Neuroendocrinology

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Concepts revised or recentered: α -fetoprotein preventing defeminization

Alpha-fetoprotein protects the developing female mouse brain from masculinization and defeminization by estrogens

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Background: Sex differences in the capacity of estrogens to exert a positive feedback on the gonadotropic axis depend on the perinatal actions of gonadal steroids. Invalidated mice for α -fetoprotein ($Afp^{-/-}$) are infertile by a possible hypothalamic defect which could be rescued by blocking estrogen production during prenatal development. In this study, the authors used $Afp^{-/-}$ females to study mechanisms by which prenatal estrogens affect the sexual differentiation of the GnRH system. They tested the hypothesis that kisspeptin could be involved in this process.

Methods: The authors first studied the capacity of $Afp^{-/-}$ females to show a steroid-induced GnRH and LH surges. $Afp^{-/-}$ females did not show a preovulatory LH surge in response to treatment with estrogen plus progesterone as $Afp^{+/+}$ and $Afp^{-/-}$ male mice. This absence of LH surge in $Afp^{-/-}$ females is associated with the absence of significant FOS activation in GnRH neurons suggesting a possible defect upstream of the GnRH neurons. The kisspeptin/GPR54 system was recently described as a key regulator of the GnRH secretion with a clear sexual dimorphism of the kisspeptin immunoreactivity in the periventricular hypothalamic nucleus (Pe). $Afp^{-/-}$ females showed male-typical kisspeptin immunoreactivity in the Pe with an absence of significant FOS double labeling in kisspeptin neurons (2.6%) after estrogen plus progesterone treatment whereas 41.6% of kisspeptin neurons were double labeled with FOS in $Afp^{+/+}$ females.

Conclusion(s): The sex difference in the ability to show preovulatory LH surge has disappeared in $Afp^{-/-}$ mice. This result suggests that the capacity to induce LH surge depends on the prenatal action of estrogens in the male hypothalamus. The authors propose that AFP protects female mice against the defeminizing effect of estrogens during prenatal development.

The sexual dimorphism to elicit a LH surge in adult mice depends on the hypothalamic regulation within the Pe. Kisspeptin is the most important GnRH secretagogue. It is expressed within the arcuate nucleus of the hypothalamus where it is negatively regulated by estrogens, whereas in the Pe region of females, estrogens exert a positive regulation on kisspeptin expression. In male mice, kisspeptin expression within the Pe is low and poorly regulated by estrogens. Kisspeptin thus became rapidly an evident candidate to explain the occurrence of the estrogen-induced LH surge in females. The physiological function of AFP during embryonic development remains largely unidentified. The observation that AFP is able to bind estrogens with high affinity in rats and mice has led to the suggestion that AFP may have a role in brain sexual differentiation. AFP protects the developing female mouse brain from masculinization and defeminization by estrogens. This paradoxical effect of estrogens initially described by using an aromatase inhibitor is confirmed in this study by studying the expression of a positively steroid-regulated gene that is involved in the LH surge. AFP has the capacity to bind estrogens. It is thus tempting to propose that AFP regulates prenatal levels of estrogens within the hypothalamus. Further studies will characterize estrogens intracellular pathways involved in defeminization from those involved in the positive feedback in adult female mice. Other mechanisms may also be involved as the GnRH1 mRNA hypothalamic level is decreased in $Afp^{-/-}$ whereas kisspeptin does not regulate GnRH gene hypothalamic expression.

An androgen-dependent sexual dimorphism visible at puberty in the rat hypothalamus

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Background: The role of estradiol in the masculinization of the perinatal brain is now well documented. Estradiol induces irreversible quantitative sex differences in cell number and expression of chemical phenotype. However, some studies have reported the role of non-aromatizable androgens. In this study, the authors have focused their analysis on postnatal development and masculinization by androgens by using the neurokinin B (NKB)-containing system of the arcuate nucleus/median eminence (ARC/ME) complex of the hypothalamus as the marker.

