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Natriuretic Hormones in Volume Natriuresis

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This review is an account of the participation of Czech and Slovak researchers in collaboration with foreign colleagues in the formulation and elaboration of the hypothesis on the existence of a natriuretic hormone. Some of the material was presented at the first International Symposium on Natriuretic Hormone, which took place at Smolenice Castle (House of Scientific Workers of the Slovak Academy of Sciences) in 1969 (Cort and Lichardus 1970), followed by two other symposia in 1980 (Lichardus *et al.* 1980) and 1984 (Dzúrik *et al.* 1985).

Experimental background

1) The natriuretic response to isotonic saline loading in the dog could not be prevented either by the glomerular filtration being kept constant (or moderately decreased) or by mineralocorticoids in plasma being kept elevated (de Wardener *et al.* 1961). Hence, a search for a "third factor" in the mechanism of natriuresis seemed to be justified.

2) A signal, independent on the integrity of vagi nerves (Pearce and Lichardus 1967), triggering natriuresis in a dog with either extracellular fluid volume (ECFV) (de Wardener *et al.* 1961) or intravascular volume expansion (Lichardus and Pearce 1966), could be conveyed by means of cross-circulation to another hydropenic dog with non-expanded ECFV. Hence, the "third factor" was evidently blood-borne. The latter experiment, in which expansion was not accompanied by hemodilution, led to the conclusion that the natriuretic activity in blood was related to a biologically active substance as hemodilution (due to saline infusion to expand ECFV) is by itself natriuretic (Lichardus and Pearce 1966, de Wardener and Clarkson 1985).

3) The operation of a blood-borne natriuretic factor in rat cross-circulation experiments was shown only when so-called sustained fluid volume expansion was achieved by urine reinfusion in the expanded donor animal (Lichardus and Ponec 1970, Pearce *et al.* 1970, Sonnenberg *et al.* 1972). This procedure apparently intensified the natriuretic signal to the recipient animal. Urea was one but not the major factor in natriuresis (Wilson and Honrath 1978)

4) Next was an attempt to clarify the basic question which emerged from the cross-circulation experiments, namely whether the appearance of a blood-borne natriuretic factor in animals with expanded ECFV was the result of a decreased concentration of an antinatriuretic or an increased concentration of a natriuretic substance. The latter possibility seemed to be more probable when a low-molecular (MW = 1000 or less) natriuretic substance, presumably of peptide nature, was

partially isolated and purified from the blood of cats and cows with acutely expanded ECFV. The natriuretic activity was detected by bio-assay in hydrated rats. The same plasma sample also decreased the short-circuit current representing active sodium transport in the frog skin (Lichardus *et al.* 1968, 1970, Sedláková *et al.* 1969). Now the name "natriuretic hormone" for the blood-borne substance seemed appropriate. Such a substance was also claimed to be present in blood of cats with natriuresis caused by bilateral common carotid arteries occlusion (for review see Cort and Lichardus 1968) and in blood and urine of patients with chronic renal failure (Spustová *et al.* 1985 among others; for review see de Wardener and Clarkson 1985).

5) The renal mechanism of action of natriuretic hormone was proposed to be *via* inhibition of the activity of the transporting enzyme, Na,K-ATPase (Kramer and Gonick 1974). The intrarenal site of the inhibition of sodium reabsorption which is critical for natriuresis due to intravascular or to the whole ECFV expansion, was localized rather in the medullary collecting ducts than in the proximal tubule (Sonnenberg 1972, Sonnenberg *et al.* 1980). However, the decreased sodium reabsorption in the proximal tubule is a consistent finding following isotonic saline loading (Dirks *et al.* 1965).

Further elaboration of the concept of an endogenous inhibitor of the Na,K-ATPase as a transporting enzyme resulted in an attractive hypothesis linking the inhibitor to digoxin-like activity found in some organs, blood and urine (see V. Schreiber in this volume) and to the pathogenesis of essential and low-renin arterial hypertension (Blaustein 1974, Haddy *et al.* 1980, de Wardener and MacGregor 1980). It was reasoned that in both cases the primary increase of ECFV triggers the secretion of the endogenous inhibitor of the sodium pump thereby increasing the intracellular sodium and secondarily also calcium concentrations in cells. The ensuing enhanced contractility and reactivity of the vascular smooth muscle cells underlies the increased vascular tone and peripheral vascular resistance that elevates blood pressure.

