PNEI REVIEW

Thymic Cryptocrine Signaling and the Immune Recognition of Self Neuroendocrine Functions

Vincent Geenen, Henri Martens, Françoise Robert, Jean-Jacques Legros[1], Marie-Paule Defresne[2], Jacques Boniver[2], Joseph Martial[3], Pierre J. Lefèbvre and Paul Franchimont

Departments of Internal Medicine and Endocrinology, Neuroendocrin-Immunology Unit, [1]Neuroendocrine Unit, [2]Department of Pathological Anatomy, University Hospital of Liège-Sart Tilman, [3]Department of Genetic Engineering, University of Liège-Sart Tilman, Liège, Belgium

SYNOPSIS: The expression of neurohypophysial (NHP)-related peptides within the thymus in various species has been described. RIA and immunocytochemical studies using different antibodies directed against various members of the NHP peptide superfamily have demonstrated the colocalization of immunoreactive (ir-)oxytocin (OT), vasopressin (VP) and neurophysins (Np) in the thymic epithelial compartments of the subcapsular cortex and medulla. The large lympho-epithelial complexes derived from the subcapsular cortex—the "thymic nurse cells" (TNC)—were demonstrated to express in their epithelial part the immunophenotype of other components from the diffuse neuroendocrine system. The model of cryptocrine signaling recently was applied to TNCs, and it was proposed that NHP-related signals could transmit information between thymic epithelial cells and immature T-lymphocytes. The existence of thymic cryptocrine signaling through NHP-signals is further supported by the identification of functional NHP receptors on an immature lymphomatous murine pre-T-cell line. Through the use of several well-characterized monoclonal antibodies, the immunodominant epitope of the NHP peptide family expressed within the thymus was shown to be located in the cyclic part of OT shared by the ancestral peptide of the family, vasotocin. The intrathymic colocalization of ir-OT and ir-VP constitutes another significant difference, with a clear-cut separation between hypothalamic OT-ergic and VP-ergic neurons. These observations, together with the failure of classical molecular biological methods to demonstrate the intrathymic expression of known hypothalamic VP and OT genes, strongly support the existence of a hitherto unidentified gene coding for a member of the NHP superfamily. In the thymus, this gene would be expressed predominantly during fetal development, and would encode a "self" NHP-related peptide which could play a fundamental role in the induction of immune tolerance for the hypothalamic-NHP system. We propose a novel, highly effective model that transposes from the cellular level to the peptide repertoire the thymic function in both positive and negative selections of T-lymphocytes. (*Progress in NeuroEndocrinImmunology* **4**:135–142, 1991)

Address correspondence to: Dr. Vincent Geenen, Neuroendocrin-Immunology Unit B-23, University Hospital of Liège-Sart Tilman, B-4000 Liège, Belgium.

For several years our group has investigated the expression by various species of neurohypophysial (NHP)-related signals and receptors within the thymus. A thorough examination of the molecular aspects underlying our initial observations suggested

that the classical neuroendocrine model established for the hypothalamic-NHP axis could not entirely explain the cell-to-cell signaling within the thymic organ. A novel form of cellular interaction, cryptocrine communication, was proposed. This new model better described the physiological properties of the thymus, the primary lymphoid organ implicated in both T-lymphocyte differentiation and induction of the fundamental process of immune tolerance for the "self" molecular structure of an organism. Moreover, our experimental observations strongly support the existence of a hitherto unidentified gene, or some other molecular mechanism (such as a different splicing of vasopressin (VP) and/or oxytocin (OT) genes), leading to the intrathymic expression of another member of the NHP peptide family. This NHP-related peptide would be expressed in humans predominantly during fetal development, and would constitute an accessory activation signal in T-cell differentiation. Through its immunodominant epitope shared with OT-like members of the NHP superfamily, it would contribute to the recognition of "self" hypothalamic-NHP functions by the maturing T-cell system.

