activity and concentrations of A, NA and DA were measured for comparison in adrenal vein blood and in venous blood from the periphery of the circulation. If DBH were released into adrenal blood, its concentration would be higher in the blood of the suprarenal vein than in the blood of the peripheral circulation.

Methods. The study was performed in 10 human subjects (for details see table), who had to undergo a diagnostic catheterization of the right heart or of renal veins. Catheterization was performed in the conscious patient using the femoral vein by the percutaneous technique and local anesthesia. Blood samples for determination of DBH and catecholamines were withdrawn from the common iliac vein and from the left suprarenal vein. X-ray contrast media or drugs were not allowed before blood sampling was finished. DBH[4,5] and catecholamines[6] in the plasma were measured radioenzymatically. Statistical analysis of the data was made with Student's paired t-test.

Results and discussion. As may be seen from the table, in 10 human subjects basal plasma DBH activity was found in the adrenal vein blood (suprarenal vein) to be as high as in the periphery of the circulation (iliac vein). This indicates that DBH, which is stored in the chromaffine cells of adrenal medulla, is not released into adrenal blood. Therefore, these results in man support the conclusion deduced from animal experiments[3] that DBH in circulating blood originates from sympathetic nerve endings and not from the adrenal medulla.

Concomitantly with DBH activity, catecholamine concentrations in blood from suprarenal and iliac vein were determined. On an average, plasma A concentration was 170 times and plasma NA concentration 11 times higher in suprarenal vein blood than in iliac vein blood, indicating that blood withdrawn from the suprarenal vein did originate from the adrenal gland. Concentrations of A and NA in the suprarenal vein varied considerably from subject to subject. These variations are in accordance with results of other investigators[7,8]. On the other hand, in the periphery of the circulation, i.e. in plasma of the iliac vein, levels of A and NA were low and variations relatively small. This indicates that the sympatho-adrenal system of the patients was not stimulated during this period of catheterization. Finally, in this study for the first time plasma DA concentration in adrenal vein blood was determined from human subjects in vivo. Plasma levels of DA in the suprarenal vein were low, but statistically significantly higher than the corresponding plasma levels in the iliac vein ($p < 0.01$).

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Antipyresis following perfusion of brain sites with vasopressin[1]

N.W. Kasting, K.E. Cooper and W.L. Veale

Division of Medical Physiology, Faculty of Medicine, The University of Calgary, Calgary, Alberta T2N1N4 (Canada), 25 September 1978

Summary. Vasopressin was found to be an effective antipyretic when it was perfused through discrete regions of the brain of the sheep.

Recent work has demonstrated that the ewe has a decreased febrile response to both bacterial endotoxin and endogenous pyrogen (EP) for a period of time extending from about 4 days before, until at least 5 h after parturition[2,3]. The hormone whose blood levels most closely parallel the afebrile condition is arginine vasopressin (AVP)[4]. AVP has been demonstrated to lower the body temperature in rats given large doses, both i.p. and i.v.[5]. AVP levels in the plasma increase with increased body temperature and with exposure to high ambient temperatures[6]. Heating (1.5 °C) the basal forebrain area, specifically the preoptic region and the ventro-lateral septum, in dogs increases AVP levels in plasma[7].

Ewes with stereotaxically implanted cannulae received an i.v. injection of endotoxin and bilateral push-pull perfusion of the brain simultaneously. The push-pull perfusion method, which has been described previously[8], permits a localized region of tissue, approximately 1.0–1.5 mm in diameter, to be perfused. The perfusion continued for the duration of the experiment or 200 min at a rate of 40 µl/min.

The body temperatures of the animals were measured by thermistor probes inserted at least 10 cm into the vagina. The body temperature of all animals was between 39.0 and 39.9 °C at the start of all experiments.

All equipment and solutions were made sterile and pyrogen free by standard procedures. The solutions used for perfusion were either sucrose solution (260 mM) or sucrose solution (260 mM) containing 0.8, 2.0, or 4.0 µg AVP/ml. The bacterial endotoxin which was administered was derived from *Salmonella abortus equi* (SAEP). A standard dose of 30 µg SAEP in 3 ml physiological saline was injected i.v. This produces a biphasic fever with a maximum rise of 1.36±0.06 °C (SEM) in unoperated animals. Perfusion sites were identified by injection of 1 µl of 0.5% bromophenol blue into the appropriate sites. The brain was perfused with 10% formal saline and sectioned on a freezing microtome.

Sites within the brain which were sensitive to AVP were found in 4 out of 9 sheep. Figure 1 shows the mean ±SEM for these 4 animals. The top curve shows the mean febrile response to SAEP during a bilateral perfusion with a solution of sucrose. This fever curve is not significantly (unpaired T-test) different from the response in control animals to the same amount of SAEP. The middle curve shows the mean response to perfusion in the same 4 sheep to the sucrose solution containing AVP at 4 µg/ml. Previous observations have shown there is an exchange of about 10% of solution in the push-pull perfusate with the tissue itself[9]. A high estimate of the AVP actually entering the tissue would probably be 3.2 µg per side or a total of 6.4 µg over the 200-min perfusion period. The curve shows that the fevers during the perfusion with AVP are significantly decreased ($p < 0.005$–paired T-test) in both the 1st and 2nd

