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DEVELOPING BRAIN AS AN ENDOCRINE ORGAN : A PARADOXICAL REALITY

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Developing brain as an endocrine organ: a paradoxical reality

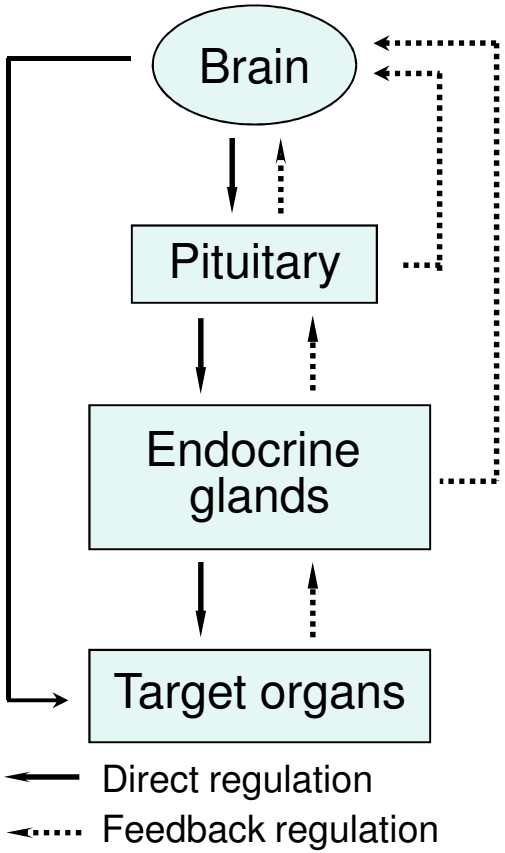
- **Endocrine functions of the brain in adulthood**

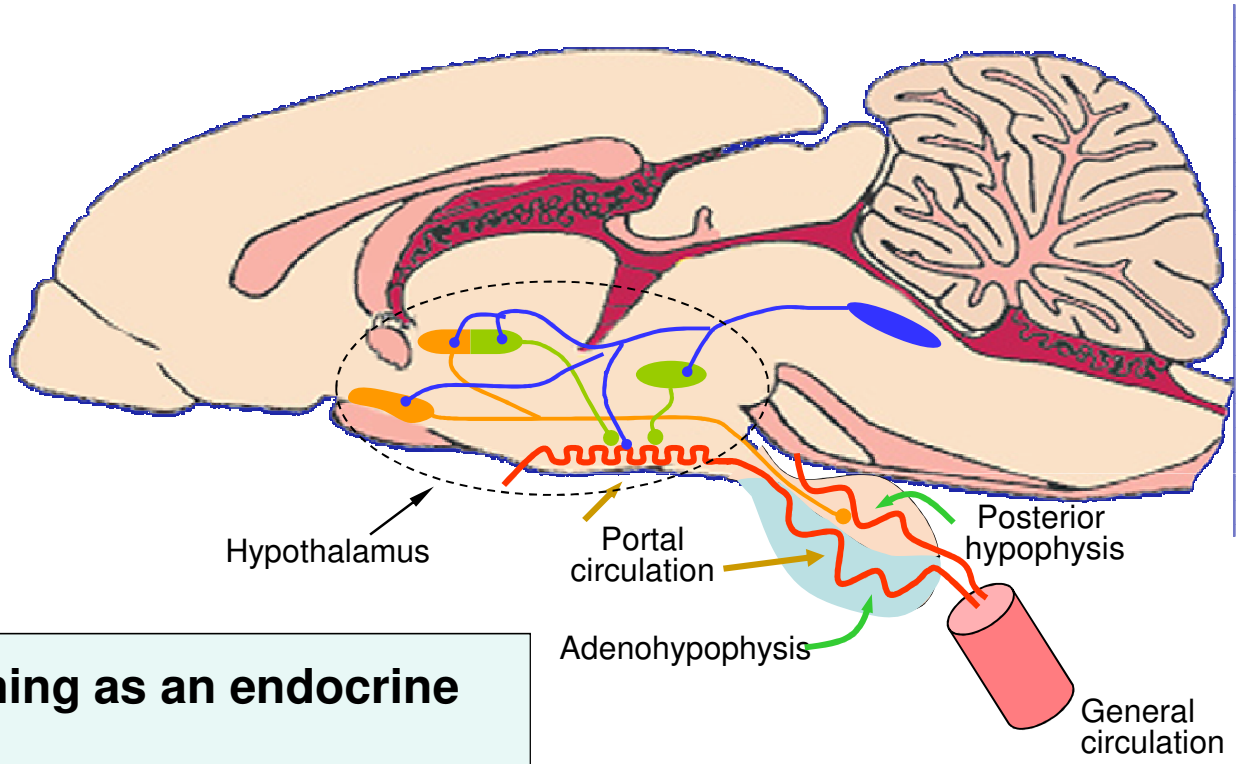
  Current concept of neuroendocrine regulations in ontogenesis and contradictions.

  Revised concept of neuroendocrine regulations in ontogenesis.

  Summary and prospect

Endocrine functions of the brain in adulthood





Criteria of the brain functioning as an endocrine organ :

- Existence of the neurons, secreting neurohormones;
- Delivery of neurohormones into the blood vessels;
- Maintaining of the physiologically active concentration of neurohormones in blood;
- Delivery of neurohormones from secretory neurons to the distant target cells via circulation.

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Endocrine functions of the brain in adulthood

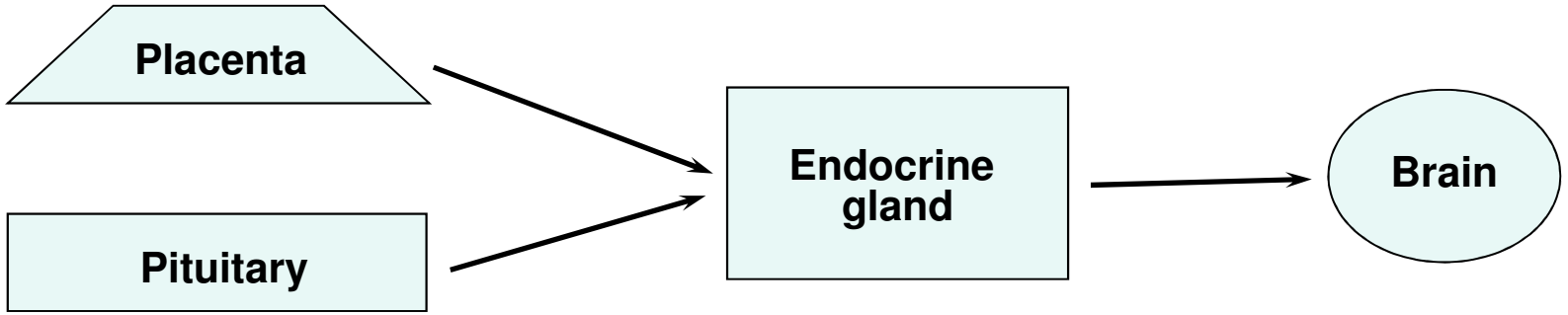
- **Current concept of neuroendocrine regulations in ontogenesis and contradictions**

