections and remained in place for the duration of the experiments, *i.e.*, for 1 or 2 weeks.

VASOPRESSIN RECEPTOR BLOCKADE

To prevent endogenous vasopressin from acting at its cardiovascular (V_1)-receptor, the selective and competitive vasopressin (V_1)-receptor blocker β-mercapto-β,β-cyclopenta-methylene-propionyl-O-Me-Tyr-Arg-Vasopressin[4] (Sigma Chemie, Deisenhofen, FRG), a blocker devoid of intrinsic agonist activity, was injected (40 μg/kg iv) in six dogs after baseline data had been obtained. This blocker is the most potent V_1-blocker yet described and has been shown to block the cardiovascular actions of exogenous vasopressin in conscious dogs[5] without affecting the renal V_2-receptors,[6] urine osmolality,[7] or plasma renin activity.[8] Pilot experiments had also indicated that neither this blocker nor epidural anesthesia exerted detectable effects on plasma osmolality. Since this antagonist interferes with the vasopressin assay, vasopressin concentrations could not be measured once the blocker had been injected.

Ten minutes after injection of the vasopressin blocker, epidural bupivacaine was injected. Since the vasopressin receptor blocker exerts its effect immediately following injection,[9,10] this 10-min time interval was of sufficient length to detect any cardiovascular effects of vasopressin receptor blockade *per se*, if present. After epidural injection of bupivacaine, variables were recorded for another 45 min.

To confirm that the vasopressin receptor block was indeed complete and maintained for the duration of the experiments, Arg-Vasopressin (Sigma) was injected (200–400 mU iv) at the conclusion of the experiments (approximately 60 min after injection of the vasopressin blocker) and found to be without detectable effects on blood pressure and heart rate. In contrast, this dose evoked an increase (10–20 mmHg) in mean arterial blood pressure and a decrease in heart rate by 6–12 min^{-1}, presumably from reflex origin, in the same dogs after epidural anesthesia but in the absence of V_1-receptor blockade.

EXPERIMENTAL PROTOCOL

The experiments were performed with the dogs under basal metabolic conditions. After an overnight fast (but with free access to water until 2 h before an experiment), the dogs were studied in the morning in a dimmed laboratory. Room temperature was kept between 23–25° C, which is the thermoneutral temperature range of dogs.[11] No drugs or fluids were given at any time unless stated specifically. After insertion of an arterial and a venous catheter, the position of the epidural catheter was confirmed by fluoroscopy. Epidural catheter position in a given dog did not vary between experimental days by more than one intervertebral space. Subsequently, the dog's head and upper trunk were placed under the plastic hood to measure oxygen consumption and the recordings commenced. Thereafter, to ensure a stable baseline before measurements were taken, at least 45 min were allowed to elapse: the dogs were then either drowsy or sleeping. After a further control period of 15 min, during which baseline values of variables were obtained, the following interventions were made:

1) Epidural anesthesia alone (n = 6): Bupivacaine 0.5% (6–13 ml; mean 8.2 ml) stored at room temperature was injected into the epidural space over 2 min, and the data were recorded for a further 45 min, *i.e.*, for a time sufficient to allow full spread of epidural blockade.

2) Vasopressin receptor blockade followed by epidural anesthesia (n = 6): The vasopressin receptor blocker was injected as described above, and the potential effects were observed for 10 min. Subsequently, the same dose of bupivacaine was injected epidurally as described under protocol 1, and the variables were recorded again for a further 45 min.

3) Epidural saline (placebo group, n = 6): Instead of bupivacaine, the same volume of normal saline was administered epidurally, and the variables were recorded for 45 min. As outlined above, these latter experiments had been carried out several weeks previously in the same dogs as part of another study[1] and serve as a comparison with the randomized interventions described under 1 and 2.