Thymic NHP-related Signals

On the basis of original observations by Ott and Scott (1), and in the line of previous works showing the peripheral expression of NHP-related peptides (2), the coexistence of immunoreactive (ir) OT and neurophysin (Np) was described in human thymic extracts. The tissue concentrations of these associated peptides were shown to be correlated inversely with the age of the patients from whom the thymuses were obtained (3). Markwick *et al.* (4) reported the presence of ir-VP in rat and murine thymus in concentrations modulated by glucocorticoid and mineralocorticoid hormonal environments. The coexistence within the same tissue of an Np-like protein associated in the structure of all NHP precursors strongly supported a local synthesis of OT/VP peptides. This conclusion was further strengthened by positive dot blot hybridizations of human thymic mRNAs with bovine OT and VP cDNA probes and by immunostaining of human thymic stromal cells with polyclonal antibodies (Abs) against OT, VP and Np (5). The epithelial nature of these reactive cells in the thymic parenchyme was demonstrated in two separate studies (6,7). Ir-NHP peptides were found in two cell subpopulations of the thymic epithelium (TE): the subcapsular cortex (SCC) and the medulla. On the basis of these immunocytochemical findings, we investigated the neuroendocrine nature of a specialized cell population derived from thymic SCC and outer cortex, the thymic nurse cells (TNC) (8). Usually isolated after enzymatic digestion and fractionated 1 × *g* sedimentation on albumin gradients, TNCs represent a particular microenvironment composed of very large epithelial cells that can enclose up to 200 actively dividing thymocytes in cytoplasmic caveoles (9). The *in vivo* existence of TNCs recently was attested by scanning electron microscopy in a study that showed "basket"-type epithelial structures in close contact with thymocytes (10). These structures closely resembled TNCs. We have demonstrated through immunocytochemistry that TNCs express in their epithelial part the phenotype of other components of the diffuse neuroendocrine system (A2B5, neuron-specific enolase), and contain ir-OT, -VP and -Np (11). The concept of cryptocrine intercellular communication recently was proposed to characterize this close cell-to-cell signaling in specialized microenvironments (*e.g.*, TNCs and testicular Sertoli cells) between a fixed stromal cell and migratory differentiating cells (12,13). According to this concept—and consistent with our own observations—NHP-related signals could mediate information between TNCs and TNC-engulfed immature T-cells. Interestingly, the expression of an OT gene recently was demonstrated in bovine Sertoli cells (14), a finding further supporting the application of the cryptocrine concept to NHP-related signal peptides within the testis and the thymus.

Using monoclonal antibodies (mAbs) against OT (15) and VP (16), a specific immunostaining of TE was observed in SCC and medullary cells, and colocalization with ir-IL-1 could be shown in the same cellular subsets (7). This observation suggests close interactions between peripheral NHP and IL-1 systems, the physiological meaning of which remains to be investigated further. More significantly, these studies revealed important differences between thymic NHP-related peptides

and the situation established within the hypothalamo-neurohypophysial axis. At this level, hypothalamic OT-ergic and VP-ergic neurons are well-separated cellular populations, and VP/OT co-localization has been found only in a minority of them (approximately 2%) (17). Moreover, the most specific OT mAb (O_{13})—which apparently has a corresponding epitope located in the tail part of the OT molecule—failed to stain any TEC, whereas a bright immunostaining of TEC was obtained with mAbs directed against an epitope located in the cyclic part of OT, which seems to be the immuno-dominant epitope representative of the NHP family. In addition, ultrastructural studies performed with the help of immunogold labeling techniques did not show classical neurosecretory granules, but instead revealed ir-OT and ir-Np in large clear vacuoles or in the cytosol of TEC (Geenen *et al.*, unpublished observations). Until now, we also failed to detect ir-NHP-related peptides in the supernatant of TEC cultures, which calls into question the classical scheme of neurosecretion in the case of TE. Interestingly, a novel type of secretory pathway recently was described for proteins that lack a hydrophobic signal sequence and that probably leave the cell through a distinct mechanism. Various tissue growth factors such as IL-1, basic and acidic fibroblast growth factors, platelet-derived growth factor, insulin-like growth factors (IGFs) and several thymosin-related peptides apparently use this pathway (18). A similar mechanism also is proposed for the translocation of peptide fragments into the endoplasmic reticulum for presentation at the cell surface by MHC molecules. Therefore, even if recent reports have confirmed the intrathymic expression of OT (19,20), there is some clear evidence that the thymus is the site of biosynthesis of peptide(s) closely related to, but distinct from, authentic hypothalamic OT or VP.