Revised concept of neuroendocrine regulations in ontogenesis

Summary and prospect

Development of the neuroendocrine regulations in ontogenesis. *Current concept*

I. Prenatal and neonatal *open-looped* neuroendocrine **system**



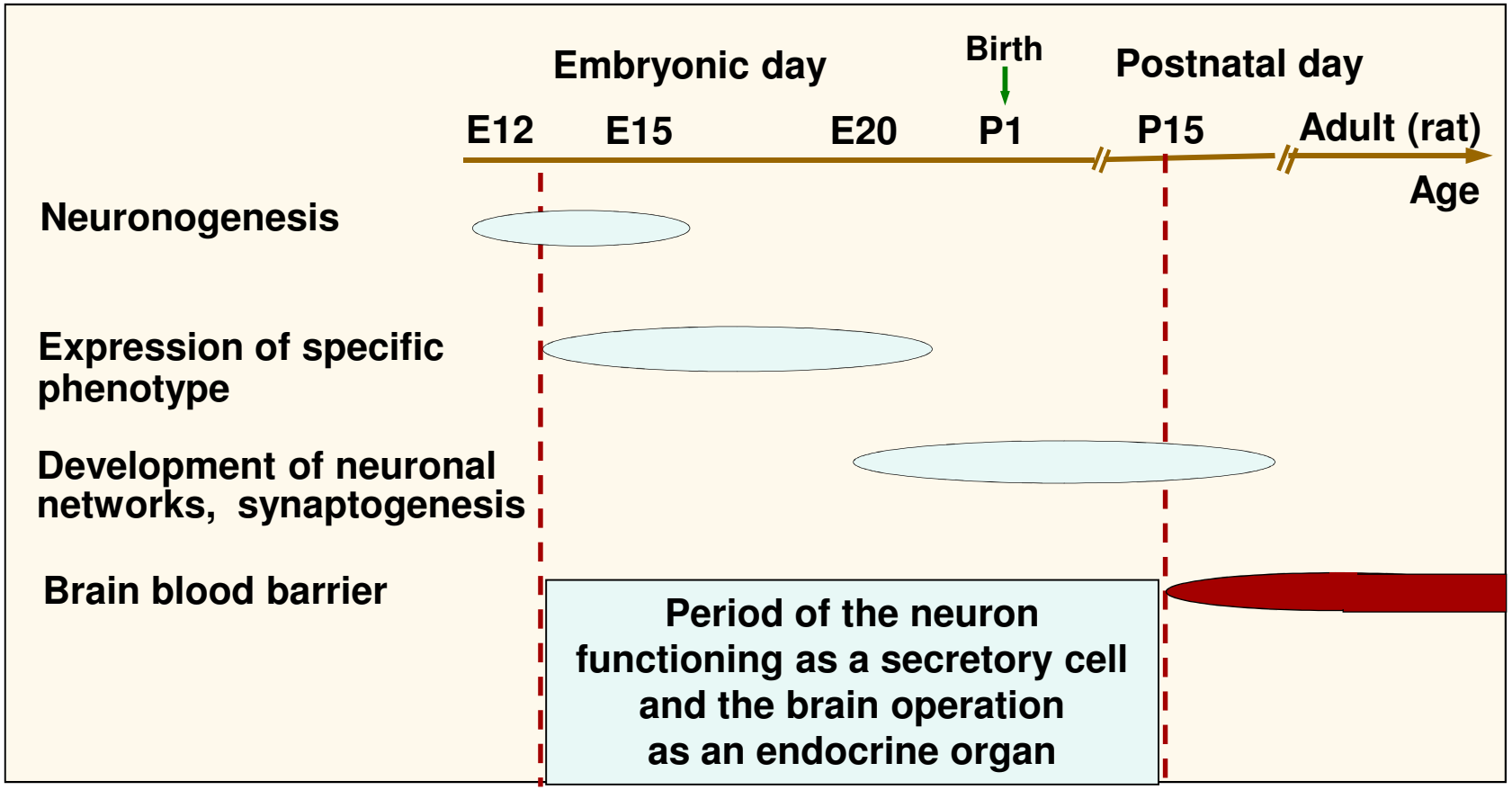
Milestones of the concept:

- The development of peripheral endocrine glands ***precedes*** that of the "endocrine" hypothalamus and the brain as a whole;
- The hypothalamic neurons begin to secrete the adenohypophysiotropic neurohormones ***after the axon sprouting to the hypophysial portal circulation***;
- Neurohormones secreted by the differentiating neurons contribute, first, to the ***autocrine and paracrine regulation*** of the neuron development and, significantly later, to the ***endocrine control*** of the adenohypophysial functions.

Dörner (1981); Daikoku et al. (1981); Gorski (1988); Jacobson (1991); Ugrumov (1991), Int. Rev. Cytol. 129, 207-267; Ugrumov (2002) Microsc Res Tech 56, 164-171.

If the hypothesis is valid:

- The concentration of the brain-derived neurohormones in general circulation before the closing of the blood brain barrier in ontogenesis should be as large as that in the hypophysial portal circulation in adulthood;
- The concentration of the brain-derived neurohormones in peripheral blood should drop under inhibition of their synthesis in the brain;
- Circulating brain-derived neurohormones should contribute to the endocrine regulation of the developing peripheral target organs and the brain itself (autoregulation)



Developing brain as an endocrine organ: a paradoxical reality

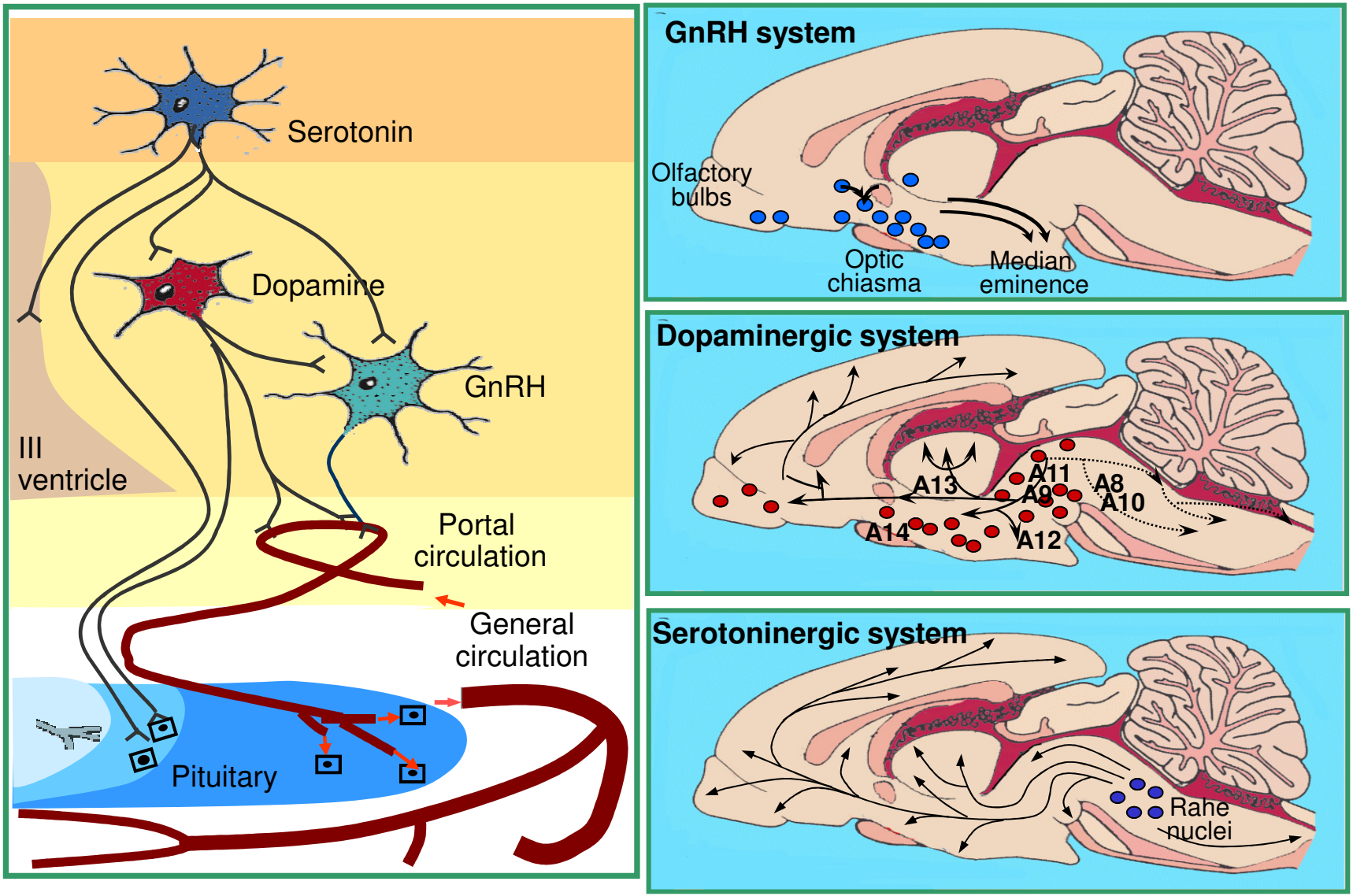
Endocrine functions of the brain in adulthood