Indeed, it was subsequently found that anti-digoxin serum decreased blood pressure in young rats with DOCA-salt hypertension (Zicha *et al.* 1985). The same anti-digoxin serum, however, was ineffective in suppressing homeostatic natriuresis induced by ECFV expansion with saline in rats (Lichardus *et al.* 1986). This finding among others illustrates that so far the question of number and nature of substances represented by the endogenous digoxin-like activity has not been satisfactorily answered and the term "digoxin-like substance" need not be a synonym for natriuretic hormone (Kovács *et al.* 1987). Furthermore, the adrenals, although secreting endogenous digoxin-like substances, apparently do not secrete a natriuretic hormone, as neither acute nor chronic adrenalectomy impair volume homeostatic natriuresis (Lichardus *et al.* 1990c). Also the recently identified inhibitor of the Na,K-ATPase is still to be tested for its natriuretic activity (M. P. Blaustein – personal communication).

6) The size of cell nuclei in the nucleus posterior hypothalami was found to be a function of salt loading in the rat (Lichardus *et al.* 1965). Electrolytic lesions in the posterior hypothalamus impaired natriuresis related to the ECFV expansion in the rat and cat (Lichardus and Jonec 1960, Cort and Lichardus 1963, Lichardus *et al.* 1969). Hence, the hypothalamus was suggested to be involved in the mechanism of volume natriuresis. The salt-dependence of the size of cell nuclei in the nucleus

posterior hypothalami was taken as evidence of hormonal activity related to body salt balance in this hypothalamic area (Lichardus *et al.* 1965, Bajusz 1967).

Interaction of hormonal and physical natriuretic factors

The more general recognition of the hypothesis on the existence of a natriuretic hormone has always been jeopardized by the inability to identify it biochemically in spite of a considerable effort in this direction in many laboratories (for reviews see e.g. de Wardener and Clarkson 1985, Sonnenberg 1986, Haber and Haupert 1987, Kramer and Lichardus 1986,1987, Kramer *et al.* 1989). This inevitably promoted the designing of more sophisticated experiments in order to keep the idea of a natriuretic hormone alive by minimizing the role of physical factors in the mechanism of volume natriuresis. For example in acute experiments in anaesthetized dogs the kidneys transplanted to the neck responded by natriuresis to the blood transfusion of their respective "donor" dogs in spite of the facts that they were denervated, blood was not diluted and the renal perfusion and venous pressures were constant (Lichardus and Nizet 1972). The degree of natriuresis was, of course, partly impaired by these procedures limiting the normal reaction of the organism to blood volume expansion. However, it should be admitted, that intrarenal hemodynamics, namely a possible redistribution of the renal blood flow and changes of peritubular hydrostatic pressure, which were not under control by just keeping the renal perfusion pressure constant, still could have played a role in the mechanism of volume natriuresis. The inevitable conclusion thus was in the first review article on natriuretic hormone, namely that the mechanism of volume natriuresis is complex and implies neural, hemodynamic and tubular metabolic factors (Lichardus 1967).

This thesis on the complex mechanism of volume natriuresis was later illustrated by a series of experiments in acutely hypophysectomized rats (Lichardus *et al.* 1973, 1976, 1990c, Lichardus and Ponec 1972a,b, 1973, 1978, Ponec and Lichardus 1973, 1977, Ponec *et al.* 1978, 1987). Acute hypophysectomy abolished almost totally the natriuretic response to both intravascular and the whole ECFV expansion. The diuretic response was normal but the increase of urine output was due to the increased excretion of free water. In contrast to control animals the acutely hypophysectomized animals failed to increase cardiac output, glomerular filtration rate and renal blood flow, and their hydrostatic pressure in the peritubular capillaries was lower (Bencsáth *et al.* 1980). Thus the resetting of the Starling forces could contribute to the mechanism of sodium retention in acutely hypophysectomized rats in addition to the humoral antinatriuretic effect in connection with the ablation of the pituitary. It was further found that the impairment of the volume natriuresis in acutely hypophysectomized rats was associated with increased activity of the sympathetic nervous and plasma renin-angiotensin systems (Lichardus *et al.* 1990b,c) probably due to the absence of circulating vasopressin (Kvetňanský *et al.* 1988, Lichardus *et al.* 1989) and stress reaction to the acute surgical procedure. Either pharmacological doses of exogenous vasopressin (Lichardus and Ponec 1973) or the application of the inhibitor of angiotensin converting enzyme Captopril (Lichardus *et al.* 1990b,c) in acutely hypophysectomized rats completely restored volume natriuresis.