Further biochemical analyses are needed to clarify the true molecular identity of these peptides. In the NHP gene superfamily, vasotocin (VT) represents a potential candidate for several reasons. VT is a structural hybrid formed by the hexapeptidic cyclic moiety of OT and the tripeptide terminal tail chain of VP. The VT precursor gene is thought to be the ancestral gene from which VP and OT genes emerged by gene duplication around 100 million years ago. The presence of two genes coding for VT precursors (VT-1 and VT-2 types) has been demonstrated in teleost fishes (21), in accordance with the tetraploid hypothesis of their evolution. Preliminary evidence was further published supporting the existence of an additional earlier duplication of the VT-1 type genes. Although VT gene expression has not been reported in mammals and is still highly controversial, there is substantial evidence supporting the existence of the peptide in mammals. Ir-VT or bioactivity has been reported in fetal pituitary and fetal/adult pineal glands from various mammalian species (22,23); ir-VT has been extracted and HPLC-characterized in ovine fetal blood, urine and amniotic fluid (24); and predominance of ir-VT over ir-OT or ir-VP in ovine fetal thymic organs has been reported (25).

Confirmation of VT as the true thymic NHP-related peptide would provide an explanation for the discrepancy in the immunocytochemical studies described with OT mAbs. The polyclonal antiserum we raised against OT, and which was employed in our first report, also displays some incomplete cross-reactivity with VT (26). In addition, whereas peripheral OT gene expression has been fully demonstrated only in the ruminant corpus luteum (27)—where OT is synthesized and secreted according to the neuroendocrine model—ir-OT or ir-VP have been described in a variety of peripheral organs (for a complete review, see 2). This peripheral expression of NHP peptides has been described even in the Brattleboro rat, which is not able to transcribe correctly the hypothalamic VP gene because of an autosomal recessive deletion in the second exon of VP precursor gene (28). A recent study has provided additional evidence supporting the expression of a novel gene in neoplastic disease or, at least, the possibility of another molecular mechanism leading to a new NHP signal (29). In relation to the questions raised above about the secretion by TEC of NHP-related signals, the same investigators have demonstrated the intramembrane expression of the NHP-related molecule. This intriguing observation raises the possibility of adhesive properties of Np-like proteins, for which the only known carrier role does not fit well with their high degree of conservation throughout species evolution.

Thymic NHP-Peptide Receptors

Because VP has been reported to exert mitogenic properties on rat thymocytes (30) and OT could stimulate glucose oxidation by rat thymocytes (31), it was reasonable to postulate the expression of NHP peptide receptors by immature T-cells. Indeed, OT receptors were described in the rat thymic gland and on rat thymocytes by Elands and co-workers (32,33) through the use of binding experiments with the new iodinated OT antagonist, OTA ($d(CH_2)_5$-[$Tyr(Me)^2$,Thr^4, $Tyr(NH_2)^9$] ornithine vasotocin). To find a stable source for immune NHP peptide receptors, we have investigated the expression of such receptors on an immature murine pre-T-cell line (RL_{12}-NP) derived from X ray-induced thymic lymphoma in C57Bl/Ka mice (34). Specific [^{3}H]VP binding sites were observed in RL_{12}-NP cell suspensions, and displacement curves with various VP and OT analogues revealed that these receptors belong to the V_1-subtype (35). However, computer analysis (LIGAND) indicated their heterogeneity and, although specific binding of [^{3}H]OT could be displaced with synthetic OT and OT agonists, we failed to obtain specific binding of [^{125}I]OTA on RL_{12}-NP cells. These receptors were nevertheless able to transduce NHP signals according to the V_1/OT models described in other cell systems, as shown by the ability of different members of the NHP peptide family to induce breakdown of RL_{12}-NP membrane phosphoinositides and a time-dependent increase of cytoplasmic inositol-phosphates. An almost complete inhibition of this transductory capacity was observed with a specific V_1 antagonist (Peninsula, n° 8109) (36). These observations suggest, consistent with the cryptocrine signaling model, that functional NHP V_1-type receptors are expressed on immature T-lymphocytes. The ability of these receptors to transduce NHP signals implies a stimulation of membrane phosphoinositidase C, as is the case in other V_1/OT systems, but they appear biochemically to belong to another V_1-subtype yet to be determined. Evidence for a novel VP receptor of the V_1 subtype on murine T-lymphocytes has been presented by Torres and Johnson (37), and [^{125}I] OTA, despite its higher specificity for uterine OT-type receptors, also can recognize VT receptors expressed in bird CNS (38).