The volume injected epidurally depended on the dogs' length, catheter position, and individual spread of nerve block as tested during previous studies.[1,2] While the dose of bupivacaine differed between individual dogs, a given dog received the same dose of bupivacaine on each occasion. Epidural anesthesia was sufficient to block most, if not all, sympathetic outflow as evidenced in all dogs by paresis of the nictitating membrane of the eye that derives its sympathetic innervation from the most cranial part of the spinal sympathetic system, *i.e.*, the upper three thoracic segments.[12] In our previous studies,[1,2] a similar dose of bupivacaine had also increased both front and hind limb skin temperatures, abolished the baroreflex-mediated blood pressure increase to bilateral carotid artery clamping, and decreased plasma norepinephrine concentrations by 20%. Analgesia, assessed by unresponsiveness to pin prick at the end of the experiments, extended up to the first intercostal space. Although the hind limbs were paralyzed, the front limb motor function appeared unimpaired. All dogs changed their mode of inspiration from a thoracic to a diaphragmatic pattern of breathing, indicating at least partial motor block of the intercostal musculature.

Blood Samples

Arterial blood samples for measurements of vasopressin concentration, renin activity, blood gas tensions, and pH_a were collected at baseline and 45 min after epidural injections. Approximately 45 ml of blood was collected for analysis during each experiment and replaced by equal volumes of saline.

Data Evaluation

Data are reported as means ± SE. The following *a priori* null hypotheses were tested statistically. 1) Within a given group, there is no difference relative to baseline in values of variables after epidural injections or vasopressin receptor blockade. These hypotheses were tested using Student's two-tailed t test for paired samples. 2) Between groups, effects do not differ, regardless of whether sympathetic blockade alone or combined vasopressin receptor and sympathetic blockade are induced. These between group hypotheses were evaluated by analysis of variance (ANOVA) for repeated measurements and followed by further analysis using Scheffe's test if indicated.[13] A null hypothesis was rejected and statistical significance assumed when $P < 0.05$.

Results

Epidural anesthesia resulted in severe hypotension in the presence, but not in the absence, of vasopressin receptor blockade. The time course of the cardiovascular changes is shown in fig. 1. When endogenous vasopressin was prevented from acting in the presence of the V_1-antagonist, mean arterial blood pressure decreased rapidly within several minutes after epidural anesthesia. Severe hypotension was sustained for the duration of the experiments so that 45 min after epidural injection of bupivacaine (*i.e.*, at a time sufficient to allow full spread of sympathetic blockade), mean arterial blood pressure had decreased from 92 ± 5 mmHg at baseline to a plateau of 60 ± 4 mmHg ($P < 0.0004$). After sympathetic blockade alone, in contrast, blood pressure decreased much less, and the decrease in pressure more slowly reached its nadir 30–45 min after epidural injection. In fact, mean arterial blood pressure attained 45 min after epidural administration of bupivacaine (79 ± 6 mmHg) was not statistically