Methods: The authors exclusively used immunohistochemistry to explore the NKB system in the hypothalamus. In adult rats they found a qualitative sexual dimorphism with ventral projection of NKB neurons to neuropils in females and capillary vessels in males. There was no sex difference in the number of NKB-immunoreactive perikarya or capillary vessels in the ARC/ME. At birth, the NKB system was immature in both sexes, and while it emerged progressively until puberty in females, it did not develop before puberty in males as it appeared at day 40. In orchidectomized males performed at day 30, NKB neurons did not appear at day 40, while normal labeling was rescued by testosterone or dihydrotestosterone (DHT) treatment. In these prepubertal orchidectomized males, the distribution of NKB-immunoreactive axons was feminized by estradiol alone. In adult females, the distribution of NKB-immunoreactive axons was feminine 30 days after ovariectomy and it was masculinized after chronic treatment with DHT.

Conclusion(s): The sexual differentiation of NKB neurons proceeds well beyond the perinatal period and includes the epigenetic action of non-aromatizable androgens. This study documents that the sexual differentiation of the brain is a continuous and partially reversible phenomena extending well beyond puberty.

Most of the sexual brain differences observed under the influence of gonadal steroids were explained by the action of estradiol. This study shows that masculinization or defeminization of some hypothalamic functions or markers could also be induced by non-aromatizable androgens. The most impressive result of this work is the strong sexual difference in the postnatal timing of NKB-containing neuron (kisspeptin neurons) maturation in the arcuate nucleus. NKB is a 10-amino-acid peptide belonging to the family of tachykinin-related peptides that also comprises substance P and neurokinin A. In the hypothalamus it plays the role of an excitatory neurotransmitter. NKB gene expression is regulated by estrogens and NKB has been involved in the regulation of GnRH secretion. The infundibulum, which is located outside the blood-brain barrier, includes part of the arcuate nucleus (ARC) and the median eminence (ME), where hypothalamic neuropeptides are released into the hypothalamic-pituitary portal system to reach anterior pituitary cells. Neurons which compose these structures are thus sensitive to humoral substances, and they are involved in positive as well as negative feedback from the periphery to the brain. This strong sexual difference in the maturation of neurons located within the ARC/ME complex may have some physiological relevance in the capacity of the hypothalamus to regulate hormonal homeostasis. Recently, kisspeptin neurons were shown to express neurokinin B, which suggests a possible sexual dimorphism of the postnatal maturation of kisspeptin neurons located within the ARC of the hypothalamus.

Hypothalamic mTOR signaling regulates food intake

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Background: Regulation of food intake and plasma fuel levels is mediated via a subset of neurons in the central nervous system. The Mammalian Target of Rapamycin protein (mTOR) is a serine-threonine kinase which is involved in cell-cycle progression and regulation of protein synthesis by nutrient. The aim of this study was to test the hypothesis that mTOR might integrate cellular fuel status with hormonal-related signaling in a specific population of hypothalamic neurons.

Methods and Results: The authors first located phosphorylated mTOR and its target, S6 kinase 1 (S6K1), in the same cells of the paraventricular (PVN) and arcuate nuclei (ARC) of rat hypothalamus. mTOR signaling colocalizes with 90% of neuropeptide Y and 45% proopiomelanocortin neurons in the arcuate nucleus. A decrease of S6K1 phosphorylation and its substrate was observed in fasted rats for 48 h whereas central administration of L-leucine (a potent stimulator of mTOR activity) in 24-hour fasted rats induced a net decrease of food intake and body weight. This anorexia was associated with an increase of mTOR signaling and a decrease of NPY gene expression in the ARC. Intracerebroventricular administration of leptin increased phosphorylation of S6K1 and S6 in the ARC. This effect on mTOR activity and the leptin's anorectic effect were blunted by rapamycin, which is a known inhibitor of mTOR activity.

Conclusion(s): mTOR is a cellular fuel sensor whose hypothalamic activity is directly tied to the regulation of energy intake.

A recently emerging concept proposes that specific neuronal populations integrate fuel availability signals such as glucose and fatty acids with hormonal signals, such as leptin. However, signaling pathways involved in this regulation were poorly understood. This study adds a new component in this CNS sensing mechanism. It shows that the CNS senses a protein module: the amino acid L-leucine. It was known that mTOR activity is critical for regulating protein synthesis in peripheral cells and that it is involved in the anabolic process. This intracellular pathway was also known to be involved in regulation of cellular growth. Now, mTOR also participates in the regulation of food intake. In the mechanism proposed in this paper, mTOR regulation by L-leucine must be considered as a fuel sensor rather than as an amino acid sensor. The modulation of mTOR signaling pathways by leptin is interesting as it suggests that leptin resistance in obesity may result from an incapacity of mTOR intracellular pathways. Altogether, these results reveal a molecular link between amino acids as fuel sensor and endocrine signals.