Even if these experiments in acutely hypophysectomized animals did not directly support the operation of a specific natriuretic hormone, it was suggested that hormonal factors taking part in the regulation of the renal vascular resistance could be necessary for the physical factors to play a role in the mechanism of natriuresis induced by acute ECFV expansion. However, the role of the physical factors seems to be rather critical in long-term regulation of ECFV as well (Cowley and Roman 1989).

Brain involvement in volume natriuresis

Further recent data on brain involvement in the volume natriuresis have supported the existence of a natriuretic hormone. It was shown that increased concentration of sodium in the cerebrospinal fluid (CSF) in the brain ventricles induces natriuresis (McKinley *et al.* 1985), and potentiates natriuresis induced by a concomitant i.v. infusion of saline, whereas the decreased concentration of sodium in CSF attenuates the renal homeostatic response (Lichardus *et al.* 1987, 1990b). This could have been caused by the release of a brain natriuretic hormone – inhibitor of Na,K-ATPase – as has been shown by others following increased sodium concentration in CSF (Jandhyala and Ansari 1986, Ulfendahl *et al.* 1986).

The sodium sensor was localized in the anterodorsal part of the third cerebral ventricle (Cox *et al.* 1987). Following electrolytic lesion of anterior third ventricle region (A3V) the experimental animals ceased to react with natriuresis either to the increase of sodium concentration in CSF or in blood. The natriuresis due to the ECFV expansion with isotonic saline was, however, at least in the sheep, undisturbed if the animals were kept forcibly in water balance before the ECFV expansion (Lichardus *et al.* 1987, 1990b). This finding is at variance with results of others who found that lesions also impaired the natriuresis induced by isotonic saline infusion (Brody and Johnson 1980, Songu-Mize *et al.* 1982). These authors claimed that the anterior third ventricle region was the site of secretion of a natriuretic hormone. Our results suggest that the A3V region is involved only indirectly in ECFV homeostasis *via* inducing a negative water balance which prevents the natriuresis following isotonic saline loading. The A3V region thus seems to be rather the site of detection of the sodium concentration in CSF or in blood and its relation to the regulation of ECFV should be further elucidated.

Atrial natriuretic peptide

Atrial natriuretic peptide (ANP) in spite of its suggestive name may be a hormone involved rather in cardiovascular regulation. The important contribution to this rapidly developing field in both physiological and clinical research was the elaboration of the first radioimmunoassay of ANP in plasma whereby ANP discovered by de Bold *et al.* (1981) was proved to be a circulating substance (Gutkowska *et al.* 1984) and the subsequent finding that some anaesthetics increased the secretion of ANP in rats (Horký *et al.* 1985). On the other hand, the pituitary was shown not to be directly involved in ANP secretion, as acute hypophysectomy did not change either basal or stimulated ANP secretion (Lichardus *et al.* 1990b,c). The constrictive effect of ANP on the efferent glomerular arteriole was visualized by means of electron-microscopy (Rovenská *et al.* 1989).

In agreement with others, we found that bilateral atrial appendectomy decreased natriuresis by 50 % following hypertonic saline infusion. However, this impairment of natriuresis seemed to be ANP-independent (Okoličány *et al.* 1989, Lichardus *et al.* 1990a).

In a series of clinically oriented studies it was confirmed that increased secretion of ANP in arterial hypertension is rather a correcting reaction to the increased blood pressure (Horký *et al.* 1987) or to the increased ECFV in chronic renal failure (Horký *et al.* 1988). In patients with liver cirrhosis the increased plasma level of ANP is caused not only by enhanced secretion but also by the decreased splanchnic extraction of the hormone (Tesař *et al.* 1989, Horký *et al.* 1990). However, the natriuretic effect of ANP in cirrhotic patients is small apparently due to the increased activity of antinatriuretic mechanisms (Horký *et al.*, 1989).

Further elaboration in the topic of the natriuretic hormones will also be proceeded in the field of neuroendocrine regulation of other body functions.

References

BAJUSZ E.: *Modern Trends in Neuroendocrinology*, Karger, Basel, 1967.