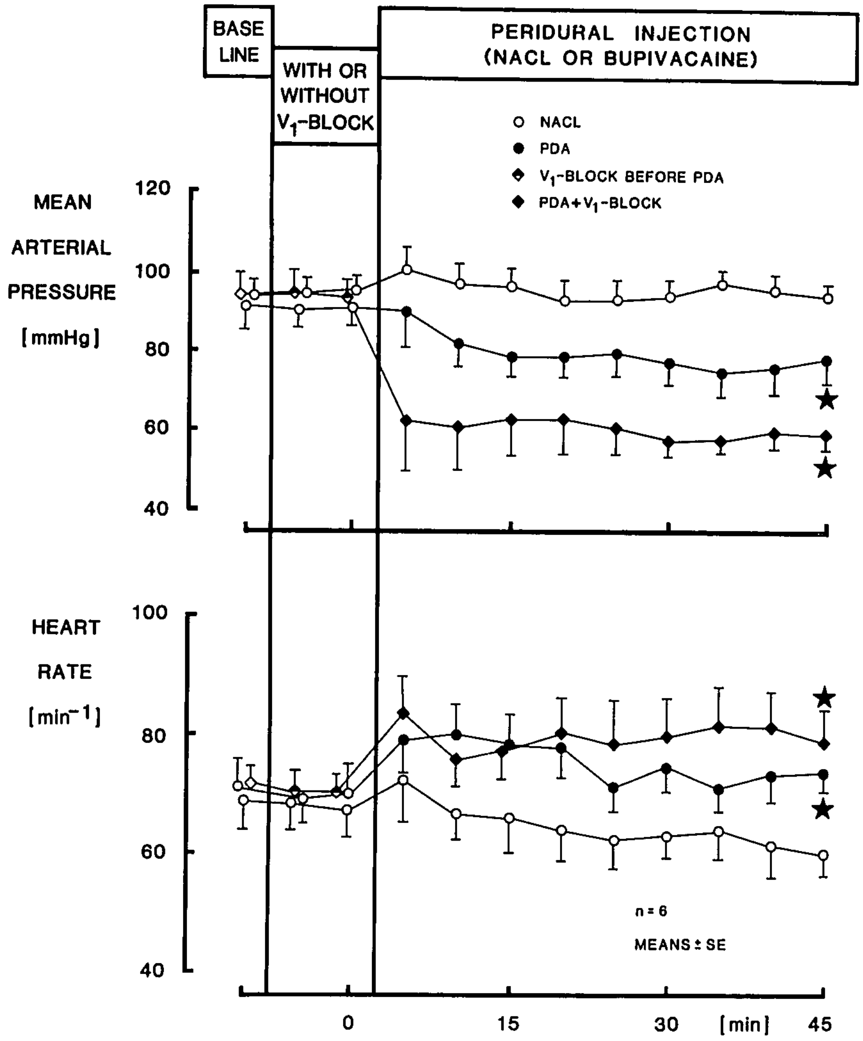

FIG. 1. Time course of changes in mean arterial blood pressure (*upper panel*) and heart rate (*lower panel*) after peridural bupivacaine 0.5% alone (filled circles), peridural bupivacaine 0.5% in the presence of vasopressin (V_1)-receptor blockade (filled diamonds), vasopressin blockade alone before peridural anesthesia (half-filled diamonds), and after peridural saline (open circles). Data represent means ± SE from six awake unsedated dogs at baseline, with or without V_1-block, and peridural injection. Either bupivacaine or saline were injected peridurally at time zero, *i.e.*, immediately after the third data point. After peridural anesthesia alone arterial blood pressure decreased only slightly over time, most likely because endogenous vasopressin release leading to increased plasma concentrations supported blood pressure. In contrast, when peridural anesthesia was induced while vasopressin was prevented from acting at its vascular (V_1)-receptor, blood pressure decreased rapidly, resulting in severe hypotension that was sustained for the duration of the experiments. Vasopressin blockade alone did not exert detectable effects. Heart rate was significantly higher after both peridural anesthesia alone and after combined vasopressin and sympathetic blockade than after peridural saline. This was caused both by a trend in heart rate to decrease over time after peridural saline, but to increase slightly after peridural blockade alone and after combined blockade. Therefore, an intact vasopressin system is important for support of arterial blood pressure during epidural anesthesia. Data were tested at 45 min after epidural injection, *i.e.*, at a time when changes had reached a plateau and sufficient time had elapsed to allow full spread of sympathetic blockade. (*Significant difference *vs.* saline, $P < 0.05$, ANOVA followed by Scheffe's test.)

different ($P = 0.08$) when compared to baseline (92 ± 5 mmHg). Statistical analysis confirmed that mean arterial blood pressure was significantly ($P = 0.0001$) lower when, in addition to sympathetic blockade, vasopressin was prevented from acting. In contrast to the decrease in blood pressure observed after epidural bupivacaine, mean arterial blood pressure remained unchanged, not only after vasopressin receptor blockade alone (92 ± 5 mmHg *vs.* 93 ± 5 mmHg; $P = 0.66$) but also after epidural saline (94 ± 4 mmHg *vs.* 95 ± 3 mmHg; $P = 0.6$).