New mechanism: role of the hypothalamus in regulating glucose homeostasis

Glucose sensing by POMC neurons regulates glucose homeostasis and is impaired in obesity

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Background: Pro-opiomelanocortin (POMC) neurons in the arcuate nucleus of the hypothalamus have been shown to be excited by glucose. It has been predicted that the excitation mechanism involved ATP-induced closure of the potassium (K_{ATP}) channel. To evaluate the contribution of this mechanism to disease states such as type 2 diabetes, the authors created a transgenic mice with defective glucose sensing specifically in POMC neurons. They then evaluated glucose sensing of POMC neurons in obese mice to see whether obesity is associated with impaired glucose sensing in POMC neurons.

Methods: A transgenic mouse expressing a mutant form of the K_{ATP} channel subunit Kir6.2 under the control of mouse POMC promoter was generated. This genetic manipulation resulted in an almost entire loss of POMC neuron excitation by glucose and it impaired the whole-body response to an intraperitoneal load of glucose (1 g/kg b.w.). Analysis of the glucose-induced MSH secretion from hypothalamic slices and electrophysiological recording showed a similar loss of glucose sensing by POMC neurons in obese mice on a high-fat diet. Hypothalamic expression of UPC2, a mitochondrial protein involved in the glucose sensing of β -pancreatic cells, is up-regulated in obese mice. Deletion of hypothalamic UPC2 prevents obesity-induced loss of glucose sensing and pharmacological inhibition of UPC2 rescued loss of glucose sensing.

Conclusion(s): Obesity-induced loss of glucose sensing in glucose-excited neurons is mediated by UPC2. This defect might have a pathogenic role in the development of type 2 diabetes.

The first evidence that CNS is involved in glycemia control was provided by Claude Bernard (1813–1878). Numerous works have characterized glucose-excited or glucose-inhibited neurons in different hypothalamic nuclei. These neurons have a critical role in regulating glucose homeostasis through secretion of pancreatic hormones, food intake, and regulation of liver glucose production. POMC neurons in the arcuate nucleus of the hypothalamus are excited by glucose; the mechanism of excitation was predicted to involve ATP-induced closure of K_{ATP} channels in the plasma membrane. This study provides evidence that glucose sensing by hypothalamic POMC neurons has an important role in controlling systemic glucose homeostasis. It also provides evidence that a UPC2 hypothalamic increase due to high-fat diet and obesity may lead to similar loss of glucose sensing in POMC neurons and β -pancreatic cells. Glucose sensing in pancreatic β cells is lost during the development of obesity-induced type 2 diabetes. This work strengthened the potential role of UPC2 in type 2 diabetes. The exact role of insulin in this hypothalamic regulation needs to be investigated.

New mechanisms: in vivo evidence of the fundamental role of kisspeptin in reproduction

Hypogonadotropic hypogonadism in mice lacking a functional Kiss1 gene

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Kiss1^{-/-} mice exhibit more variable hypogonadism than Gpr54^{-/-} mice

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Background: The G-protein-coupled receptor 54 is central to acquisition of reproductive competency in mammals. Kisspeptins which are encoded by Kiss1 gene were characterized as GPR54 ligands by a pharmacological in vitro approach. Administration of kisspeptins stimulates the GnRH release by the hypothalamus in several species and therefore LH and FSH plasma levels. The aim of these studies was to confirm that kisspeptins are the authentic agonists of GPR54 in vivo and to determine whether these ligands have other physiological functions independent of GPR54 stimulation.