Physiology and Pathology of Thymic Interactions Between the NHP Family and the Immune System

The thymus has long been known to play a fundamental role in the complex process of T-cell differentiation and in the shaping of the whole T-cell repertoire. A fascinating and intense debate surrounds the molecular mechanisms underlying the dual role of the thymus in T-lymphocyte positive and negative selections, the latter leading to the induction of immune tolerance for the self molecular structure. At the cellular level, it is increasingly clear that TEC may control both tolerogenic influences (39,40) and the delivery of accessory signals during T-cell differentiation (Table 1). These signals may rise either from the shortly distant exchanges of soluble messengers between TEC and immature T-cells, or from direct cell-to-cell contacts mediated by adhesion molecules (41,42) (for a complete review, see 43). It seems rational in light of these findings to transpose consideration of the duality of thymic function in T-lymphocyte selections from the cellular level to the level of molecules detected within TEC. Although the precise identity of the NHP gene expressed within the thymus remains to be elucidated, effective cryptocrine signaling occurs within the thymus and is partially mediated through NHP-related signals and functional receptors. The previously described mitogenic and metabolic properties of NHP-related peptides agree with the known mediation of mitogenic signals through the hydrolysis of phosphoinositides by receptors coupled to phosphoinositidase C in the cell membrane. Moreover, in human pathology, a disturbance of this cryptocrine cell-to-cell signaling could affect either the NHP-related signals (leading to a paraneoplastic syndrome of water intoxication, which is commonly associated with the existence of thymomas or of thymic carcinomas) (44), or the NHP peptide receptors (leading to a potential implication in the development of T-cell lymphomas) (35,36). Therefore, it is attractive to propose an implication of paracrine/cryptocrine signaling in the process of T-cell positive selection.

Another implication of the intrathymic expression of NHP-related peptide(s) deserves further attention. We have shown that the immunodominant NHP epitope present in TEC was located in the cyclic part shared by OT and VT. Following

Table 1. Pathological and physiological implications of the interactions between the NHP family and the immune system. The "self" NHP epitope is located in the cyclic part shared by the OT molecule and the ancestral peptide of the family (VT).

	Positive selection (cryptocrine signaling)	**Negative selection (self NHP epitope presentation)**
Physiology	Accessory signal in T-cell differentiation/activation	Tolerance of reproductive functions (preservation of species)
Pathology	Third cause of paraneoplastic VP secretion (Schwartz-Bartter) = thymomas (**signal**)	Autoimmune hypothalamitis against VP-ergic neurons ("idiopathic" diabetes insipidus)
	Implication in the biology of T-cell lymphoma (oncogenesis?) (**receptor**)	Breakdown of tolerance by active immunization against VP
	Immunomodulation by OT/VP agonists and antagonists (**receptor**)	Frequence and titers of Abs against NHP peptides (VP > OT > VT)

the self peptide model (45), the presentation by MHC molecules of this 6-amino acid epitope representative of the NHP family (the self NHP peptide) could contribute to the induction of immune tolerance for the NHP functions. This tolerogenic effect would result from the clonal deletion of highly reactive T-cells harboring a randomly rearranged T-cell receptor offering the exact configuration for the MHC/self NHP peptide association. A strong tolerance of OT/VT molecules would result from the process, and because OT/VT are closely involved in separate levels of the reproductive functions, this phenomenon could be highly significant for the protection and the preservation of the species. Because the cyclic part of VP differs by one residue, lower protection would result. Indeed, some autoimmune processes against VP-ergic neurons (autoimmune hypothalamitis) have been described (46) and have been implicated in the etiopathogeny of idiopathic diabetes insipidus. Such autoimmune processes have never been described against central or peripheral OT-producing cells. The frequency and the titers of Abs directed against the different members of the NHP peptide superfamily (VP > OT > VT) also provide indirect support for this working model.