The marked decrease in arterial blood pressure after combined sympathetic and vasopressin blockade cannot be attributed to differences in heart rate (fig. 1). Despite hypotension after combined vasopressin and sympathetic blockade, mean heart rate failed to change significantly relative to baseline. Heart rate also remained unchanged after epidural anesthesia alone, vasopressin receptor blockade alone, and epidural saline. Nevertheless, comparison between groups revealed that 45 min after epidural injections, heart rate was significantly ($P = 0.02$) higher after sympathetic blockade alone and after combined vasopressin and sympathetic blockade than in the saline group.

Heart rate variability (fig. 2) decreased markedly after combined vasopressin and sympathetic blockade (from 56 ± 7 min^{-1} to 15 ± 3 min^{-1}; $P = 0.002$), diminished moderately after sympathetic blockade alone (from 52 ± 3 min^{-1} to 41 ± 5 min^{-1}; $P = 0.013$), but remained unchanged after epidural saline (from 42 ± 7 min^{-1} to 42 ± 5 min^{-1}; $P = 0.96$).

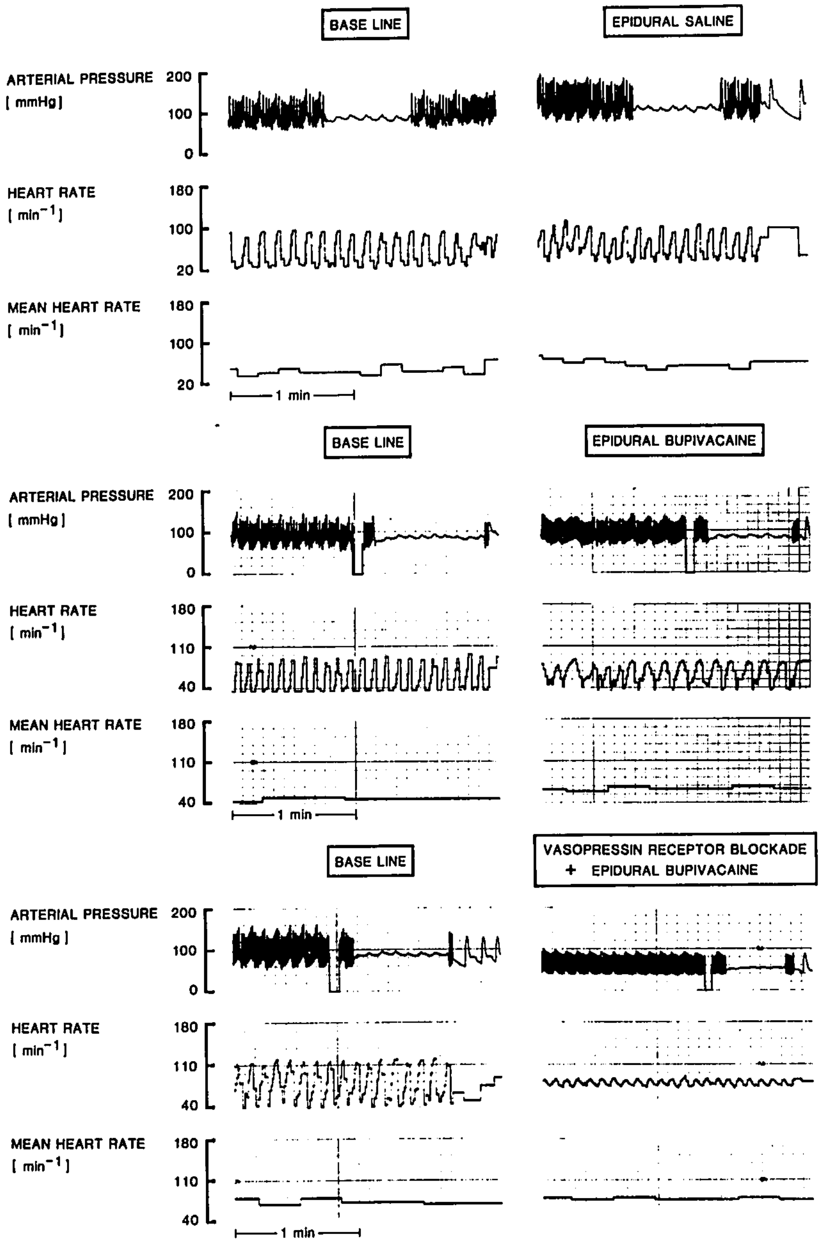

FIG. 2. Effects of peridural anesthesia alone and in combination with vasopressin (V_1)-receptor blockade on arterial blood pressure, beat-to-beat heart rate, and mean heart rate (averaged over 20-s periods). Changes are contrasted with the response in the intact innervated state after injection of epidural saline. Original recordings represent, in a single dog studied on different days, the states at baseline (*left*) and 45 min (*right*) after peridural saline (*top*), peridural anesthesia alone (*center*), and peridural anesthesia in the presence of vasopressin (V_1)-receptor blockade (*bottom*). Mean arterial blood pressure is obtained and shown for each state by briefly activating an electric filter. With the sympathetic nervous system intact (epidural saline), no change in variables is seen. With epidural blockade alone mean arterial blood pressure decreases only slightly, most likely because here endogenous vasopressin supported blood pressure. However, in the presence of vasopressin (V_1)-receptor blockade there is a marked fall in mean arterial blood pressure after sympathetic blockade by peridural anesthesia. Also note that after combined blockade the fluctuations in heart rate have disappeared almost completely, in contrast to peridural saline and peridural bupivacaine alone. Since these fluctuations are believed to represent waxing and waning of tonic efferent vagal activity, it is likely that there was a substantial compensatory withdrawal of efferent vagal tone to defend blood pressure during combined vasopressin receptor and sympathetic blockade. Thus, an intact vasopressin system is important to support blood pressure during widespread peridural anesthesia, and prevents severe hypotension.

The contribution of the vasopressin system to the support of arterial pressure is even more apparent from figure 3, where the maximum change in mean arterial blood pressure observed in each dog is shown for each group to account for the somewhat different time course of the cardiovascular changes. Here, the degree of hypotension was shown to almost triple ($P = 0.0001$) in the absence of an intact vasopressin system during epidural anesthesia compared to epidural anesthesia alone.

Sympathetic blockade evoked an increase in vasopressin concentrations while renin activity did not change (table 1). In every dog, vasopressin concentrations increased 45 min after epidural bupivacaine. On the average, vasopressin increased significantly ($P = 0.008$) from 3.4 ± 3 $pg \cdot ml^{-1}$ to 16.2 ± 3.2 $pg \cdot ml^{-1}$ after epidural anesthesia but did not change after epidural saline.

Renin activity failed to increase significantly despite the marked hypotension observed after combined sympathetic and vasopressin blockade. It is noteworthy, however, that in three of the dogs, renin activity increased after combined blockade but not following epidural blockade alone. Whole body oxygen consumption, even during hypotension, remained within the normal range of basal metabolic rate (*i.e.*, around 4 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$)