BENCSÁTH P., SZÉNASI G., PONEC J., TAKÁCS L., LICHARDUS B.: Renal sodium excretion in acutely hypophysectomized rats with expanded extracellular fluid volume. In: *Hormonal Regulation of Sodium Excretion*. B. LICHARDUS, R.W.SCHRIER, J.PONEC (eds), Elsevier/North Holland, Amsterdam, 1980, pp. 299–306.

BLAUSTEIN M.P.: Sodium ions, calcium ions, blood pressure regulation and hypertension: a reassessment and a hypothesis. *Am. J. Physiol.* 232: C165–C173, 1974.

BRODY M.J., JOHNSON A. K.: Role of anteroventral third ventricle region in fluid and electrolyte balance, arterial pressure regulation and hypertension. In: *Frontiers in Neuroendocrinology*. L. MARTINI, W.F. GANONG (eds), Raven Press, New York, 1980, pp. 249–292.

CORT J.H., LICHARDUS B.: The effect of cervical vagotomy and posterior hypothalamic lesions on the saluretic response to dextran infusion. *Physiol. Bohemoslov.* 12: 300–303, 1963.

CORT J.H., LICHARDUS B.: Natriuretic hormone, *Nephron* 5: 401–408, 1968.

CORT J.H., LICHARDUS B. (EDS): *Regulation of Body Fluid Volumes by the Kidney*. Karger, Basel, 1970, 192 pp.

COWLEY A.W., ROMAN R.J.: Control of blood and extracellular volume. *Bailliere's Clin. Endocrinol. Metab.* 3: 331–369, 1989.

COX P.S., DENTON D.A., MOUW D.R., TARJAN E.: Natriuresis induced by localized perfusion within the third cerebral ventricle of sheep. *Am. J. Physiol.* 252: R1–R6, 1987.

DEBOLD A.J., BORENSTEIN H.B., VERESS A.T, SONNENBERG H.: A rapid and potent natriuretic response to intravenous injection of atrial myocardial extract in rats. *Life Sci.* 28: 88–94, 1981.

DIRKS J.H., CIRKSENA J.W., BERLINER R.W.: The effect of saline infusion on sodium reabsorption by the proximal tubule in the dog. *J. Clin. Invest.* 44: 1160–1170, 1965.

DZÚRIK R., LICHARDUS B., GUDER, W. (EDS): *Kidney Metabolism and Function*. Kluwer Academic Publ., Dordrecht, 1985, 302 pp.

GUTKOWSKA J., HORKÝ K., THIBAULT G., JANUSZEWICZ P., CANTIN M., GENEST J.: Atrial natriuretic factor is a circulating hormone. *Biochem. Biophys. Res. Commun.* 125: 315–321, 1984.

HABER E., HAUPERT G.T.: The search for a hypothalamic Na,K-ATPase inhibitor. *Hypertension* 9: 315–324, 1987.

HADDY F.J., PAMNANI M.B., CLOUGH P.L.: Role of a humoral factor in low-renin hypertension. In: *Hormonal Regulation of Sodium Excretion*. B. LICHARDUS, R.W.SCHRIER, J. PONEC (eds), Elsevier/North Holland, Amsterdam, 1980,pp. 379–385.

HORKÝ K., GUTKOWSKA J., GARCIA R., CANTIN M., GENEST J: Atrial natriuretic factor – its possible role in the pathogenesis and therapy of arterial hypertension. *Cor Vasa* 29: 49–55, 1987.

HORKÝ K., GUTKOWSKA J., THIBAULT G., GARCIA R., GENEST J., CANTIN M.: Effect of different anesthetics on immunoreactive atrial natriuretic factor concentrations in plasma. *Biochem. Biophys. Res. Commun.* **129**: 651–657, 1985.

HORKÝ K., TESAŘ V , ASCHERMANN M.: Heart production, renal and splanchnic extraction of atrial natriuretic factor in hypertensive and non-hypertensive subjects. *J Hypertens* **8** (Suppl 3): S47, 1990.

HORKÝ K., TESAŘ V., LACHMANOVÁ J, DVOŘÁKOVÁ J., WIDIMSKÝ J.: Atrial natriuretic factor and its role in the regulation of electrolyte, volume and pressor homeostasis. *Czechoslov. Med.* **12**: 1–21, 1989.

HORKÝ K., WIDIMSKÝ J JR., ŠRÁMKOVÁ J., LACHMANOVÁ J.: Atrial natriuretic peptide concentration and natriuretic hormone activity in plasma of patients with chronic renal failure. *Horm. Metab. Res.* **20**: 709–712, 1988.