This model can be applied easily to other hormone or neural-related peptide families. The expression of the preprotachykinin-A (PPT-A) gene was demonstrated within the rat thymus (47). Interestingly, neurokinin A (NKA)—and not substance P (SP)—was in fact the peptide encoded by PPT-A gene which was expressed by TEC. The involvement of NKA in T-lymphocyte positive selection is strongly suggested by the mitogenic properties of NKA on thymocytes, whereas SP did not exert any significant mitogenic action on this cell type (48). Again, NKA shares a common immunodominant epitope with SP and NKB and therefore could represent the tachykinin (TK) family during the process of T-cell differentiation and shape the T-cell repertory so that any potential TK autoreactive T-cell would be energized or deleted. With regard to the insulin superfamily, IGFs were shown to be expressed within the thymus, both at the mRNA and protein levels (49). Given the high homology between the primary structures of insulin and IGFs, the presentation by MHC of immunodominant epitopes common in the insulin/IGF family within the thymus could contribute to the induction of immune tolerance for the pancreatic islet cell endocrine function. A molecular disturbance in this fine-tuned process would lead to the emergence of autoreactive T-cells against epitopes representative of the insulin superfamily, and this could intervene in the emergence of autoimmune insulin-dependent diabetes. This tolerogenic effect postulated for thymic IGFs does not exclude their potential implication in T-cell positive selection, which is strongly supported by the recent demonstration of IGF-mediated signaling in the development of T-cell lymphomas (50).

Integration in the Cellular and Biochemical Evolution of Communication

As shown in Figure 1, the evolution of cell-to-cell signaling has progressed from a primitive stage

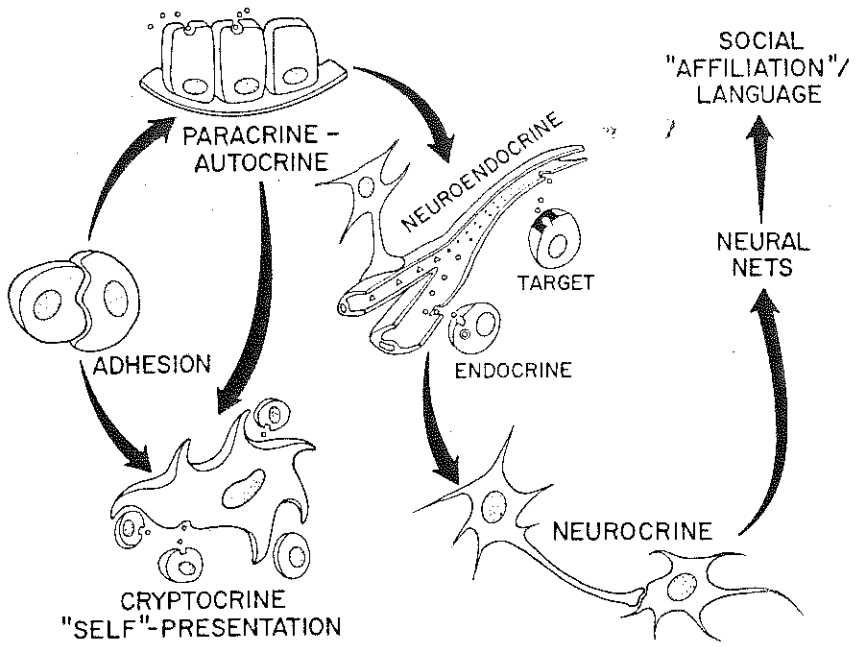

Figure 1. Evolution of intercellular signaling.

of cell-cell adhesion after the first division of the conceptus until the most complex neural networks which have permitted the establishment of social links between the individuals, as well as the elaboration of a recognition code between them under the form of language. This evolutionary aspect of intercellular communication appears now to have its counterpart in the organization of the human genome (Table 2). In recent years, the progress of molecular biology has led to the identification of new members of hormonal gene families. These factors were not "hormones" transported by bloodstream, but yet played a fundamental role in organogenesis and in embryological development by paracrine/autocrine signaling. The contribution of these factors to the oncogenetic processes is well documented, whereas their overexpression may lead to their secretion in the bloodstream and to the emergence of clinical paraneoplastic syndromes resulting from their cross-reactive affinity for peripheral hormone receptors. As presented and discussed in this review, the cryptocrine stage evidenced at the thymic level introduces an obligatory step in ontogeny, implying the recognition of the "self" molecular identity of the cell by the T-cell immune system along its differentiation. Further investigation of the self gene repertoire expressed within the thymus should be a fruitful area for research, and the definition of the self molecular identity of the cell should contribute to a better understanding of endocrine-specific T-cell-mediated autoimmune disorders.

