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# Factors involved in the development of pituitary and hypothalamus: a short review

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## Abstract

A large amount of complex hormone associated processes occurring continuously in the human organism is necessary to maintain homeostasis in response to various internal and external conditions. In the same time, as the hormones use the bloodstream as their transmission medium, it is essential that their expression is strictly controlled to maintain their activity only when it is required. Because of that, the endocrine system evolved complex, self-regulating machinery that allows for precise signalling to the glands to initiate hormone expression, as well as equally quick negative feedback in the moment of reaching the optimal blood hormone concentration. The pituitary gland serves as the true endocrine part of that system, expressing a range of hormones that mostly serve as regulators of sub-systems serving different functions, scattered around organisms. The hypothalamus is the neuroendocrine part of the hypothalamic-pituitary axis, meaning it integrates the neuronal and hormonal signals, effectively linking the nervous and endocrine systems. The processes of hypothalamus and pituitary development share some significant similarities, which is unsurprising considering their close association and anatomical proximity at the base of the brain. Arising in highly overlapping developmental timeframes, they are both initially patterned by the gradients of extrinsic signalling molecules. After the initial lineage commitment, in both of those structures, intrinsic factors expressed by the distinct cell populations sustain the morphogenesis to result in a final complexly patterned structure. In this short review, the processes of the pituitary and hypothalamus development are described, with the most important factors driving them discussed.

**Running title:** Factors of pituitary and hypothalamus development

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## Functional overview and interactions

A large amount of complex hormone associated processes occurring continuously in the human organism is necessary to maintain homeostasis in response to various internal and external conditions. In the same time, as the hormones use the bloodstream as their transmission medium, it is essential that their expression is strictly controlled to maintain their activity only when it is required. Because of that, the endocrine system evolved complex, self-regulating machinery that allows for precise signalling to the glands to initiate hormone expression, as well as equally quick negative feedback in the moment of reaching the optimal blood hormone concentration [1]. The pituitary gland and the hypothalamus lie in the centre of these regulatory processes, engaging in bi-directional dialogue that successfully links the neural and endocrine systems.

The pituitary gland serves as the true endocrine part of that system, expressing a range of hormones that mostly serve as regulators of sub-systems serving different functions, scattered around organisms. Located at the base of the brain, this pea sized structure is divided into anterior and posterior lobes that both serve different functions. The anterior lobe releases most of the hormones, such as growth hormone (GH; ensures proper growth and composition of developing organism and ensures that the bone and muscle mass stay in norm in adults), adrenocorticotropic hormone (ACTH; stimulating the adrenal glands), thyroid-stimulating hormone (TSH; stimulates hormone production in the thyroid glands), follicle-stimulating hormone (FSH; regulates the menstrual cycle by ensuring follicle maturation), luteinising hormone (LH; regulates the menstrual cycle causing ovulation), and prolactin (stimulates production of the breast milk during lactation). The posterior lobe meanwhile, releases two hormones that also impact the entirety of the organism, but serve separate distinct functions [2,3]. Anti-diuretic hormone (ADH), acts to compensate for the lack of water in the organism by stimulating kidney resorption, also serving a role in increasing blood pressure through arteriole constriction [4]. Oxytocin, on the other hand, is mostly an agent promoting processes associated with birth (e.g. uterine contractions) and lactation. However, there is a broad range of functions attributed to this hormone, such as roles in forming social behaviour and behavioural differences between sexes, as well as antidepressant properties [5,6]. The posterior lobe of the pituitary also serves as a link to the hypothalamus, housing the endings of hypothalamic nerves. It is important to note that, in contrary to the anterior lobe, the hormones are just stored and released from the posterior pituitary, being produced in the hypothalamus [2].

The hypothalamus is the neuroendocrine part of the hypothalamic-pituitary axis, meaning it integrates the neuronal and hormonal signals, effectively linking the nervous and endocrine systems [7]. It is the place of production of the posterior pituitary hormones (ADH is produced in its supraoptic nucleus; Oxytocin is produced in its paraventricular nucleus), as well as a range of hormones that control the anterior pituitary lobe, such as thyrotropin-releasing hormone, corticotropin-releasing hormone, dopamine, growth-hormone-releasing hormone, gonadotropin-releasing hormone, and somatostatin [8]. The former group, the releasing neurohormones, are produced by the neurons of the hypothalamus in response to nerve signals. They are then transported along the axons to their terminals, where they are released into the hypophyseal portal system (system of blood vessels connecting the hypothalamus with the pituitary) which allows them to rapidly reach the anterior pituitary and exert their effects [9]. The hormones released by the pituitary are then released into the bloodstream, with their high blood levels being received by the hypothalamus on a basis of negative feedback, stopping the pituitary stimulation [10].