JANDHYALA B.S., ANSARI A.F.: Elevation of sodium levels in the cerebral ventricles of anaesthetized dogs triggers the release of an inhibitor of ouabain-sensitive sodium, potassium-ATPase into the circulation. *Clin. Sci.* **70**: 103–110, 1986.

KOVÁCS L., BIRČÁK J., LICHARDUS B.: Endogenous digoxin-like substance in the urine of preterm infants with late hyponatremia. *Eur. J. Pediat.* **146**: 622, 1987.

KRAMER H.J., GONICK H.C.: Effect of extracellular volume expansion on renal Na-K, ATPase and cell metabolism. *Nephron* **12**: 281–296, 1974.

KRAMER J.H., LICHARDUS B.: Atrial natriuretic hormones. Thirty years after the discovery of atrial volume receptors. *Klin. Wochenschr.* **64**: 719–731, 1986.

KRAMER J.H., LICHARDUS B.: Regulation of body fluid volume and disorders of sodium homeostasis. In: *Current Nephrology*, vol. 10, H.C. GONICK (ed.), Year Book Med. Publ., Chicago, 1987, pp. 221–226.

KRAMER J.H., LICHARDUS B., WARDENER H.E. DE: Natriuretic hormones and disorders of sodium homeostasis. In: *Current Nephrology*, vol. 12, H.C. GONICK (ed.), Year Book Med. Publ., Chicago, 1989, pp. 39–86.

KVETŇANSKÝ, R., LICHARDUS B., JEŽOVÁ D., OPRŠALOVÁ Z., MAKARA G.B.: Vasopressin and 1-deamino-8-D-arginine vasopressin (dDAVP) reduce elevated plasma catecholamine levels in rats with hypothalamic deafferentation. *Cell. Mol. Neurobiol.* **8**: 225–324, 1988.

LICHARDUS B.: Volume reflex – the experimental model to evidence a probable existence of a natriuretic hormone. *Endocrinol. exp.* **1**: 181–190, 1967.

LICHARDUS B., JONEC V.: Influence of hypothalamic lesions on water and salt metabolism in the rat. *Vnitř. Lék.* **6**: 634–638, 1960. (in Slovak)

LICHARDUS B., JONEC V., STRÁŽOVCOVÁ A.: Chronic electrolytic lesion in the posterior hypothalamus decreases natriuresis during extracellular fluid volume expansion in rats. *Endocrinol. Exp.* **3**: 141–146, 1969.

LICHARDUS B., KVETŇANSKÝ R., MAKARA G.B., OPRŠALOVÁ Z., MICHAJLOVSKIJ N., FÖLDES O., JEŽOVÁ D.: Circulating vasopressin attenuates the increased activity of the sympathetic nervous system induced by anterolateral deafferentation of the hypothalamus. In: *Progress in Neuroendocrine Research*. K.D. DÖHLER, M. PAWLIKOVSKI, (eds), Birkhäuser Verlag, Basel, 1989, pp. 91–97.

LICHARDUS B., MITRO A., CORT J.H.: Size of cell nuclei in hypothalamus of the rat as a function of salt loading. *Am. J. Physiol.* **208**: 1075–1077, 1965.

LICHARDUS B., NIZET A.: Water and sodium excretion following blood volume expansion under conditions of constant arterial, venous and plasma oncotic pressures and constant haematocrit. *Clin. Sci.* **42**: 701–709, 1972.

LICHARDUS B., OKOLIČÁNY J., HORKÝ K., JEŽOVÁ D., GABAUER I., PONEC J.: Atrial appendectomy impairs non-ANP induced natriuresis. *Abstracts Int. Symp. "A Decade of ANF Research"*, Ottawa, 1990, p. 18/97, 1990a.

LICHARDUS B., OKOLIČÁNY J., MCKINLEY M.J., DENTON D.A., PONEC J.: Brain involvement in the regulation of renal sodium excretion. *Klin. Wochenschr.* **65** (Suppl. VIII): 33–39, 1987.

LICHARDUS B. PEARCE J.W.: Evidence for a humoral natriuretic factor released by blood volume expansion. *Nature* **209**: 407–409, 1966.

LICHARDUS B., PLIŠKA V., UHRÍN , U , BARTH T.: The cow as a model for investigating natriuretic activity. *Lancet* **1**: 127–129, 1968.