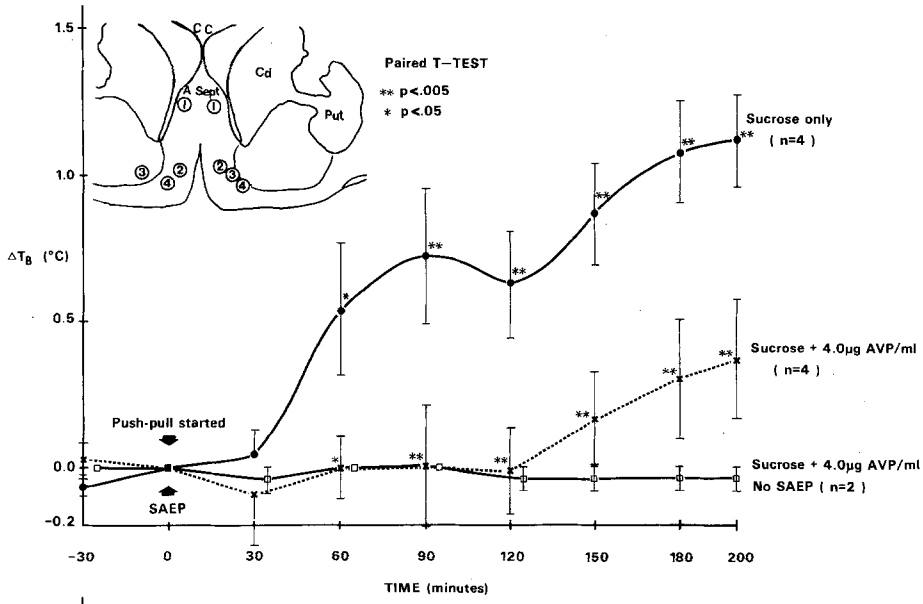

Fig. 1. The upper curve (●) represents the mean change in body temperature in response to endotoxin during push-pull perfusion with sucrose in sensitive sites in four animals. The middle curve (×) represents the mean change in body temperature in response to endotoxin during push-pull perfusion (40 µl/min) with sucrose containing AVP (4.0 µg/ml) in the same 4 sites as the upper curve. The bottom curve (□) represents the mean change in body temperature during push-pull perfusion in 2 of the above animals without endotoxin. Vertical bars represent ±1 SE of mean. – The insert shows the sites sensitive to AVP antipyresis, CC: corpus callosum, A Sept: septal area, Cd: caudate nucleus, Put: putamen.

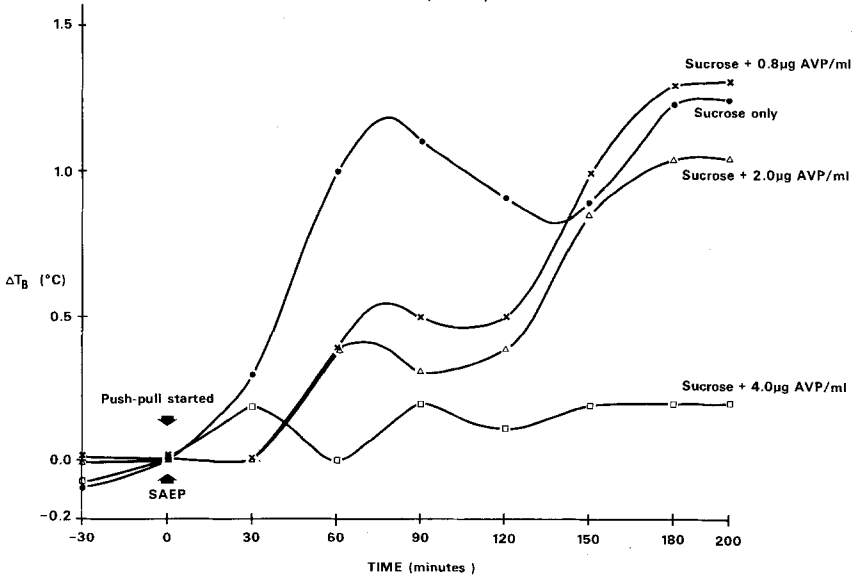

Fig. 2. These curves represent changes in body temperature of 1 ewe in response to an endotoxin challenge during push-pull perfusion of the septal area with sucrose solution containing varying concentrations of AVP.

peaks. The lower curve represents the mean change in body temperature of 2 of these animals to perfusion with sucrose and AVP solution in the sensitive sites but without the SAEP challenges. The perfusion of AVP had virtually no effect on normal body temperature.

An example of a dose-response relationship to varying concentrations of AVP is shown in figure 2. These curves represent the febrile respone of 1 ewe during perfusion with sucrose only, sucrose with 0.8 µg AVP/ml, 2.0 µg/ml and 4.0 µg/ml, to an endotoxin-induced fever.

The insert in figure 1 shows the sensitive sites. At least 1 of each pair of sites was located in the septal area, about 2–3 mm anterior to the optic chiasm. Unresponsive sites were found in the posterior hypothalamus, lateral hypothalamus, fornix, anterior hypothalamus, preoptic hypothalamus, ventral surface of the septal region and in the rostrum of the corpus callosum.

The results suggest that AVP can act to reduce fever significantly in amounts estimated to be maximally 6.4 µg over a period of 200 min and perhaps markedly less than that value. This can be compared with the antipyretic effects of salicylate at 6-30 µg delivered centrally in the rabbit[10] or of cortisol at 2.5 µg as a central injection in the rabbit[11].

This present demonstration suggests that AVP may have a role as an endogenous antipyretic in the mammalian brain in certain circumstances, such as the antipyresis in the term ewe and perhaps the newborn lamb.

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