In this way, the hypothalamus and the pituitary work in close relation to maintain the homeostasis of the organism, through the expression of adequate hormones that influence further downstream endocrine pathways.

## Development of the Hypothalamus

Hypothalamus is a highly complex structure is divided into different regions that serve their different respective functions. The development processes are also region dependent, with different regulating factors. However, in these differences only arise in the later development, with early neurogenesis proceeding in a similar manner [11]. During the closing of the neural tube, three rostral swellings appear. These structures, the prosencephalon (forebrain), mesencephalon (midbrain), and rhombencephalon, become the basis of the developing brain. The forebrain undergoes further expansion, which results in a formation of a telencephalic (endbrain) vesicle, with the remaining prosencephalon becoming the diencephalon (interbrain) [12]. The primordial hypothalamus is induced in the medial portion of prosencephalon [13]. Initially, its induction is based on the inhibition of Wnt signals from the posterior mesoderm by the anterior neuroectodermal Wnt antagonist expression. This results in a gradient that determines the A/P axis, initiating the patterning of the specific hypothalamic regions [14]. Shh expressed by the axial mesoderm that underlies the neural plate acts as a ventralising signal for the CNS development, also playing an important role in patterning of the hypothalamus [15]. Nodal, a TGFβ ligand, expression by the prechordal mesoderm also shows involvement in hypothalamus patterning in zebrafish and chick, but doesn't seem to play a role this process in mice, which leads to presumption that its function is species-specific [16].

The mentioned early signals lead to establishment of distinct A/P and D/V gradients, which both function to differentiate the distinct hypothalamic cell types. The anterior-posterior gradient influences the formation of four regions, the preoptic, anterior, tuberal and mamillary region. In the same time, the dorsal-ventral gradient results in its distinct division into the alar, basal and floor plate territories, consistent with those observed in the rest of the neural tube. These gradient affect the cells of the hypothalamus, causing the expression of population-specific factors that guide the further development [17]. Shh is considered crucial to the development of the rostral hypothalamus, as while its initially expressed throughout the structure, later it becomes restricted to its rostral regions [18]. The restriction process occurs through the activation of Shh enhancers in the rostral region by the Sox2/Sox3, as well as caudal repression of this gene by Tbx2/Tbx3 [19,20]. This pattern of expression causes anteriorisation of the Shh affected cells, with the process proven to be highly conserved across the vertebrate models [17]. The posteriorisation of the hypothalamus is mostly regulated by the Wnt signalling pathways [21]. This process occurs similarly to the Shh mediated anteriorisation, with Wnt pathway ligands expressed in the caudal hypothalamus and inhibited in its rostral part by repression of genes that encode these ligands[22]. Again, the process has been shown to be highly conserved across the vertebrate species. Afterwards, the specific cells types, induced through the combined pattern of A/P/D/V specific factors, express upregulation of lineage-specific intrinsic factors that further commit them towards the final cell fate. As the hypothalamus is a highly complex structure, containing a broad range of neuronal cell type, the morphogens expressed are numerous and arrange in distinct patterns [17].

The timeframe of hypothalamic neurogenesis is quite well researched, mostly on the rat model. It reports the appearance of the hypothalamic primordium around embryonic day 10 (E10), with appearance of primitive neuromeric folds at E12-E13. Around E14 first signs of differentiated cell lineages appear, with some of them reaching their fully differentiated state as soon as E15-E17 and the hypothalamus reaching its final organization by E21 [11].

## Development of the Pituitary

The development of pituitary is closely linked to the hypothalamus, occurring in tandem with the development of specific hypothalamic nuclei. Starting at the midline portion of the region of the neural plate from which the ventral diencephalon rises (the anterior neural ridge), the development proceeds towards pituitary formation through neural diencephalon induction [23]. The de facto pituitary organogenesis begins around E8.5 (embryonic day 8.5) in the murine model, with the appearance of Rathke's pouch (RP), the thickened invagination of the anterior pituitary placode of the oral ectoderm. The dorsal portion of the pouch contacts the midline of the ventral diencephalon, evagination of which (around E10) acts as the main organizer for its patterning and differentiation of its cells [24].

