early as the 4–5 days after birth; the cytoplasmic differentiation and growth proceeds more slowly and is continued until the adult-like stage (rats aged 3–4 weeks). These ultrastructural features mainly concern the progressive evolution of the morphologic and functional intraneuronal apparatus designated by us as the 'nucleus-ribosome system'. The NRS is essentially involved in the production of m-RNA and r-RNA and in the biosynthesis of neuronal proteins during the maturational period, as well as during the functioning of adult Purkinje cells.

Besides the cell body evolution, the dendritic arborization develops extensively, starting from the 2nd postnatal week. Intracerebellar connections are gradually established as the synaptogenesis proceeds and the neuronal prolongements become myelinized.

A comparative evaluation of maturational processes, implied in the behavioral development and in certain brain structures development, indicates that the 2nd week following birth constitutes a crucial phase in the neurobehavioral maturation of the rat. This assertion is further supported by the neurochemical and neurophysiological changes that have been reported by several investigators to occur at this time in the developing rat brain.

To conclude, the described neurobehavioral model, which has been assessed in the course of the rat postnatal development, may be considered in an attempt to integrate structural data with some functional aspects in the maturing brain. This model in normally growing rats may be used as a reference point to evaluate the modifications possibly induced by pharmacological and toxic agents on the prenatal and postnatal neurobehavioral development of the rat.

1 Acknowledgment. We thank Mrs D. Huot-Blais for her secretarial assistance.
2 G. Lapointe, Thesis, 1977.
3 J. Altman and K. Sudarshan, Anim. Behav. *23*, 896 (1975).
4 J. Altman, J. comp. Neurol. *145*, 399 (1972).
5 M.W. Fox, Anim. Behav. *13*, 234 (1965).
6 D. Wahlsten, Brain Res. *72*, 251 (1974).
7 Detailed criteria of the scoring system are available from the authors upon request.
8 G. Lapointe, K.N. Lin and G. Nosal, Annls ACFAS *43*, 101 (1975).
9 G. Lapointe, K.N. Lin and G. Nosal, Proc. Can. Fed. Biol. Soc. *18*, 108 (1975).
10 G. Nosal and C. Radouco-Thomas, Adv. Cytopharmac. *1*, 443 (1971).
11 G. Nosal, K.N. Lin and G. Lapointe, Acta neurol. latinoam. *21*, 1 (1975).
12 G. Nosal, G. Lapointe and K.N. Lin, Vie Méd. Can. franç. *4*, 109 (1975).

Dopamine-β-hydroxylase, adrenaline, noradrenaline and dopamine in the venous blood of adrenal gland of man: A comparison with levels in the periphery of the circulation[1]

G. Planz and Roswitha Planz

Abteilung Innere Medizin II, Klinikum der Rheinisch-Westfälischen Technischen Hochschule Aachen, Goethestrasse 27–29, D-5100 Aachen (Federal Republic of Germany), 2 May 1978

Summary. In 10 human subjects plasma dopamine-β-hydroxylase activity was found in the adrenal vein blood to be as high as in the periphery of the circulation. Adrenaline concentration in the adrenal vein blood was in the mean 170 times, noradrenaline concentration 11 times and dopamine concentration little higher than levels in the periphery.

Adrenaline (A), noradrenaline (NA) and dopamine (DA) as well as the enzyme dopamine-β-hydroxylase (DBH), which are all circulating in human blood, originate from the sympatho-adrenal system[2]. During activity of sympathetic nerves, NA, DA and DBH are released from the nerve endings by an exocytotic process into the extraneuronal space, then they reach the bloodstream secondarily. Adrenaline is a product of the adrenal medulla only; it is secreted directly into the adrenal blood. Venous blood of the adrenal gland leaves the organ by way of the suprarenal vein to enter the common circulation. The enzyme DBH, which catalizes the synthesis of NA from DA, is stored in the adrenal medulla as well as in the sympathetic nerves. It is not known in man whether DBH is released from the adrenal medulla into the blood. Animal experiments in vivo suggest that circulating DBH mainly originates from the sympathetic nerves rather than from the adrenal medulla[3]. In order to ascertain in man whether DBH, which is stored in the adrenal medulla, is released into adrenal blood together with the adrenal catecholamines, DBH

Comparison of catecholamine concentrations and dopamine-β-hydroxylase (DBH) activity in the plasma of iliac vein and plasma of suprarenal vein. Study in 10 human subjects: No. 1–5 have normal blood pressure, No. 6–9 are patients with essential hypertension, and subject No. 10 is a woman with terminal renal insufficiency and primary nephrosclerosis (f, female; m, male)

Subject No.	Age (years)	Sex	Blood pressure (mm Hg)	Plasma DBH activity (units/ml)		Plasma catecholamine concentration (ng/ml)					
				Iliac vein	Suprarenal vein	Iliac vein			Suprarenal vein		
						A	NA	DA	A	NA	DA
1	19	m	110/ 70	181	191 (106%)	0.10	0.38	0.19	18.83	2.67	0.30
2	35	m	130/ 80	193	196 (102%)	0.08	0.19	0.14	9.28	1.61	0.23
3	42	f	140/ 80	70	67 (96%)	0.13	0.34	0.21	11.80	7.01	0.26
4	28	m	140/ 90	293	291 (99%)	0.07	0.12	0.12	13.42	1.52	0.16
5	43	m	140/ 90	78	79 (101%)	0.04	0.13	0.20	8.15	0.91	0.23
6	54	m	150/100	68	74 (109%)	0.04	0.26	0.13	5.53	0.43	0.15
7	52	m	170/110	224	230 (103%)	0.07	0.30	0.20	4.25	1.17	0.23
8	56	m	200/130	190	181 (95%)	0.07	0.10	0.18	17.85	3.65	0.15
9	47	m	250/160	88	82 (93%)	0.10	0.07	0.21	13.90	2.30	0.30
10	40	f	200/120	38	37 (97%)	0.14	0.26	0.40	33.26	4.08	0.70
		n=10	$\bar{X} \pm SD$	142±85	143±85	0.08±0.03	0.22±0.11	0.20±0.08	13.63±8.41	2.54±1.96	0.27±0.16

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 ($p < 0.01$).

1 This study was supported by the Deutsche Forschungsgemeinschaft.
2 J. Axelrod, Pharmac. Rev. *24*, 233 (1972).
3 R. Weinshilboum and J. Axelrod, Science *173*, 931 (1971).
4 R.M. Weinshilboum and J. Axelrod, Circulation Res. *28*, 307 (1971).
5 G. Planz, H.W. Gierlichs, A. Hawlina, R. Planz, W. Stephany and K.H. Rahn, Klin. Wschr. *54*, 561 (1976).
6 M. Da Prada and G. Zürcher, Life Sci. *19*, 1161 (1976).
7 V. De Quattro, A.H. Margolin and L.O. Stocks, J. clin. Endocr. Metab. *30*, 138 (1970).
8 J.D. Sapira and K. Bron, J. clin. Endocr. Metab. *33*, 436 (1971).

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