Current concept of neuroendocrine regulations in ontogenesis and contradictions

➨ **Revised concept of neuroendocrine regulations in ontogenesis**

Summary and prospect

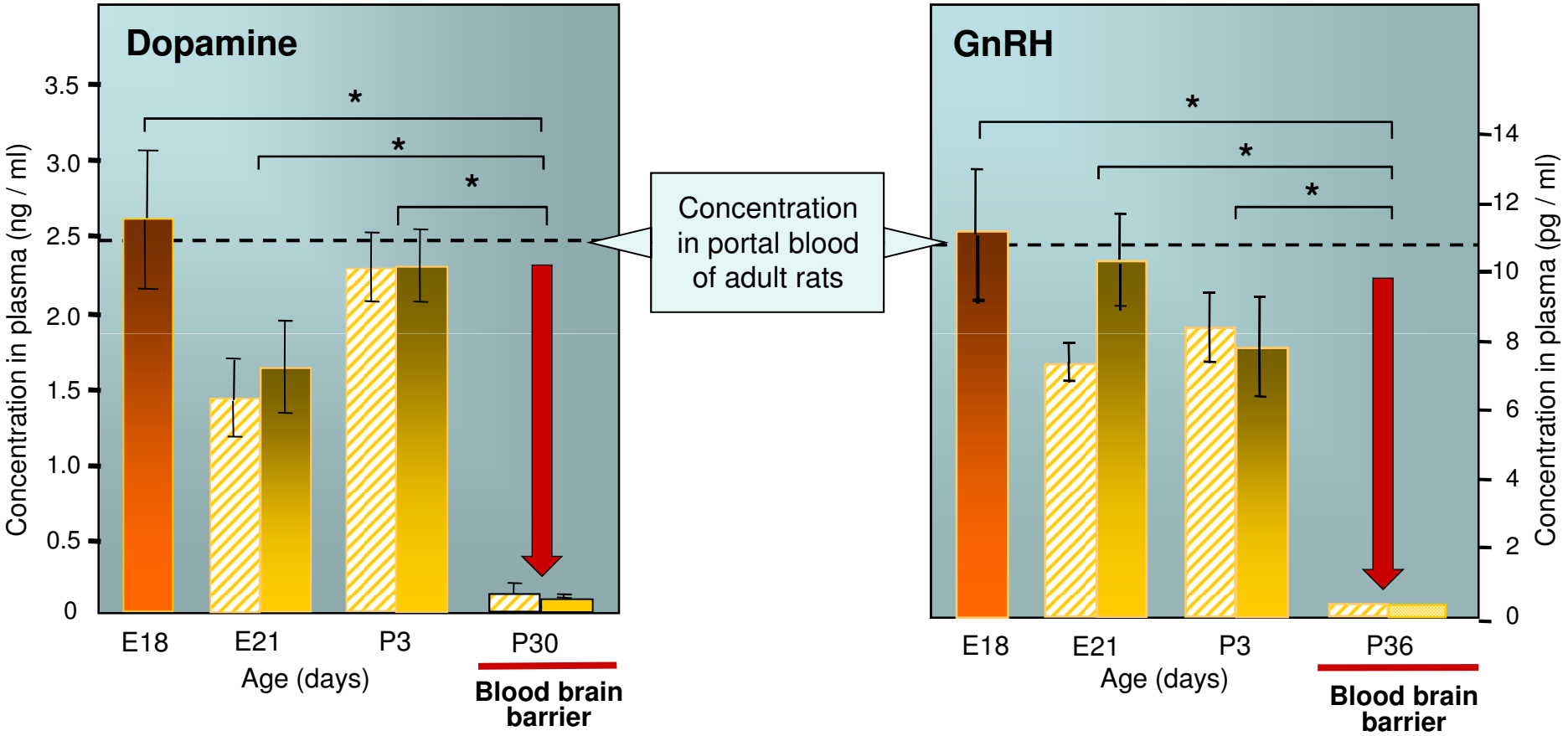
GnRH, dopamine and serotonin as markers of brain endocrine activity in ontogenesis



Whether the concentration of neurohormones
in peripheral blood in ontogenesis before
the blood brain barrier closing is sufficient
to provide an endocrine control of the target organs

?

Concentration of neurohormones in general circulation in rats in ontogenesis



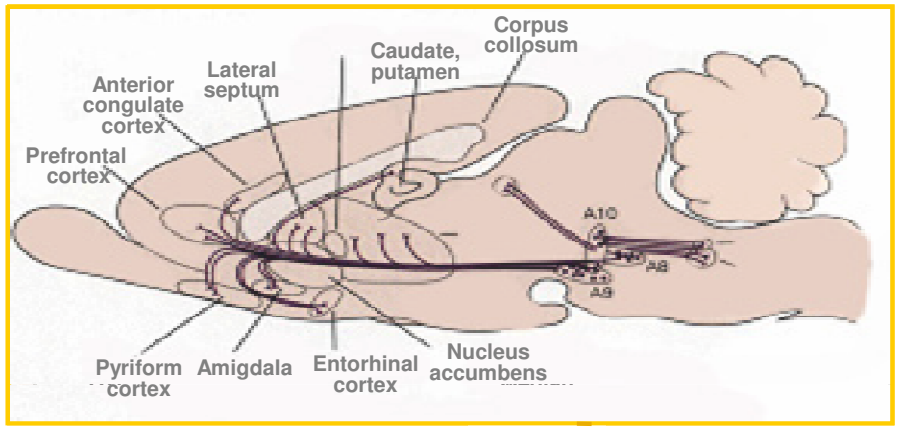
Ugrumov et al. (2005) *Comp. Biochem. Physiol. A 141, 271-279*; Ugrumov (2010) *Neurochem. Res. 35, 837-850;* Ugrumov et al. (2012) *Mol. Cell. Endocrinol. 348, 78-86*.

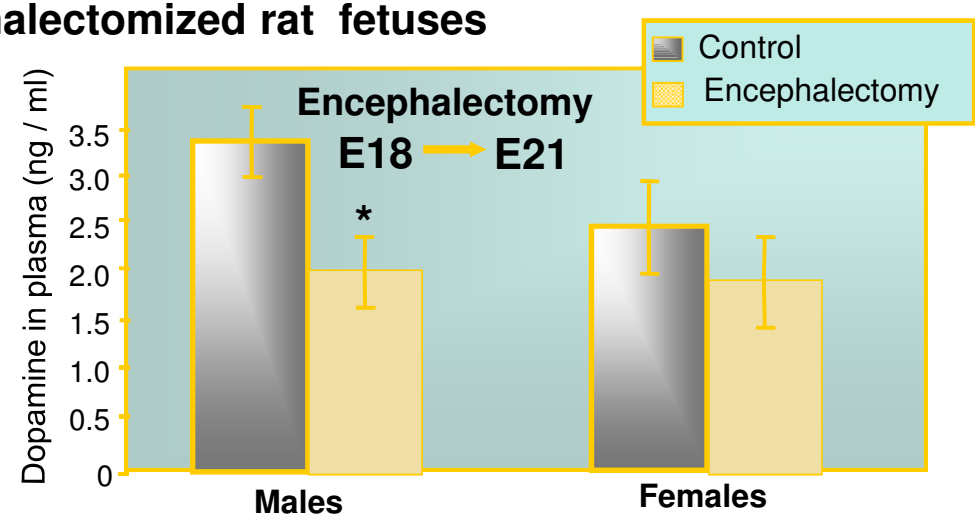
Whether the developing brain
is a principal source of circulating neurohormones

?