The initial stage of development is regulated by the extrinsic signals from the mentioned ventral diencephalon, as well as oral ectoderm. The latter mostly expresses bone morphogenetic protein (BMP), Wnt, and fibroblast growth factor (FGF) family members. All of those groups of factors were proven to have an essential role in early differentiation of the Rathke's pouch [25]. The application of Noggin, an agonist for BMP4, *in vivo* causes absence of most of the pituitary cell types, as well as an arrest of its development right after invagination (E10) [26]. FGF signalling induces the Lhx3/P-Lim genes necessary for the developmental processes occurring after RP invagination, with its inhibition resulting in proliferation failure and apoptosis [27]. The most important extrinsic factor associated with oral ectoderm is undoubtedly Shh. Its expression is not observed in primordial pituitary before E10, which is interesting as its widely expressed in the oral ectoderm. However, it plays a major role in the later periods, working together with FGF signals to maintain ventral Lhx3 expression, which was proven through research of you-too zebrafish mutants and murine models treated with Shh inhibitors [28].

From E10.5 to E17.5, the six endocrine cell types of the mature pituitary appear in a fashion initially orchestrated by the induction by dorsal and ventral signalling molecules, complemented by an array of intrinsic and ventral mesenchymal signals [29]. The developing gland expresses factors such as BMP2 and Wnt4, stimulating proliferation of ventral cell types. The ventral-dorsal gradient of BMP2 present at the initial stages of RP differentiation unifies across the primordial pituitary by E12.5 [30]. Different extrinsic mesenchymal signals create further gradients that condition the differential development of pituitary cells. The ventral mesenchyme expressed IHH (Indian hedgehog), Wnt4 and BMP2. In the same time, the BMP2 inhibiting signal in the form of Chordin is expressed by the caudal portion of the mesenchyme. Gradients established in that way need to be further supplemented in order to create the final pattern of pituitary differentiation [26].

The signals regulating the steps of pituitary cell types differentiation arise progressively in response to the described gradients, creating further conditions that, combining with the initial signals, result in the final cell phenotypes [29]. Already mentioned Lhx3 is one of the most important factors, necessary for the development of most of the pituitary endocrine cells. Studies in mice confirmed that mutation in the gene encoding this factor leads

to failure in development of Rathke's pouch, leaving only a rudimentary number of corticotropes, which indicates that this developmental pathway is Lhx3 independent [27]. The process of corticotrope differentiation is closely linked with the development of melanotropes. They are both dependent on the expression of a Tbx19 transcription factor, which has been proven the through the association of Tbx19 gene mutations with defective ACTH production in humans. Cells influenced by this factor become corticotropes in the ventral region of the pituitary and melanotropes in its dorsal region [31]. Somatotropes, lactotropes, thyrotropes and gonadotropes arise through the co-operative action of a Prop-1 and Rpx/Hesx1 (a repressor that is present in pituitary development from the early stages) [32,33]. The initial expression of Prop-1 is detected around E10. However, initially Prop-1 dimerizes with Rpx/Hesx1, which exhibits the gene activation properties of the former. This process permits the initial differentiation of the pituitary, permitting the development of Prop-1 dependent lineages around E13.5, through Rpx/Hesx1 downregulation [32]. Further development of the specific cell lineages is dependent on the Pit-1 and GATA-2 expression. Somatotropes and lactotropes develop in a Pit-1 dependent manner, with gonadotropes developing due to GATA-2 interaction [34]. Somatotropes and lactotropes are then further differentiated due to differential binding of Pit-1 to multiple binding sites on the growth hormone gene in both of the cells, presumably regulated by another cell-type specific transcriptional activator [35]. Thyrotropes develop under the influence of both Pit-1 and GATA-2 [34]. All of these processes facilitate the complete differentiation of pituitary cell types, ending around embryonic day 17.5 [29].

## Conclusions

In conclusion, the processes of hypothalamus and pituitary development share some significant similarities, which is unsurprising considering their close association and anatomical proximity. Arising in highly overlapping developmental timeframes, they are both initially patterned by the gradients of extrinsic signalling molecules. After the initial lineage commitment, in both of those structures, intrinsic factors expressed by the distinct cell populations sustain the morphogenesis to result in a final complexly patterned structure. Hence, while the early developmental processes are very similar, relying on the same signalling pathways and transcription factors, the later development, while co-dependent, is mostly divergent. The same tendency applies to the conservation of the mechanisms of development across the vertebrate species, with the early patterning usually mostly conserved across the animal models, with various major differences in the later differentiation. The close association between the hypothalamus and pituitary development, as well as their extensive functional co-dependence, reflects in the effects of developmental defects and experimental outcomes. Signalling factor encoding gene mutations, as well as controlled knock-outs or pathway inhibitions often lead to impairment of the function of both of the structures. However, the high similarity of the early patterning process across the vertebrate models allows for relatively easy transcription of experimental results to conclusions that can be applied to the processes occurring in humans.

## Ethical approval

The conducted research is not related to either human or animal use.

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**Conflict of interest statement**
The authors declare they have no conflict of interest.

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