LICHARDUS B., PLIŠKA V., UHRÍN V, BARTH, T.: Natriuretic and antinatriferic activities in deproteinized bovine plasma after dextran infusion. In: *Regulation of Body Fluid Volumes by the Kidney*. J.H. CORT, B. LICHARDUS (eds), Karger, Basel, 1970, pp. 114-121.

LICHARDUS B., PONEC J.: Conditions for biological evidence of a "natriuretic hormone" in experiments with rat cross-circulation. *Physiol. Bohemoslov.* **19**: 330, 1970.

LICHARDUS B., PONEC J.: Effect of hypophysectomy on sodium excretion in rats without blood dilution during blood volume expansion. *Experientia* **28**: 471–472, 1972a.

LICHARDUS B., PONEC J.: Neurohypohyseal origin of humoral factor restoring volume natriuresis in acutely hypophysectomized rats. *Experientia* **28**: 1443–1444, 1972b.

LICHARDUS B., PONEC J.: On the role of the hypophysis in the renal mechanisms of body fluid volume regulation. *Endokrinologie* **61**:403–412, 1973.

LICHARDUS B., PONEC J.: Acute hypophysectomy – a model for the study of hormonal mechanisms of natriuresis. In: *Natriuretic Hormone*. H.J. KRAMER, F KRÜCK (eds), Springer, Berlin, 1978, pp. 6–14.

LICHARDUS B., PONEC J., ALBRECHT I.: Factors promoting sodium excretion. In: *Endocrinology*, Proc. 4th Int. Congr. Endocrinol., Washington 1972, R. ROBINSON (ed.), Excerpta Medica, Princeton, 1973, pp. 729–732.

LICHARDUS B., PONEC J., MCKINLEY M.J., OKOLIČÁNY J., GABAUER I., STYK J., BAKOŠ P., OLIVER C., MICHAJLOUSKIJ, N.: The anterior third ventricle region (A3V) is a receptor site for the composition rather than volume of body fluids. In: *Circulating Regulatory Factors and Neuroendocrine Function*. J.C.PORTER, D.JEŽOVÁ (eds), Plenum Press, New York, 1990b, pp. 211–226.

LICHARDUS B., PONEC J., OKOLIČÁNY J. FÖLDES O., KVETŇANSKÝ R., OLIVER C., MICHAJLOVSKIJ N.: The pituitary and the adrenals are not directly involved in natriuresis due to expansion of the extracellular fluid volume. *Acta Physiol. Scand.* **139** (Suppl. 591): 97–99, 1990c.

LICHARDUS B., PONEC J., TUREK R.: On the role of the decreased renal vascular resistance in the mechanism of volume natriuresis. *Experientia* **32**: 884-885, 1976.

LICHARDUS B., SCHRIER R.W., PONEC J. (EDS): *Hormonal Regulation of Sodium Excretion*. Elsevier/North Holland, Amsterdam, 1980, 410 pp.

LICHARDUS B., ZICHA J., PONEC J., ŠTOLBA P, POHLOVÁ I.: Anti-digoxin serum with antipressoric properties is ineffective in attenuating natriuresis during extracellular fluid volume expansion. *Physiol. Bohemoslov.* **35**: 361, 1986.

MCKINLEY M.J., CONGIU M., DENTON D.A., LICHARDUS B., PARK R.G., TARJAN E., WEISSINGER R.S.: Cerebrospinal fluid composition and homeostatic responses to dehydration. In: *Vasopressin*. R.W.SCHRIER (ed.), Raven Press, New York, 1985, pp. 229–310.

OKOLIČÁNY J., LICHARDUS B., GABAUER I., PONEC J.: Bilateral acute atrial auriectomy reduced diuresis and natriuresis following hypertonic sodium load in anesthetized dogs. *Physiol. Bohemoslov.* **38**: 179–187, 1989.

PEARCE J.W., LICHARDUS B.: Effect of vagotomy and renal denervation on renal responses to blood volume expansion. *Can. J. Physiol. Pharmacol.* **45**: 689–703, 1967.

PEARCE J.W., SONNENBERG H., LICHARDUS B., VERESS A.T: Interaction of extrarenal and intrarenal factors in "volume natriuresis". In: *Regulation of Body Fluid Yolumes by the Kidney*. J.H. CORT, B. LICHARDUS (eds), Karger, Basel, 1970, pp. 72–92.