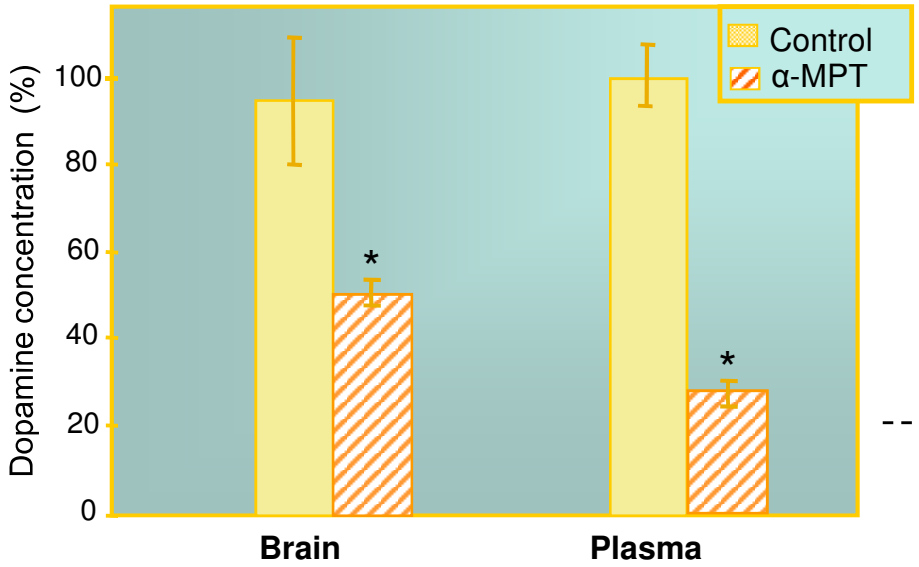
Delivery of brain-derived dopamine into the general circulation in rats in ontogenesis

I. Dopamine in plasma of encephalectomized rat fetuses





II. Dopamine in the brain and plasma following an inhibition of its synthesis in the brain

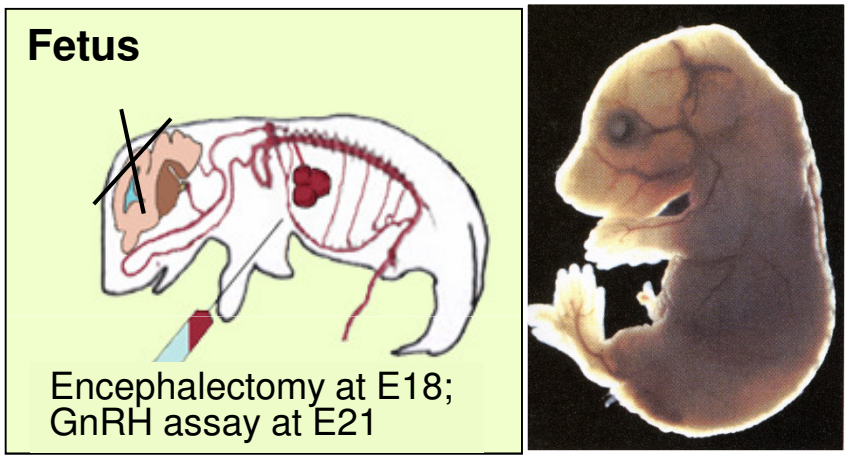


Animals: rats at the 3rd postnatal day;
Inhibitor: *α-methyl-p-tyrosine (α-MPT)*
Administration: lateral ventricle

Ugrumov (2010) *Neurochem. Res., 35, 837-850;*
Ugrumov et al. (2012). *Mol. Cell. Endocrinol. 348, 78-86.*

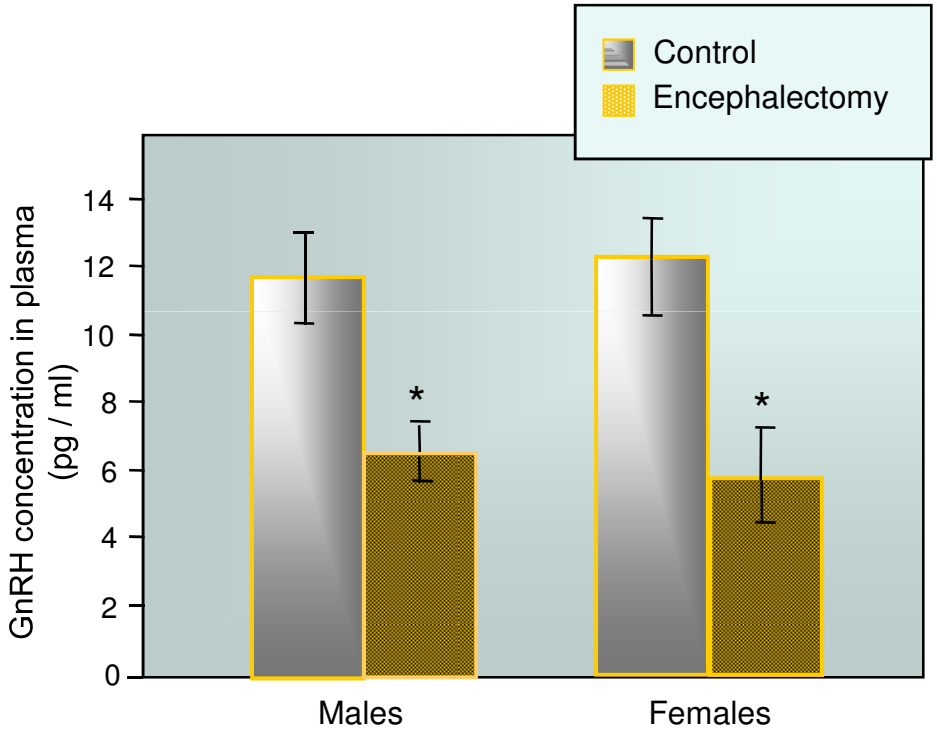
Delivery of brain-derived GnRH into the general circulation in rats in ontogenesis

Microsurgical lesion of GnRH neurons in fetal brain



Inhibition of GnRH synthesis in the brain

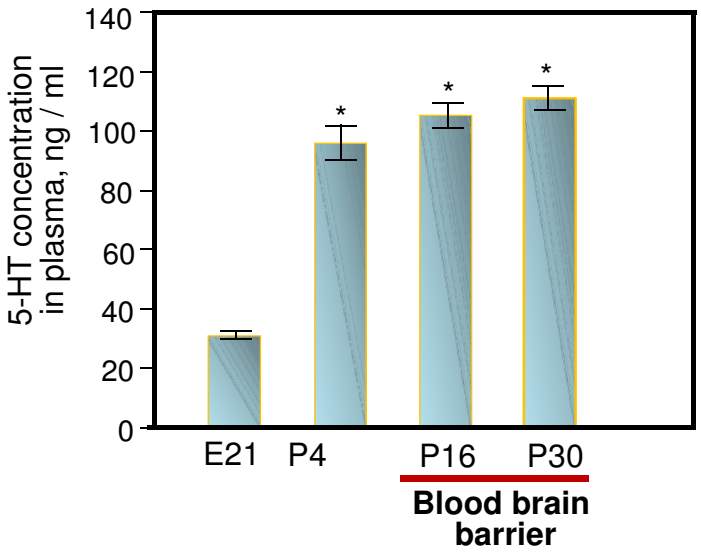
Neonates: intracerebral administration of GnRH si-RNA (*in progress*)

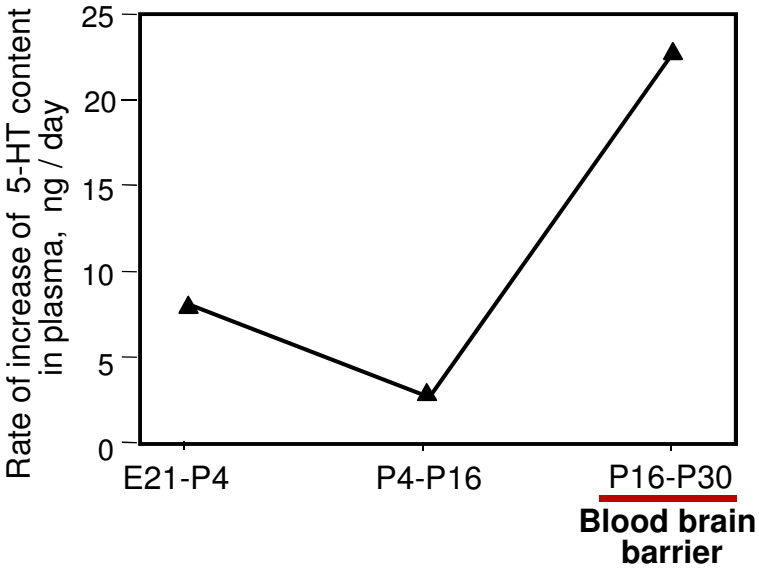


Ugrumov et al. (2005) *Comp. Biochem.Physiol. A 141, 271-279*; Ugrumov (2010) *Neurochem. Res., 35, 837-850.*