Methods: *Article 1:* Kiss1 gene was invalidated by homologous recombination within the two coding exons. Kiss1 null mice (Kiss1^{-/-} Ca, Ca for Cambridge) are viable and healthy but fail to undergo sexual maturation. Mutant female mice do not progress through the estrous cycle, have thread-like uteri and small ovaries. Mutant males have small testes and spermatogenesis arrests mainly at the early haploid stage. Both sexes have low circulating gonadotropin and sex steroid levels. Pituitary responds to

GnRH with a normal increase of LH and FSH levels. Peripheral kisspeptin administration increases plasma LH concentration. *Article 2*: In this paper, the authors have compared phenotypes caused by GPR54 and Kiss1 invalidation. The strategy for disrupting the Kiss1 gene was to replace exon 1 with the neomycin/G418 cassette whereas they replaced exon 2 of GPR54 gene by the same cassette. Both knockout mice were viable. The majority of Kiss1^{-/-} (Kiss1^{-/-}_Bo) and GPR54^{-/-} (GPR54^{-/-}_Bo) male mice lack preputial separation, and have smaller testes compared to control. GPR54^{-/-} female mice have smaller ovaries and uteri than wild-type mice. In contrast, Kiss1^{-/-}_Bo female mice demonstrate two distinct phenotypes: half have markedly reduced gonadal weights, whereas half exhibit persistent vaginal cornification and have gonadal weight comparable with those of wild-type females. FSH level is significantly lower in knockout mice compared to wild-type. Hormonal analyses of both knockout mice were identical except that GPR54^{-/-} did not respond to GnRH stimulation.

Conclusion(s): The phenotype due to Kiss1 invalidation results in gonadotropic deficiency although the phenotype appears to be less severe when compared to GPR54-invalidated mice. Kiss1 does not play a vital role in any physiological processes other than activation of the hypothalamic-pituitary-gonadal axis. Variable phenotypes may be observed in Kiss1^{-/-} mice.

GPR54 inactivation was first described in humans, with a phenotype of isolated gonadotropin deficiency without anosmia, identical to the phenotype described for GnRH receptor inactivation. Most human cases published to date show partial gonadotropin deficiency with a persistent response to GnRH stimulation. Complete gonadotropin deficiency with blunted pituitary response to GnRH stimulation has been observed in only a few cases. This variable pituitary response to GnRH stimulation is not correlated to the functional defect of the receptor, as variable gonadotropin deficiency may be observed in the same family. The fact that kisspeptin inactivation results in gonadotropic deficiency is consistent with the GPR54/kisspeptin receptor-ligand pair being necessary and required for progress through puberty and the acquisition of adult reproductive capabilities. *Article 2* reports that Kiss1 invalidation results in a more modest phenotype than GPR54 invalidation, whereas *Article 1* concluded that both have identical phenotypes. The reasons for these differences are not clear. Both groups used the same mice strains with different strategies to invalidate Kiss1. In *Article 1*, exons 1 and 2 have been deleted whereas in *Article 2*, the deletion was restricted to exon 1. An alternative initiation site of the translation is thus possible in Kiss1^{-/-}_Bo mice. The phenotype of the new mice line (reported in *Article 2*) invalidated for GPR54 was unexpected. The incapacity of GnRH to stimulate LH release by the pituitary is a new finding. Up to now, it was claimed that kisspeptins act at the hypothalamus level. This result is an additional argument supporting that kisspeptins also regulate the gonadotropic axis at the pituitary level.

New genes involved in diseases: prokineticin 2 – a novel actor of the gonadotropic axis development

Loss-of-function mutation in the prokineticin 2 gene causes Kallmann syndrome and normosmic idiopathic hypogonadotropic hypogonadism

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Background: Isolated gonadotropin-releasing hormone (GnRH) deficiency in the human presents either as normosmic hypogonadotropic hypogonadism (nHH) or with anosmia (Kallmann syndrome). Loss-of-function mutations have been described in 6 genes which encode for protein involved in the development of the GnRH neurons or in functional regulation of the hypothalamopituitary unit. In this paper, the authors have tested the hypothesis that mutations of ProK2 initially described in Kallmann syndrome may also cause nHH.

Methods: 50 nIHH and 50 KS probands were examined for mutations in the ProK2 gene. A homozygous single-pair deletion in exon 2 was identified in one proband with KS, in his brother with KS and in his sister with IHH and normal sense of smell. One heterozygous brother was asymptomatic and both parents had normal reproductive histories. The mutation induced a frameshift of the coding sequence and the synthesis of a truncated ProK2 protein of 27 amino acids rather than 81 in mature form that lacks bioactivity. By analogy with this phenotype, quantification of GnRH neurons by immunohistochemistry in ProK2-invalidated mice showed a dramatic decrease of GnRH labeling in the median eminence and in the preoptic area. The GnRH neurons' migration was arrested in forebrain after crossing the cribiform plate in ProK2^{-/-} mice.