PONEC J., LICHARDUS B.: On the role of antidiuretic hormone in volume natriuresis and polyuria in rats. *Experientia* **29**: 1353, 1973.

PONEC J., LICHARDUS B.: Effect of small doses of antidiuretic hormone on renal excretion of water and sodium in acutely hypophysectomized rats. *Experientia* **33**: 685–686, 1977.

PONEC J., LICHARDUS B., OKOLIČÁNY J.: The effect of atrial natriuretic factor on natriuresis in acutely hypophysectomized saline-loaded rats. *Biomed. Biochim. Acta* **46**: 959–963, 1987.

PONEC J., TUREK R., LICHARDUS B.: Relation between the cortico-papillary osmotic gradient and saline diuresis in normal and acutely hypophysectomized rats. *Nephron* **20**: 336–342, 1978.

ROVENSKÁ E., PONEC J, LICHARDUS B.: Ultrastructure of renal efferent glomerular arteriole fixed during the infusion of atrial natriuretic peptide. *Exp. Clin. Endocrinol.* **94**: 215–218, 1989.

SEDLÁKOVÁ E., LICHARDUS B., CORT J.H.: Plasma saluretic activity: its nature and relation to oxytocin analogues. *Science* **164**: 580–582, 1969.

SONGU-MIZE E., BEALER S.L., CALDWELL R.W.: Effect of AV3V lesions on development of DOCA-salt hypertension and vascular Na-pump activity. *Hypertension* **4**: 575–580, 1982.

SONNENBERG H.: Renal response to blood volume expansion: distal tubular function and urinary excretion. *Am. J. Physiol.* **223**: 916–924, 1972.

SONNENBERG H.: Natriuretic factors. In: *Kidney Hormones*. vol. III, J.W. FISHER (ed), Academic Press, London, 1986, pp. 661–692.

SONNENBERG H., CHONG C.K., MILOJEVIČ S., VERESS A.T.: Site of action of plasma natriuretic factor in the rat kidney. In: *Hormonal Regulation of Sodium Excretion*. B. LICHARDUS, R.W. SCHRIER, J. PONEC (eds), Elsevier/North Holland, Amsterdam, 1980, pp. 357–363.

SONNENBERG H., VERESS A.T., PEARCE J.W.: A humoral component of the natriuretic mechanism in sustained blood volume expansion. *J. Clin. Invest.* **51**: 2631–2644, 1972.

SPUSTOVÁ V., GERYKOVÁ M., LICHARDUS B., DZÚRIK R.: Analytical identity of an inhibitor of sodium transport isolated from human urine. *Nephron* **39**: 18–20, 1985.

TESAŘ U, HORKÝ K., PETRTÝL J., KOZÁKOVÁ M., GREGOROVÁ I., BRODANOVÁ M., KORDAČ V., JIRSA M.JR.: Atrial natriuretic factor in liver cirrhosis – the influence of volume expansion. *Horm. Metab. Res.* **21**: 519–522, 1989.

ULFENDAHL H.R., GORANSSON A., HANSELL P., KARLSSON, M., SJÖQUIST M.: Natriuresis obtained by stimulation of the cerebroventricular system with sodium ions indicated a blood-borne natriuretic factor. *Acta Physiol. Scand.* **127**: 269–272, 1986.

WARDENER H.E. DE, CLARKSON E.M.: Concept of natriuretic hormone. *Physiol. Rev.* **65**: 658–759, 1985.

WARDENER H.E. DE, MACGREGOR G.: The natriuretic hormone and essential hypertension. In: *Hormonal Regulation of Sodium Excretion*. B. LICHARDUS, R.W. SCHRIER, J. PONEC (eds), Elsevier/North Holland, Amsterdam, 1980, pp. 387–392.

WARDENER H.E. DE, MILLS I.H., CLAPHAM W.F., HAYTER C.J.: Studies on the efferent mechanism of the sodium diuresis which follows the administration of intravenous saline in the dog. *Clin. Sci.* **21**: 249–258, 1961.

WILSON D.R., HONRATH U.: Cross-circulation study of natriuretic factors in rats with reduced nephron mass. *Am. J. Physiol.* **235**: F465–F472, 1978.

ZICHA J., KUNEŠ J., ŠTOLBA P.: Endogenous digoxin-like factor contributes to the elevation of systemic resistance in rats exposed to high-salt intake from prepuberty. *J. Hypertens.* **3** (Suppl. 3): S17–S19, 1985.

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