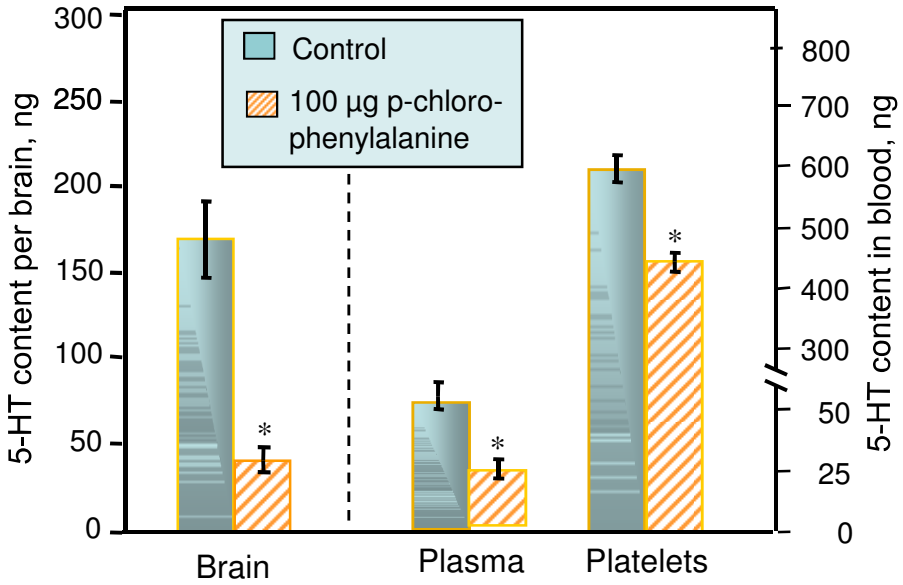
Delivery of brain-derived serotonin into the general circulation in rats in ontogenesis

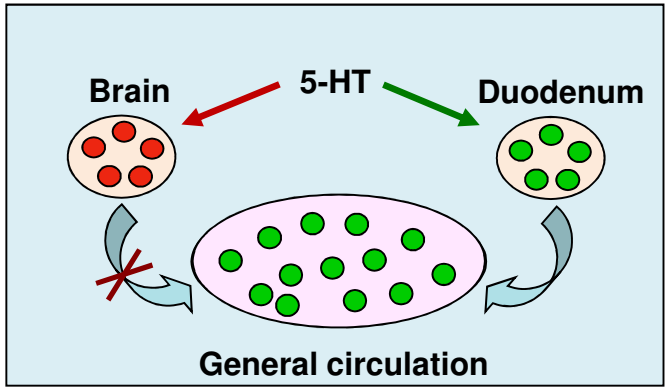
I. Serotonin (5-HT) in blood of perinatal rats





II. Serotonin in the brain and blood following inhibition of its synthesis in the brain





E, embryonic day
P, postnatal day

Zubova et al. (2014) *Molecular and Cellular Endocrinol. 393, 92-98.*

Whether the brain-derived neurohormones provide a direct endocrine action on peripheral targets and the brain itself

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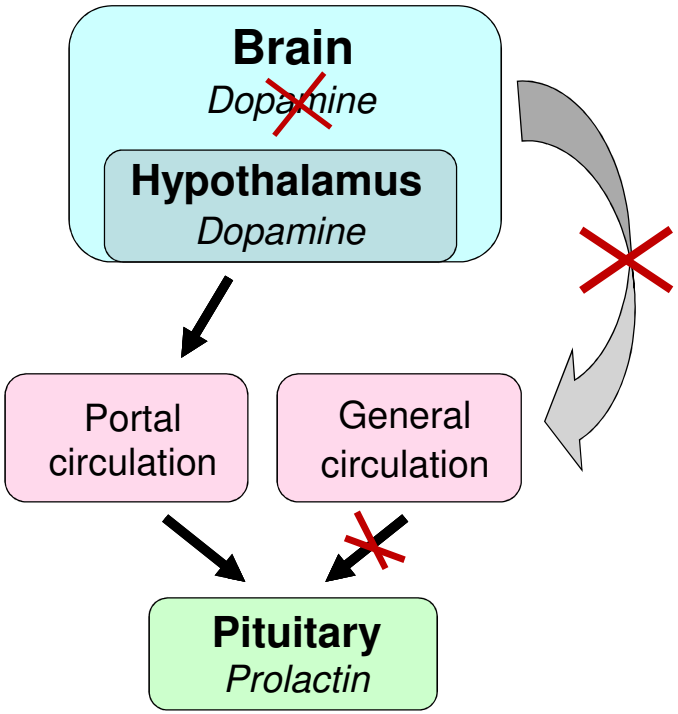
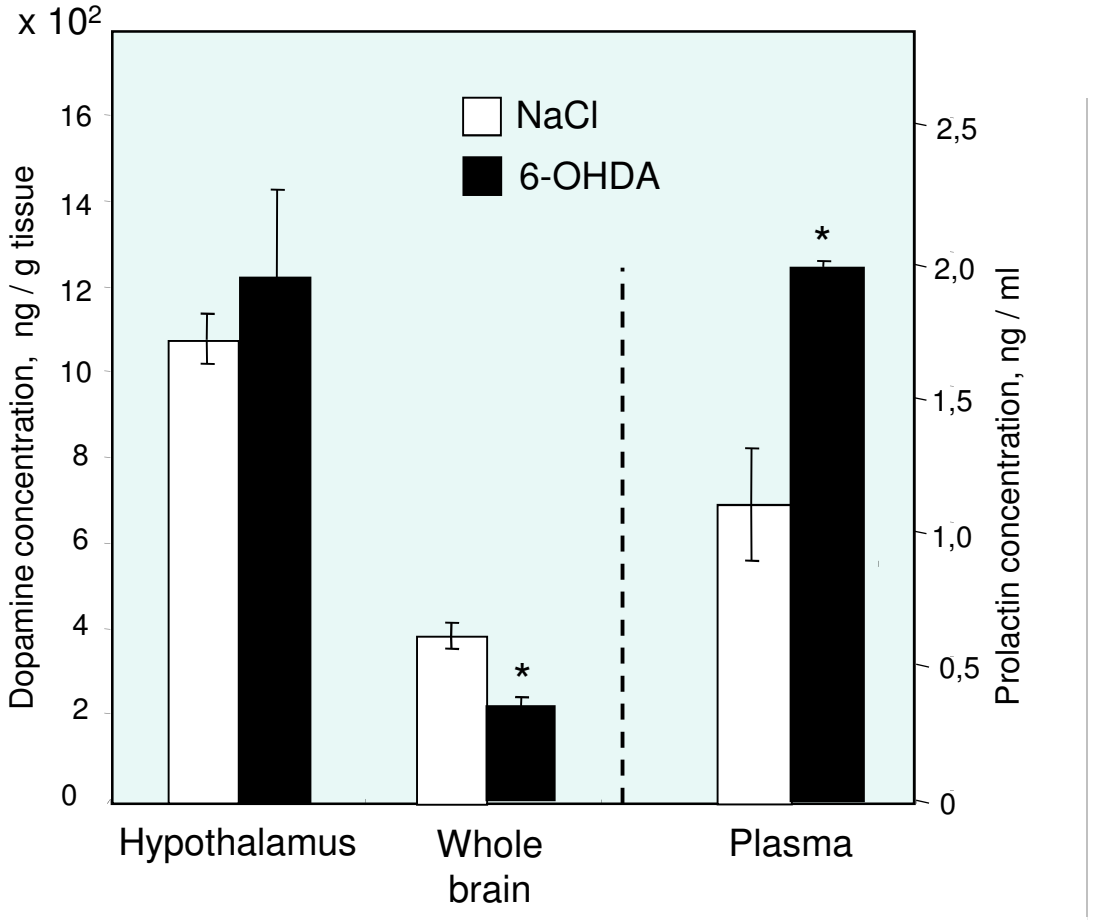
Potential targets for circulating brain-derived GnRH and monoamines in the developing organism