Table 2. From classical endocrinology to intercellular signaling: conceptualization applied to the neurohypophysial peptide system by analogy with other recently described endocrine gene molecular evolutions.

Physiological Functions	Hormones	Autocrine/Paracrine Factors	Paraneoplasic Syndromes
Glucose metabolism	Insulin	Insulin-like growth factors	Hypoglycemia (51)
Calcium metabolism	Parathormone (PTH) Calcitonin	PTH-related peptide Calcitonin gene-related peptide (53)	Hypercalcemia (52) ?
Water metabolism	VP	VT?; another VP/OT-like peptide?	Water intoxication Hyponatremia
Reproduction/Parturition/ Lactation	OT	VT?; another VP/OT-like peptide?	Other?

ACKNOWLEDGMENTS: This work is supported by the Fund for Scientific Medical Research of Belgium (Grant 3.4562.90), by the Special Research Fund of the University of Liège, by UCB-Bioproducts (Braine-l'Alleud, Belgium), by the Ministere de la Region Wallonne, by a CGRI-INSERM cooperation agreement, by the Association Française contre les Myopathies (AFM), and by the European Science Foundation (Neuroimmunomodulation Network). V. Geenen is a Research Associate of the National Fund for Scientific Research (Belgium); F. Robert is Chargé de Recherches 1ère Classe INSERM (France). Our gratitude is extended to Dr. Pierre Bonnet for Figure 1.

REFERENCES

1. Ott I, Scott JC 1910 The galactogogue action of the thymus and corpus luteum. Proc Soc Exp Biol 8:49
2. Clements JA, Funder JW 1986 Arginine vasopressin (AVP) and AVP-like immunoreactivity in peripheral tissues. Endocr Rev 7:449
3. Geenen V, Legros JJ, Franchimont P, Baudrihaye M, Defresne MP, Boniver J 1986 The neuroendocrine thymus: coexistence of oxytocin and neurophysin in the human thymus. Science 232:508
4. Markwick AJ, Lolait SJ, Funder JW 1986 Immunoreactive arginine vasopressin in the rat thymus. Endocrinology 119:1060
5. Geenen V, Legros JJ, Franchimont P, Defresne MP, Boniver J, Ivell R, Richter D 1987 The thymus as a neuroendocrine organ. Synthesis of vasopressin and oxytocin in human thymic epithelium. Ann NY Acad Sci 496:56
6. Moll UM, Lane BL, Robert F, Geenen V, Legros JJ 1988 The neuroendocrine thymus. Abundant occurrence of oxytocin-, vasopressin-, and neurophysin-like peptides in epithelial cells. Histochemistry 89:385
7. Robert F, Geenen V, Schoenen J, Burgeon E, De Groote D, Defresne MP, Legros JJ, Franchimont P 1991 Colocalization of immunoreactive oxytocin, vasopressin and interleukin-1 in human thymic epithelial neuroendocrine cells. Brain Behav Immun 5:102
8. Wekerle H, Ketelsen UP 1980 Thymic nurse cells—Ia bearing epithelium involved in T lymphocyte differentiation? Nature 183:402
9. Wekerle H, Ketelsen UP, Ernst M 1980 Thymic nurse cells lymphoepithelial cell complexes in murine thymuses: morphological and serological characterization. J Exp Med 151:925