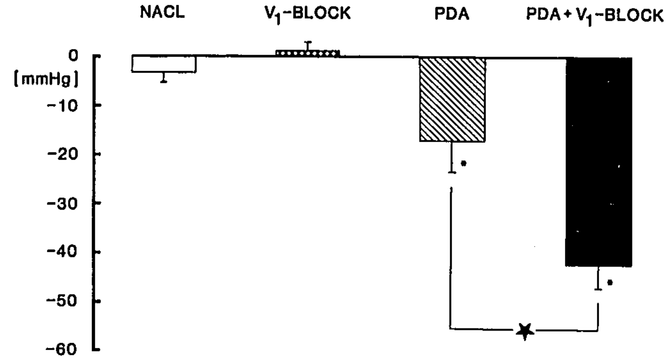

FIG. 3. Maximum change in arterial blood pressure from baseline after peridural saline (open column), vasopressin receptor blockade alone (column with crosses), peridural anesthesia alone (striped column), and peridural anesthesia in the presence of vasopressin (V_1)-receptor blockade (solid column). Data represent means ± SE from six awake dogs. Mean arterial blood pressure decreased moderately after peridural anesthesia, but markedly after combined vasopressin receptor and sympathetic blockade induced by peridural anesthesia. When vasopressin was prevented from acting at its V_1-receptor, the decrease in arterial pressure after epidural anesthesia significantly (almost threefold) exceeded the fall in pressure observed after epidural anesthesia alone, and resulted in severe hypotension. In contrast, neither vasopressin receptor blockade alone nor peridural saline alone exerted detectable effects. Thus, an intact vasopressin system serves in an important manner to prevent blood pressure from decreasing during peridural blockade. (*$P < 0.05$ *vs.* baseline and between epidural groups.)

and did not differ between groups at any time. Blood gas tensions and pH_a were not altered significantly by any intervention.

Discussion

Severe hypotension was induced by epidural anesthesia only when, in addition to blockade of efferent sympathetic tone, endogenous vasopressin also was prevented from acting at its vascular receptors. In contrast, sympathetic blockade by epidural anesthesia alone or the vasopressin receptor antagonist alone had only a small or no detectable effect on blood pressure. In other words, loss of neurogenic vasomotor control during high epidural anesthesia can be compensated for by an intact vasopressin system and arterial blood pressure maintained, most likely, by release of vasopressin.

These results emerged when sympathetic efferents were largely, if not completely, eliminated by high epidural anesthesia (see Methods section). Confounding influences on the cardiovascular response to sympathetic blockade or hormone release, such as anesthetics, mechanical ventilation, alterations in blood gas tensions or *p*H, surgery, ambient temperature, fluid balance, or drug interventions, were either excluded or kept constant.[14–19] Each dog received the same amount of epidural bupivacaine on different days, and the tip of the epidural catheter remained at the same anatomic position in each dog. Thus, similar bupivacaine concentrations in the blood and, consistent with paresis of the nictitating membrane and the extent of analgesia at the end of the experiments, also a similar extent of sympathetic blockade should have resulted in those experimental groups where bupivacaine was injected epidurally. Finally, the low baseline values of blood pressure, heart rate, and oxygen consumption (the latter corresponding to the basal metabolic rate[3]) indicate that the animals were calm and accustomed to the experiments. Thus, the cardiovascular response seen in our experiments is connected with the functional properties of spinal sympathetic outflow in awake dogs and cannot be attributed either to a different extent or degree of sympathetic blockade, or to the presence of bupivacaine in the blood.

Our conclusions rest on the tenable premise that profound hypotension observed during epidural anesthesia after pretreatment with the competitive vasopressin antagonist does indeed represent the consequences of preventing the action of endogenous vasopressin. Although

TABLE 1. Vasopressin Concentrations and Renin Activity in Plasma

	Vasopressin ($pg \cdot ml^{-1}$)		Renin ($ng \cdot ml^{-1} \cdot h^{-1}$)	
	Baseline	45 Min After Epidural Injection	Baseline	45 Min After Epidural Injection
Epidural anesthesia	3.4 ± 0.3	16.2 ± 3.2*	0.6 ± 0.1	0.6 ± 0.3
V_1-blockade + epidural anesthesia	5.1 ± 1.1	Not measured	0.7 ± 0.1	1.6 ± 0.5
Epidural saline	1.2 ± 0.4	1.6 ± 0.5	0.6 ± 0.2	0.7 ± 0.2