Conclusion(s): The phenotype due to inactivation mutations of ProK2 is highly variable. These mutations may be observed in patients with isolated gonadotropic deficiency and a normal sense of smell.

Four genes (KAL1, FGFR1, ProK2 and ProKR2) have now been described in Kallmann syndrome (KS). They encode for proteins involved in the olfactory bulb development. The abnormal migration of the GnRH neurons thus results from the developmental defect of the olfactory tract. Most of the patients described to date had anosmia or hyposmia associated with a partial or complete olfactory bulb agenesis. In very few cases of KS due to FGFR1 mutations, the sense of smell is normal which indicates that FGFR1 has its own effect on GnRH neurons migration. The fact that reversible phenotype was observed in few patients harboring FGFR1 mutations indicates that FGFR1 pathways may also be involved in the normal maturation of the gonadotropic axis. Mutations of ProK2 and ProKR2 were initially described in patients with dominant transmission of KS. The description of ProK2 mutations in patients with a normal sense of smell confirms that olfactory bulb development depends on several genes which can compensate their function with each other. As previously reported for FGFR1 mutations, it also suggests a possible direct effect of ProK2 on GnRH neurons' migration and maturation. ProK2 and ProKR2 are expressed within the suprachiasmatic nucleus and ProK2 serves as a chemoattractant for neuronal progenitor. A similar attractant effect on GnRH neurons is thus an interesting hypothesis to explain how isolated gonadotropic deficiency can be associated with normal olfactory bulb development in a patient with mutation of ProK2. Finally, this report highlights that oligogenic models of transmission must be considered in isolated gonadotropic deficiency.

Concepts revised or recentered: the high plasticity of the GnRH system

Gonadotropin-releasing hormone neuron requirements for puberty, ovulation, and fertility

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Background: GnRH neurons are the critical output cells of the neuronal network controlling fertility in mammalian species. The level of functional redundancy within the GnRH neuron population is unknown. This group recently described a transgenic mouse line which exhibits a marked allele-dependent reduction in GnRH neuron number within their brain. The aim of this study was to precise the GnRH neuron requirement for normal reproduction.

Methods: In a program to generate GnRH promoter transgenic mice, this group generated a mouse line (GnR23) in which the transgene integration resulted in a 26-kDa deletion of chromosome 5 at 67 kb 3' to Epha5. This integration induced a profound up-regulation of Epha5 mRNA and protein expression in the developing mouse brain. Migration of GnRH neurons was arrested in the nose in GnR23. Wild-type mice have approximately 600 GnRH neurons compared with approximately 200 (34%) and 70 (12%) GnRH neurons in GnR23^{+/-} and GnR23^{-/-} mice. Male GnR23^{-/-} exhibited normal fertility. In contrast, female GnR23^{-/-} mice were subfertile, failing to produce normal litters, did not have estrous cycles and did not ovulate. GnR23^{-/-} mice are unable to generate a LH surge, whereas the first cycle at puberty appeared normal.

Conclusion(s): These results indicate that between 12 and 34% of the GnRH neuron population is required for cyclical control in adult female mice, suggesting that substantial redundancy exists within the GnRH neurons.

GnRH neurons exist as a scattered population within the hypothalamus. Several results have suggested that the number of GnRH neurons required for a normal reproductive function is quite low. This was demonstrated when normal fertility was restored by seminal grafting in the mutant hypogonadal mouse which exhibits a defective GnRH synthesis. Kallmann syndrome (KS) results from a defect of GnRH migration, and thus, the gonadotropin deficiency is explained by the low number of GnRH neurons within the hypothalamus. In fact, the dominant form of KS phenotype may be restricted to anosmia and olfactory bulb agenesis. We can suspect that the number of GnRH neurons migrating to the hypothalamus is low but sufficient for normal reproductive function.

The results reported in this paper confirmed that GnRH secretion has to reach a threshold which depends on the number of hypothalamic GnRH neurons. They also suggest that GnRH secretagogues involved in GnRH release increase in this context the low number of GnRH neurons. The expression level of kisspeptins increases at puberty and it is modulated by sexual steroids. This paper suggests that a short paracrine loop between GnRH and kisspeptin neurons might be an additional pathway to finely regulate the amount of hypothalamic GnRH release. This paper definitively confirms the high plasticity of the GnRH system.