10. Van Ewijk W 1988 Cell surface topography of thymic microenvironments. Lab Invest 59:579
11. Geenen V, Defresne MP, Robert F, Legros JJ, Franchimont P, Boniver J 1988 Immunocytochemical evidence that thymic nurse cells are neuroendocrine cells. Neuroendocrinology 47:365
12. Funder JW 1990 Paracrine, cryptocrine, acrocrine. Mol Cell Endocrinol 70:C21
13. Geenen V, Robert F, Martens H, Benhida A, De Giovanni G, Defresne MP, Boniver J, Legros JJ, Martial J, Franchimont P 1991 Biosynthesis and paracrine/cryptocrine actions of "self" neurohypophysial-related peptides in the thymus. Mol Cell Endocrinol 76:C27
14. Ang HL, Ungefroren H, De Bree F, Foo NC, Carter D, Burbach JPH, Ivell R, Murphy D 1991 Testicular oxytocin gene expression in seminiferous tubules of cattle and transgenic mice. Endocrinology 128:2110
15. Robert F, Leon-Henri BP, Chapleur-Chateau MM, Girr MN, Burlet AJ 1985 Comparison of three immunoassays in the screening and characterization of monoclonal antibodies against arginine-vasopressin. J Neuroimmunol 9:205
16. Burgeon E, Chapleur M, Schoenen J, Remichius D, Legros JJ, Geenen V, Robert F 1991 Monoclonal antibodies to oxytocin: production and characterization. J Neuroimmunol 31:235
17. Kiyama H, Emson PC 1990 Evidence for the co-expression of oxytocin and vasopressin messenger ribonucleic acids in magnocellular neurosecretory cells: simultaneous demonstration of two neurophysin messenger ribonucleic acids by hybridization histochemistry. J Neuroendocrinol 2:257
18. Muesch A, Hartmann E, Rohde K, Rubartelli A, Sitia R, Rapoport TA 1990 A novel class of secretory proteins. Trends Biochem Sci 15:86
19. Argiolas A, Melis MR, Stancampiano R, Mauri A, Gessa GL 1990 Hypothalamic modulation of immunoreactive oxytocin in the rat thymus. Peptides 11:539
20. Argiolas A, Gessa GL, Melis MR, Stancampiano R, Vaccari A 1990 Effects of neonatal and adult thyroid dysfunction on thymic oxytocin. Neuroendocrinology 52:556
21. Morley SD, Schönrock C, Heierhorst J, Figueroa J, Lederis K, Richter D 1990 Vasotocin genes in the teleost fish *Catostomus commersoni*: gene structure, exon-intron boundary, and hormone precursor organization. Biochemistry 29:2506
22. Pavel S 1975 Vasotocin biosynthesis by neurohypophysial cells from human fetuses. Evidence for its ependymal origin. Neuroendocrinology 19:150
23. Pavel S, Goldstein R, Calb M 1975 Vasotocin content of the pineal gland of foetal, newborn and adult male rats. J Endocrinol 66:283
24. Ervin MG, Leake RD, Ross MG, Calvario GC, Fischer DA 1985 Arginine vasotocin in ovine fetal blood, urine, and amniotic fluid. J Clin Invest 75:1696
25. Ervin MG, Polk DH, Humme JA, Ross MG, Leake RD, Fisher DA 1988 Immunoreactive vasotocin, vasopressin and oxytocin in ovine fetal and neonatal thymus glands. Clin Res 36:217A
26. Geenen V, Legros JJ, Hazée-Hagelstein MT, Louis-Kohn F, Lecomte-Yerna MJ, Demoulin A, Franchimont P 1985