GnRH	Dopamine	Serotonin
Brain: hippocampus, septum, amigdala – GnRH-R (type II) (Badr et al., 1989)	**Brain:** suprachiasmatic nucleus – D1 (Weaver et al., 1992; Strother et al., 1998)	**Brain:** GnRH neurons (Pronina …Ugrumov, 2003a,b)
Pituitary: gonadotropes – GnRH-R (type I)	**Pituitary:** lactotropes – D2 (Felder eta l., 1989)	**Heart:** cardiomyocytes (Etienne et al., 2004)
Testis: Leydig cells - GnRH-R (type II) (Raeside et al., 1984; Hbert et al., 1991; Botte et al., 1998)	**Kidney:** proximal tubule cells, cortical collecting duct, blood vessels – D1, D2 (Felder et al., 1989;Carey, 2001)	**Blood vessels** (Etienne et al., 2004)
Ovaries: interstitial, granulosa, and luteal cells - GnRH-R (type II) (Botte et al., 1998; Kogo et sl., 1999)		
Immunocompetent cells: liver lymphocytes and thymocytes (Zakharova…Ugrumov, 2000)		

Endocrine regulation of prolactin secretion by brain-derived dopamine in neonatal rats

In vivo study

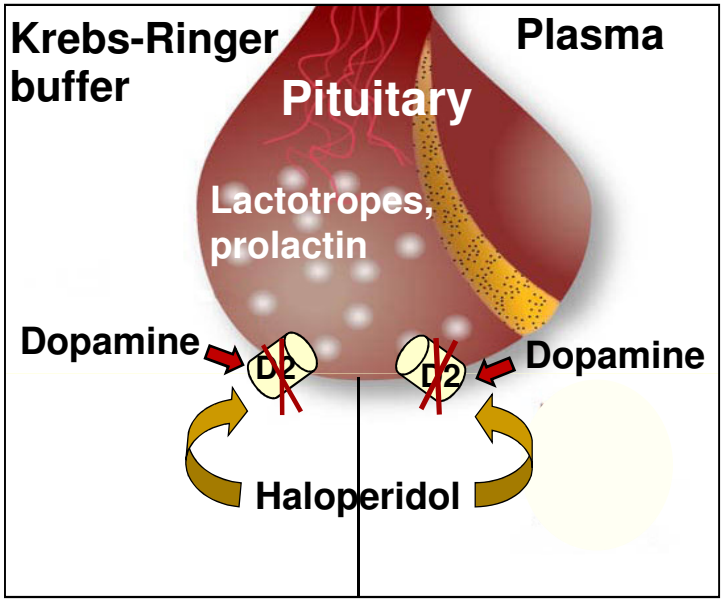




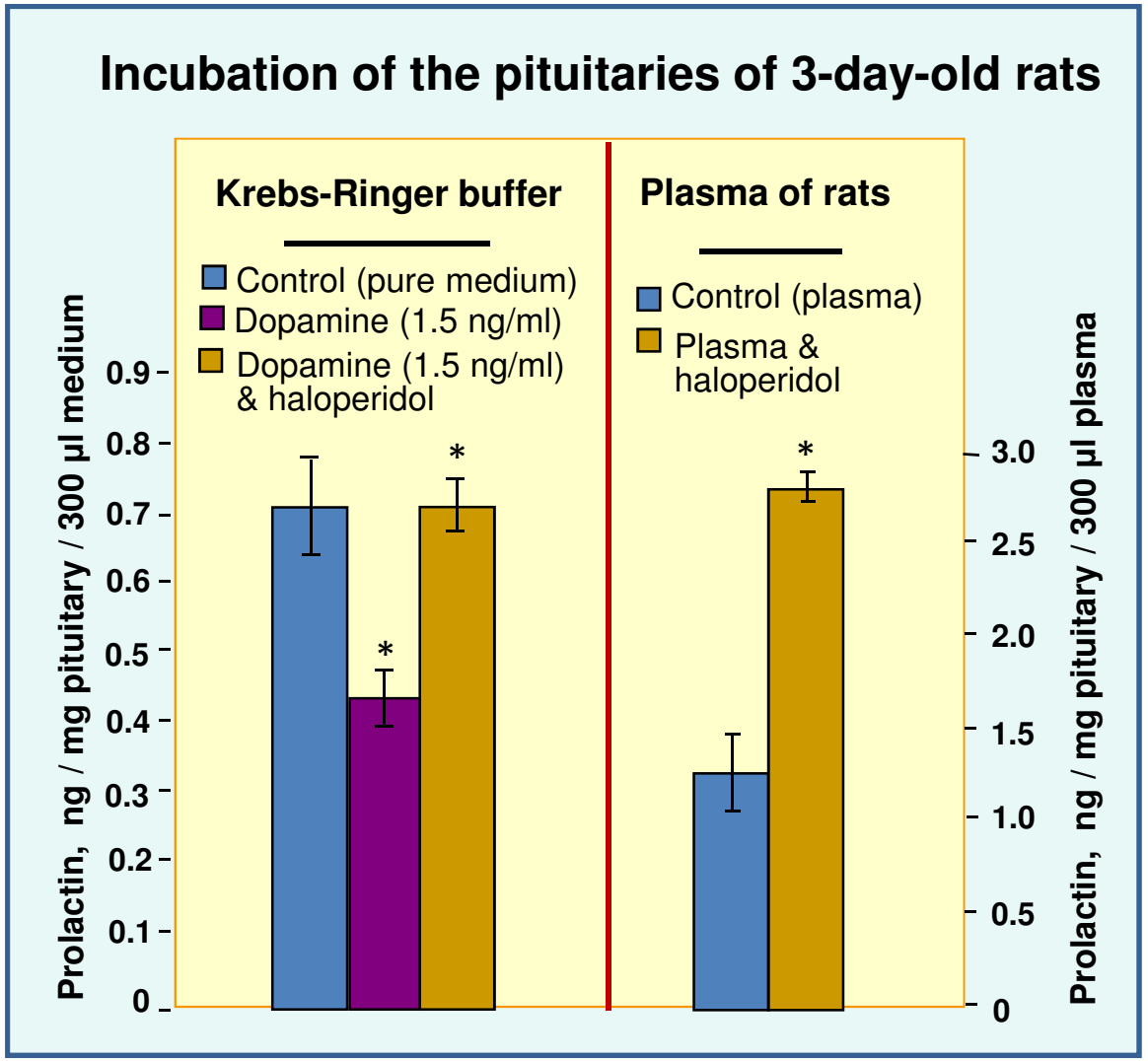
Zubova et al, in preparation

Endocrine regulation of prolactin secretion by brain-derived dopamine in neonatal rats