The observation that female mice need more GnRH neurons to be fertile than males is interesting. In humans, girls are more prone to have advanced puberty than boys, the latter are more prone for delayed puberty than girls. Therefore, this sexual dimorphism does not seem to be due to the amount of GnRH secretion, but probably results from an additional signal which has to be characterized.

Food for thought: androgens are directly involved in circadian behavior

A role for androgens in regulating circadian behavior and the suprachiasmatic nucleus

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Background: The suprachiasmatic nucleus (SCN) of the hypothalamus is the locus of a master circadian clock controlling behavioral and physiological rhythms. Gonadectomy results in a lengthened free-running period, decreased precision of daily onset of running, and elimination of early-evening activity bouts. Androgen treatment restores these responses. The aim of this study was to explore how androgens may regulate circadian behavior by studying the localization of androgen receptor (AR) expression in mouse suprachiasmatic nucleus.

Methods: The authors first confirmed in gonadectomized (GDX) males an increase of the circadian period, precision of the activity onset was severely reduced, and activity bout length was reduced. After replacement with testosterone or dihydrotestosterone, all parameters were restored to normal values. Confocal analysis with an antibody against AR showed a high expression within the ventrolateral core of the SCN. This localization has been confirmed by using transgenic mice. AR expression in SCN is not rhythmic. AR expression in SCN is reduced in GDX males, testosterone treatment restores AR expression to normal levels. AR-positive cells express FOS after a light pulse, this response is reduced in GDX animals but it was restored after DHT treatment.

Conclusion(s): This study confirms previous findings that SCN regulates circadian rhythms in gonadal hormone secretion and in turn, androgens act on their receptors within the SCN to alter circadian function.

Serum levels of testosterone have to be taken at 8 a.m. due its circadian rhythm. The role of SCN in regulating the rhythmic secretion of gonadal androgens is well known but the effects of androgens on SCN are less understood. This study supports the notion of a neuroendocrine feedback loop in the circadian system. This result may have some importance in the management of androgen treatment. It remains necessary to prove this concept in humans.

Conserved sensory-neurosecretory cell types in annelid and fish forebrain: insights into hypothalamus evolution

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Background: Neurosecretory brain centers secrete neuropeptides and non-peptidergic neuromodulators to regulate major developmental and physiological processes as growth, metabolism and reproduction. These centers are located within the hypothalamus and the preoptic area of the brain. The aim of this work was to understand the evolutionary origin of these centers.

Methods: To identify conserved components of the neurosecretory centers, the authors characterized and compared neurons that expressed vasopressin and oxytocin in the developing forebrain of the annelid *Platynereis dumerilii* and of the zebrafish. A molecular fingerprint based on the expression of several markers was found similar in vasotocinergic neurons of both species. These neurons express the same tissue-restricted microRNA, Mir-7, and conserved cell-type specific combinations of transcription factors. Mir-7 also labels another shared population of neurons containing RFamides.

Conclusion(s): Vasotocinergic and RFamidergic neurons appear to be directly sensory in annelid and fish. The authors propose that cell types with dual sensory-neurosecretory properties were the starting point for the evolution of the neurosecretory brain centers.

Despite its importance, the functional anatomy and physiopathology of disorders related to defects of the hypothalamus are poorly understood. Recently, new experimental approaches have led to consider the characterization of neuronal networks involved in this regulation. Several new neuropeptides have been described in several species but the molecular basis of the major part of the hypothalamic regulations remains to be defined. This paper proposes an original approach to improve our understanding which is based on comparison between species of molecular fingerprints of a specific neuron. Their findings indicate that sensory-neurosecretory cell types have been present at the start of bilaterian brain evolution. During evolution, several specific neurons engaged toward a single function have emerged to form the hypothalamus. In accordance with this theory, it is known that the hypothalamus integrates multiple sensory inputs as light, temperature, and chemical stimuli. The fact that GnRH and olfactory neurons probably originate from the same stem cell also supports results presented in this paper. A link between odorants and reproduction has been described in several species. The phenotype due to hypothalamic deregulation is highly variable and it was suspected that this variability is related to environmental factors. The modulation of the phenotype of hypothalamic related diseases by sensory stimuli may be more direct than previously suspected.