Release of immunoreactive oxytocin and neurophysin I by cultured bovine luteinizing granulosa cells. Acta Endocrinol 110:263
27. Fehm S, Ivell R, Koll R, Schams D, Fields M, Richter D 1987 Expression of the oxytocin gene in the large luteal cells of the bovine corpus luteum. FEBS Lett 210:45
28. Ivell R, Burbach JPH, Van Leeuwen FW 1990 The molecular biology of the Brattleboro rat. Front Neuroendocrinol 11:313
29. Rosenbaum LC, Neuwelt EA, Van Tol HHM, Peng Loh Y, Verbalis JG, Hellstrom I, Hellström KE, Nilaver G 1990 Expression of neurophysin-related precursor in cell membranes of a small-cell lung carcinoma. Proc Natl Acad Sci USA 87:9928
30. Whitfield JF, MacManus JP, Ginan DJ 1970 The possible mediation by cyclic AMP of the stimulation of thymocyte proliferation by vasopressin and the inhibition of this mitogenic action by thyrocalcitonin. J Cell Physiol 76:75
31. Goren HJ, Okabe T, Lederis K, Hollenberg MD 1984 Oxytocin stimulates glucose oxidation in rat thymocytes. Proc West Pharmacol Soc 27:461
32. Elands J, Resink A, De Kloet ER 1988 Oxytocin receptors in the rat thymic gland. Eur J Pharmacol 151:345
33. Elands J, Resink A, De Kloet ER 1990 Neurohypophysial hormone receptors in the rat thymus, spleen, and lymphocytes. Endocrinology 126:2703
34. Lieberman M, Declève A, Ricciardi-Castagnoli P, Boniver J, Finn OJ, Kaplan HS 1971 Establishment, characterization and virus expression of cell lines derived from radiation and virus-induced lymphomas of C57 BL/Ka mice. Int J Cancer 24:168
35. Geenen V, Robert F, Fatemi M, Defresne MP, Boniver J, Legros JJ, Franchimont P 1988 Vasopressin and oxytocin: thymic signals and receptors in T-cell ontogeny. In Yoshida S, Share L (eds) Recent Progress in Posterior Pituitary Hormones. Elsevier, New York, p 303
36. Geenen V, Martens H, Robert F, Defresne MP, Boniver J, Legros JJ, Franchimont P Implication of thymic neuropeptide signals and receptors in the biology of T-cell lymphomas. Endocrine Society, 73rd Annual Meeting, Washington, DC, 1991, Abstract 1016
37. Torres BA, Johnson HM 1988 Arginine vasopressin (AVP) replacement of helper cell requirement in IFN-γ production. Evidence for a novel AVP receptor on mouse lymphocytes. J Immunol 140:2179
38. Voorhuis TAM, Elands JPM, De Kloet ER 1990 Vasotocin target sites in the capsular region surrounding the nucleus robustus archistrialis of the canary brain. J Neuroendocrinol 2:653
39. Marrack P, McCormack J, Kappler J 1989 Presentation of antigen, foreign major histocompatibility complex proteins and self by thymus cortical epithelium. Nature 338:503
40. Webb SR, Sprent J 1990 Tolerogenicity of thymic epithelium. Eur J Immunol 20:2525
41. Savino W, Dardenne M, Papiernik M, Bach JF 1982 Thymic hormone-containing cells. Characterization and localization of serum thymic factor in young mouse thymus studied by monoclonal antibodies. J Exp Med 156:628
42. Brunet JF, Hirsch MR, Naquet P, Uberla K, Lipinski M, Goridis C 1989 Developmentally regulated expression of the neural cell adhesion molecule by mouse thymocytes. Eur J Immunol 19:837
43. Boyd RL, Hugo P 1991 Towards an integrated view of thymopoiesis. Immunol Today 12:71
44. Rosai J, Levine GD, Weber WR, Higa E 1976 Carcinoid tumors and oat cell carcinomas of the thymus. Pathol Anat 11:201
45. Kourilsky P, Chaouat G, Rabourdin-Combe C, Claverie JM 1987 Working principles in the immune system implied by the "peptidic self" model. Proc Natl Acad Sci USA 84:3400
46. Scherbaum WA, Bottazzo GF, Czernichow P, Wass JAH, Doniach D 1985 Role of autoimmunity in central diabetes insipidus. Front Horm Res 13:232
47. Ericsson A, Geenen V, Robert F, Legros JJ, Vrindts-Gevaert Y, Franchimont P, Brené S, Persson H 1990 Expression of preprotachykinin-A and neuropeptide Y messenger RNA in the thymus. Mol Endocrinol 4:1211
48. Söder O, Hellström P 1989 The tachykinins neurokinin A and physaelaemin stimulate murine thymocyte proliferation. Int Arch Appl Immunol 90:91
49. Han VKM, D'Ercole AJ, Lund PK 1987 Cellular localization of somatomedin (insulin-like growth factor) messenger RNA in the human fetus. Science 286:193
50. Gjerset RA, Yeargin J, Volkman SK, Vila V, Arya J, Haas M 1990 Insulin-like growth factor-I supports proliferation of autocrine thymic lymphoma cells with a pre-T cell phenotype. J Immunol 145:3497
51. Daughaday WH, Rotwein P 1989 Insulin-like growth factors I and II. Peptide, messenger ribonucleic acids and gene structures, serum and tissue concentrations. Endocr Rev 10:68
52. Broadus AE, Mangin M, Ikeda K, Insogna KL, Weir EC, Burtis WJ, Stewart AF 1988 Humoral hypercalcemia of cancer. Identification of a novel parathyroid hormone-like peptide. N Engl J Med 319:556
53. Rosenfeld MG, Mermod JJ, Amara SG, Swanson LW, Sawchenko PE, Rivier J, Vale WW, Evans RM 1983 Production of a novel neuropeptide encoded by the calcitonin gene via tissue-specific RNA processing. Nature 304:129