Data are means (±SE) from six conscious dogs studied on different occasions. With sympathetic blockade by epidural anesthesia alone vasopressin concentrations significantly increased whereas renin activity remained unchanged. After pretreatment with a competitive vasopressin receptor blocker, vasopressin concentrations could not be measured since the blocker interferes with the vasopressin assay (see methods). Of note, there was no significant difference in baseline concentrations of either vasopressin or renin activity before epidural anesthesia. Despite hypotension, renin activity did not change in a systematic fashion when both vasopressin's action and spinal sympathetic efferent drive were blocked, although in some dogs, renin activity slightly increased. (*$P < 0.05$ compared to baseline).

the structure and functional role of the vasopressin receptors in the various peripheral tissues and in the central nervous system are only incompletely understood, and different vasopressin receptor subpopulations also may exist in the cardiovascular system, the prevailing evidence is that endogenous vasopressin exerts its peripheral effects *via* receptors present in vascular smooth muscle (labeled V_1-receptors) and its long-term water conserving effects *via* different (V_2) receptors in the kidney.[20,21] Since the vasopressin antagonist used in our study is considered specific for V_1-receptors,[5,6,8,10] the effects seen after injection of this antagonist in combination with epidural anesthesia relative to those seen after epidural anesthesia alone should reflect solely those of V_1-receptor blockade. This is further supported by recent results during induced hemorrhage in dogs showing a similar decrease in blood pressure and vascular resistance after either V_1- or combined $V_1 + V_2$ receptor blockade.[10]

The marked hypotension observed after sympathetic blockade in the presence, but not in the absence, of vasopressin receptor blockade cannot be attributed to differences in heart rate. In fact, heart rate was similar after epidural blockade with or without V_1-receptor block despite the much greater hypotension under the former condition. Of note, heart rate increased after sympathetic blockade relative to the epidural saline group while beat-to-beat heart rate variability diminished markedly after combined sympathetic and vasopressin blockade and, to a moderate degree, during sympathetic blockade alone. This likely reflects a compensatory withdrawal of efferent vagal tone, since beat-to-beat heart rate fluctuations are believed to represent solely the waxing and waning of the tonically active cardiac vagal tone in conscious dogs.[22]

When endogenous vasopressin was allowed to act at its receptors during epidural anesthesia and in the face of a several-fold increase in plasma vasopressin concentrations, blood pressure decreased surprisingly little despite blockade of most, if not all, sympathetic efferents. In contrast, when endogenous vasopressin was prevented from acting during epidural anesthesia, the decrease in mean arterial blood pressure almost tripled and severe hypotension ensued. Since vasopressin concentrations at baseline were not different between groups before administration of epidural bupivacaine, we can infer that the increased vasopressin concentrations observed during epidural anesthesia, much like in our previous study,[1] were vasoactive and did support arterial blood pressure. This role of vasopressin was only unmasked when, in addition to vasopressin receptor blockade, a compensatory increase in efferent sympathetic drive was prevented by epidural anesthesia.

Vasopressin is a very potent vasoconstrictor, even at physiologic concentrations.[9,23,24] However, under normal conditions, most of its direct vascular actions are buffered by baroreflexes and only unmasked by baroreceptor denervation[24] or after destruction of the central nervous system.[9,25] This explains why, much like in our study, blockade of V_1-receptors alone in the presence of an intact sympathetic system failed to exert demonstrable cardiovascular effects not only in humans[26] and dogs[27] with low vasopressin plasma concentrations but also in dehydrated dogs with elevated vasopressin concentrations.[27] Only after prior chronic sinoaortic and cardiac denervation was the impact of endogenous vasopressin on arterial pressure unmasked in the latter study,[27] so that under the latter conditions, injection of the vasopressin receptor antagonist did decrease arterial blood pressure.