In vitro study



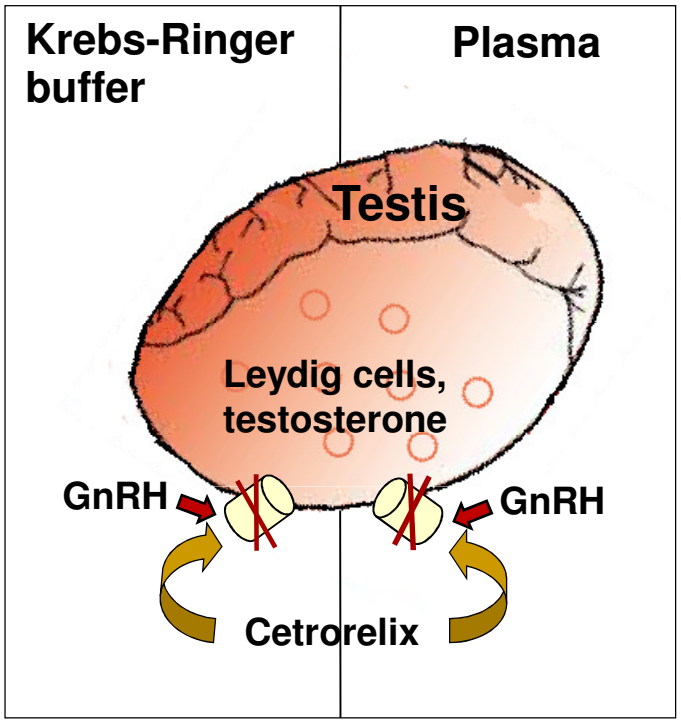
D2, dopamine receptors

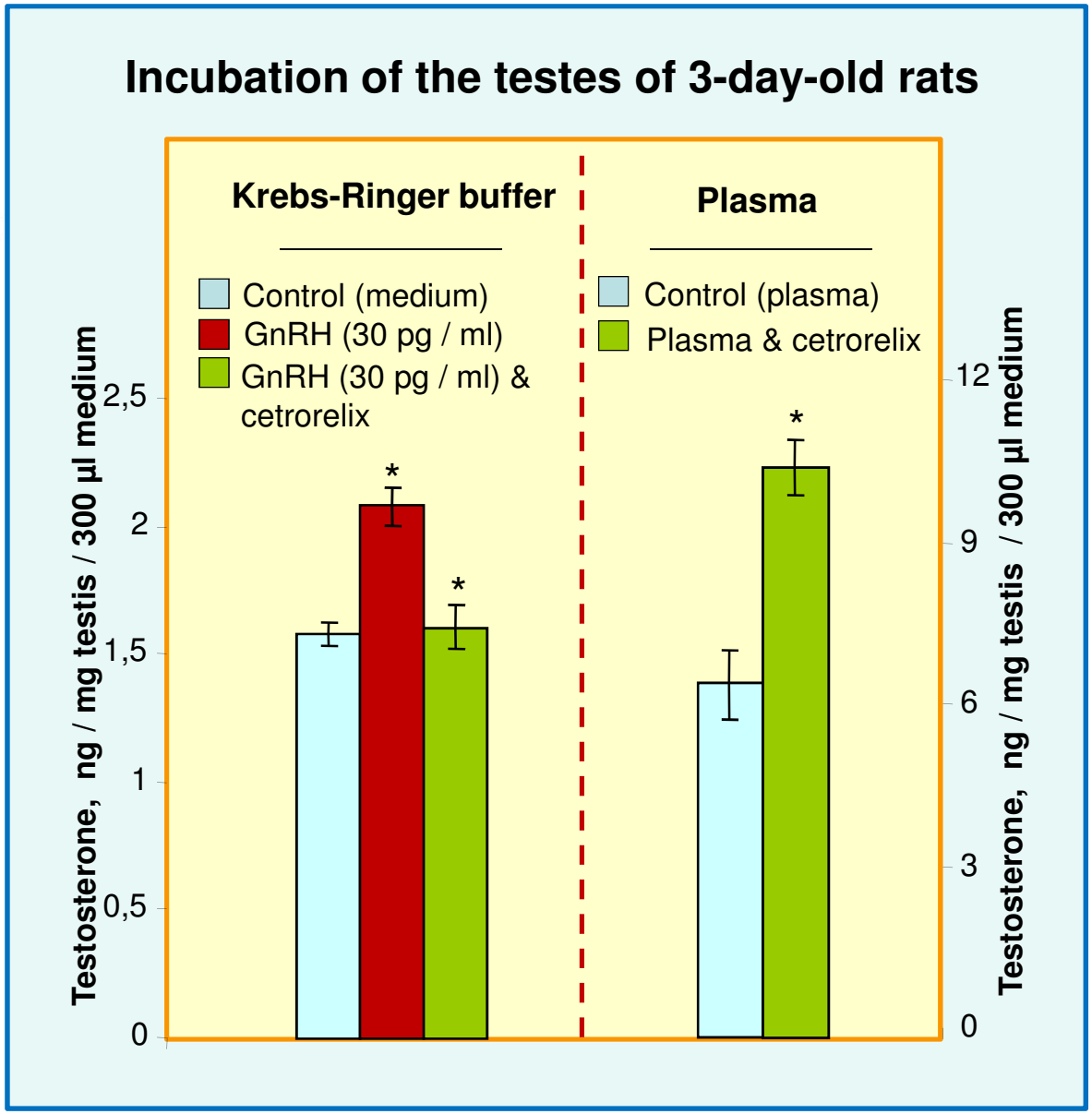


Zubova et al, in preparation

Endocrine regulation of testosterone secretion by brain-derived GnRH in neonatal rats