There is now evidence indicating that in animals both the vasopressin and the renin-angiotensin system can function in an important manner as a back-up system working in concert with and assisting the sympathetic nervous system in defending blood pressure during conditions such as hemorrhage,[28,29] pharmacologic blockade of the autonomic nervous system,[30] or dehydration.[8,31]

Much to our surprise, renin activity failed to increase in a systematic fashion when marked hypotension was evoked by combined sympathetic and vasopressin blockade. In general, both a decrease in systemic blood pressure and a local decrease in renal perfusion pressure are able to mediate renin release, even in surgically denervated kidneys. However, it is unclear at present to what degree this renin response is neurally mediated or independent of efferent and afferent renal innervation in intact humans or animals. Since a decrease in mean arterial blood pressure by 15–25 mmHg below resting blood pressure is a potent stimulus for renin release in humans[32] and conscious intact dogs,[33] and a selective decrease in renal artery pressure by as little as 10–15 mmHg (at unchanged or increased aortic pressures) also increases renin activity,[34–37] the 32-mmHg fall in arterial blood pressure observed in our study after combined blockade certainly should have been a strong stimulus for renin release under normal conditions. The unresponsiveness of the renin system despite marked hypotension is therefore most likely a unique feature of epidural blockade of sympathetic efferents to the kidney that can stimulate renin secretion *via* renal β_1-receptors[38].

Activation of the sympathetic system by clamping the carotid arteries in conscious dogs shifts by $\sim$17 mmHg (from a threshold pressure of 93 mmHg and at maintained aortic pressure) the relationship between renin release and local renal perfusion pressure, *e.g.*, renin release is now evoked at a higher pressure.[33,37] Similarly, more renin was secreted from denervated kidneys for the same decrease in local renal perfusion pressure when sympathetic drive was increased by electrostimulation of the distal end of the severed renal nerve.[39] That during sympathetic blockade by epidural anesthesia even marked hypotension fails to trigger renin release in a systematic fashion thus appears to imply that the contribution of sympathetic fibers to mediating renin release is much greater than hitherto believed. Also, and in contrast to the activation of the vasopressin system after diminution of sympathetic efferent drive, the renin angiotensin system alone may be unable under these conditions to function as a back-up system maintaining arterial blood pressure in a normotensive range or only moderately hypotensive range.

The role of endogenous vasopressin in supporting arterial blood pressure when sympathetic vasomotor control is attenuated does not appear to be a matter of species differences. Patients suffering from severe autonomic dysfunction (Shy-Drager's syndrome), but not normal subjects, markedly increase their blood pressure in response to a low-dose vasopressin infusion,[40,41] most likely because the former group is unable to reflexly buffer the vasopressin effects. Circumstantial clinical evidence supports the hypothesis that vasopressin also can be released during epidural anesthesia in humans. During epidural anesthesia in elderly humans with a variable sensory block between T-4 and T-10, vasopressin concentrations increased, although nonsignificantly, when the circulation was stressed by an upright tilt of the subjects.[42] In contrast, when the extent of sympathetic blockade was presumably even less (mean sensory block T-10) during lumbar epidural anesthesia, vasopressin concentrations remained unchanged in another study.[43] Thus, vasopressin release also would be expected to occur in humans when, during more extensive epidural or spinal anesthesia also involving the upper thoracic dermatomes, support of arterial pressure by increased efferent sympathetic drive from unblocked body regions is progressively diminished. If this is indeed the case, our study argues for an important role of endogenous vasopressin in support of blood pressure as a "last line of defense" during high epidural anesthesia.

In summary, in awake and unsedated dogs, loss of most, if not all, efferent sympathetic drive by high epidural anesthesia 1) is associated with hemodynamically effective increases in vasopressin concentrations and induces severe hypotension when endogenous vasopressin is prevented from acting at its V_1-receptors, and 2) suppresses the neurally mediated renin release known to occur in response to hypotension. Thus, among the hormonal systems that can support arterial blood pressure, an intact vasopressin system plays an important role in blood pressure support when spinal sympathetic outflow is selectively and markedly attenuated by epidural anesthesia and prevents severe hypotension.

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