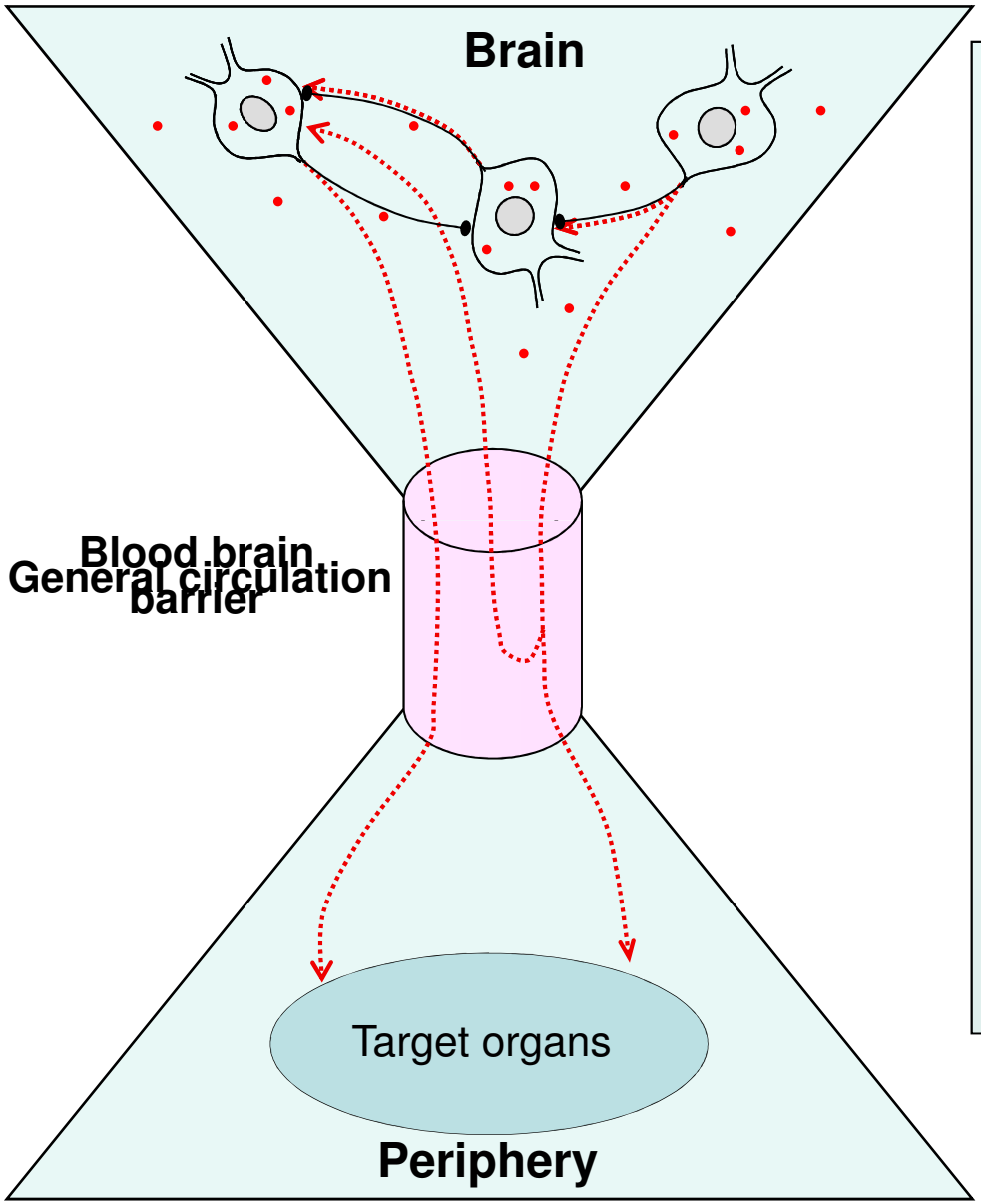
In vitro study



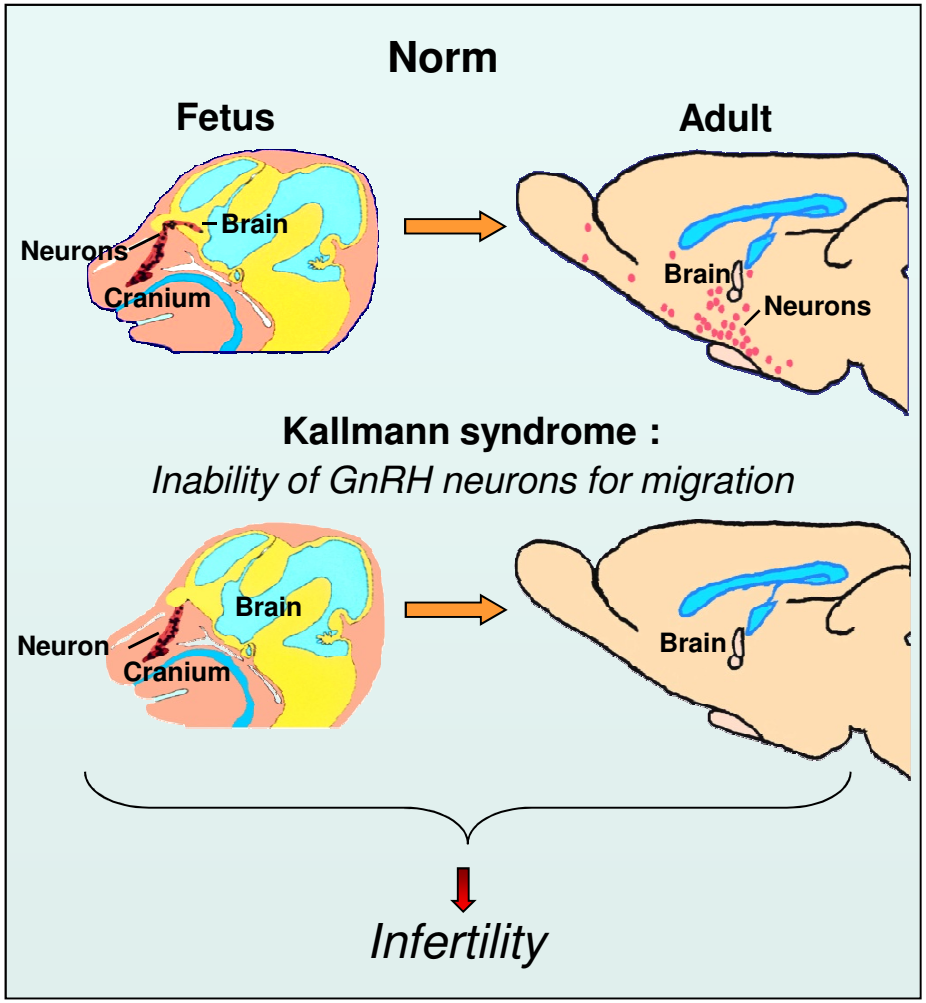


Bondarenko et al., in preparation

Developing brain as a multipotent endocrine



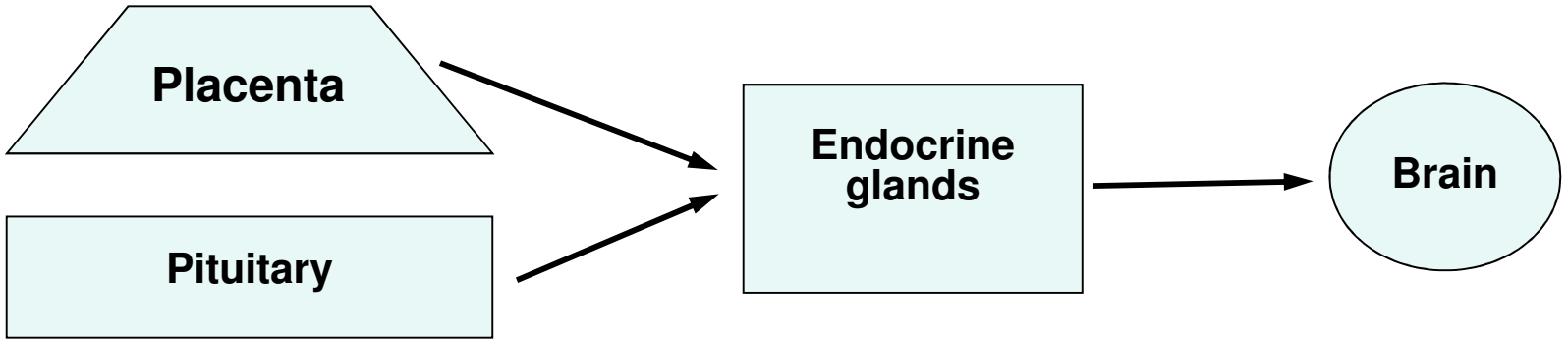
Congenital diseases



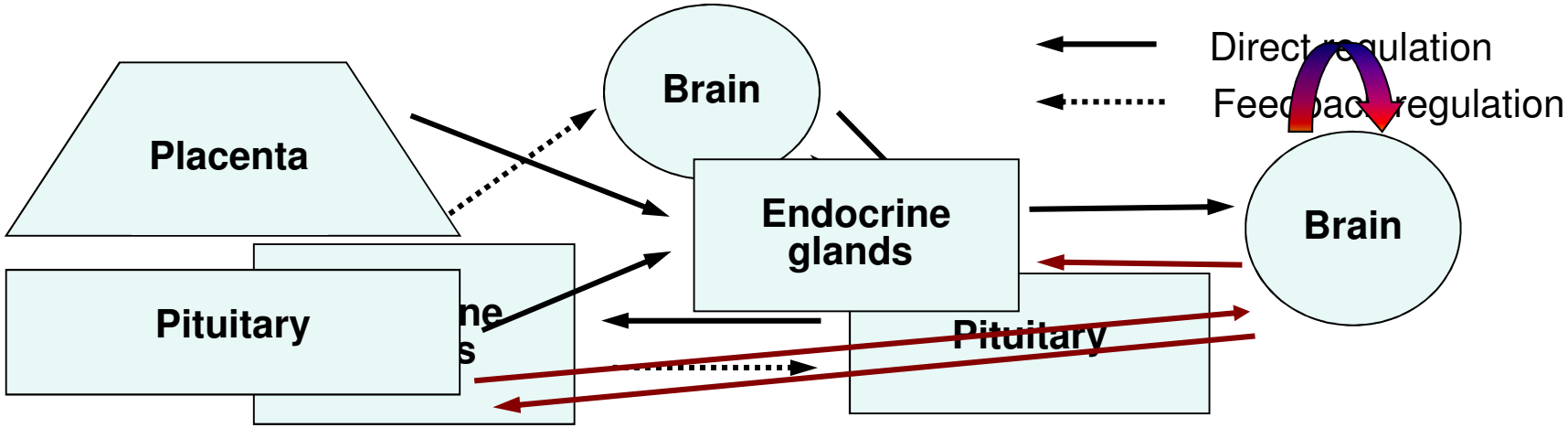
Pronina T., Ugrumov M. et al. (2003a,b) *J. Neuroendocrinol. 15, 549-558; J. Neuroendocrinol.* 15, 925-932;
Fechner A. et al. (2008) *Obstet. Gynecol. Surv. 63,189-194.*

Neuroendocrine regulations in ontogenesis: *current and revised concepts*

I. Prenatal *open-looped* regulatory system



III. *Reciprocal* regulatory system in ontogenesis, before the blood brain barrier closure *(Ugrumov, 2010)*



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The concept on the role of the brain in neuroendocrine regulations in ontogenesis: in the past, at present and in the future

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In the past. The brain does not participate in neuroendocrine regulations up to its complete "maturation", in rodents at prepuberty.

At present. The developing brain provides the paraadenohypophysial endocrine regulations of peripheral target organs and the brain itself in ontogenesis, over a period from the neuron origin till the establishment of synaptic interneuronal relations and the blood brain barrier closing.

In the future.
It should be ascertain:

- Whether the brain-derived neurohormones contribute to the paradenohypophysial endocrine regulation either of functioning or morphogenesis of the target organs;
- What is the functional significance of a temporal combination of paracrine and endocrine regulations of the target cells by the same neurohormones;
- What is a role of impairing metabolism of the brain-derived neurohormones in the development of congenital diseases

Thanks for your attention

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