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The insulin-like growth factor-1 system in the adult mammalian brain and its implications in central maternal adaptation

Arpád Dobolyi[a,*], András H. Lékó[a,b,c,1]

[a] MTA-ELTE Laboratory of Molecular and Systems Neurobiology, Department of Physiology and Neurobiology, Hungarian Academy of Sciences and Eötvös Loránd University, Budapest, Hungary
[b] Laboratory of Neuromorphology, Department of Anatomy, Histology and Embryology, Semmelweis University, Budapest, Hungary
[c] Department of Psychiatry and Psychotherapy, Semmelweis University, Budapest, Hungary

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ABSTRACT

Our knowledge on the bioavailability and actions of insulin-like growth factor-1 (IGF-1) has markedly expanded in recent years as novel mechanisms were discovered on IGF binding proteins (IGFBPs) and their ability to release IGF-1. The new discoveries allowed a better understanding of the endogenous physiological actions of IGF-1 and also its applicability in therapeutics. The focus of the present review is to summarize novel findings on the neuronal, neuroendocrine and neuroplastic actions of IGF-1 in the adult brain. As most of the new regulatory mechanisms were described in the periphery, their implications on brain IGF system will also be covered. In addition, novel findings on the effects of IGF-1 on lactation and maternal behavior are described. Based on the enormous neuroplastic changes related to the peripartum period, IGF-1 has great but largely unexplored potential in maternal adaptation of the brain, which is highlighted in the present review.

1. Introduction

Insulin-like growth factor-1 (IGF-1) regulates the development and functioning of different organs. There are 2 separate proteins structurally related to IGF-1 in mammals, IGF-2 and insulin. IGF-1 and -2 exert their actions via the IGF-1 receptor (IGF-1R), to which IGF-1 binds with higher affinity than IGF-2 (Werner and LeRoith, 2014). Insulin acts on a separate insulin receptor (IR). IGF-1R and IR are both heterotetramers made up by 2 alpha and 2 beta chains. The alpha chains bind the ligand and the beta chains trigger intracellular signaling (Pollak et al., 2004). There is a structurally different IGF-2 receptor, which binds IGF-2 and, to a lesser degree, IGF-1, too, but does not seem to have a signal transduction capability (Kelley et al., 2002) making its role enigmatic until the very day. Insulin can bind only to the insulin receptor, through which it exerts its well-established metabolic and other functions in the periphery as well as in the brain, and will not be a subject of the present review. Rather, we will focus on IGF-1 and the IGF-1R actions, and mention IGF-2 only if necessary for understanding IGF-1 actions.

IGF-1 is released into the circulation from the liver in response to growth hormone (GH) secreted predominantly from the pituitary and exerts its actions as a member of the growth hormone releasing hormone (GHRH)-GH-IGF-1 axis (Chia, 2014). As a growth-promoting hormone, it is not surprising that IGF-1 is involved in maternal alterations during pregnancy and the postpartum period. An elevated serum IGF-1 level is present in females during pregnancy (Gargosky et al., 1990), which contributes to the development of the fetus (Elhddad and Lashen, 2013). IGF-1 also plays a part in the development and maintenance of mammary gland epithelial cells during lactation (Trott et al., 2008). The brain is a target of IGF-1, too, as it can penetrate through the blood-brain barrier (Fernandez and Torres-Aleman, 2012; Werner and LeRoith, 2014). In addition, IGF-1 can be synthesized in different types of brain cells, neurons as well as glial cells, especially during brain development but also in the adult. The locally released IGF-1 may have paracrine and autocrine functions (Bondy et al., 1990). The bioavailability of IGF-1 is regulated by different IGF binding proteins (IGFBPs), which can often bind IGF-1 at very high affinity (Forbes et al., 2012). Many of the IGFBPs have been detected in different parts of the brain suggesting their involvement in neuronal function (Bondy and Lee, 1993; Lee et al., 1993). In addition, a new class of proteases, pregnancy-associated plasma proteins (PAPP-As) have been identified, which can selectively act on IGFBPs to influence their binding ability to IGF-1 (Fujimoto et al., 2017; Oxvig, 2015). Based on recent data it also

* Corresponding author at: MTA-ELTE Laboratory of Molecular and Systems Neurobiology, Department of Physiology and Neurobiology, Hungarian Academy of Sciences and Eötvös Loránd University, 1C Pázmány Péter sétány, Budapest 1117, Hungary.
E-mail address: dobolyi.arpad@ttk.elte.hu (A. Dobolyi).
[1] Department of Psychiatry and Psychotherapy, Semmelweis University, 6 Balassa utca, Budapest 1085, Hungary.

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seems likely that these proteases have regulatory proteins, the stanniocalcins (STCs). The complexity of the IGF-1 system is further enhanced by IGF-1-derived peptides, such as cyclic glycine proline (cGP), which may stimulate IGF-1 action (Guan et al., 2013). The major pathway, through which IGF-1 exerts its functions, is via the IGF-1 receptor (IGF- 1R), a transmembrane receptor possessing tyrosine kinase activity, which is widespread in the brain (Dyer et al., 2016). IGF-1 affects a variety of different neural processes including neuronal development, neuroplasticity, neuromodulation, neuroprotection, neuroendocrine control. These actions of IGF-1 will be reviewed in the present paper by also considering the complexity of the IGF-1 system where information is available on binding proteins and other IGF ligands. Furthermore, some recent data suggest that IGF-1 inhibits prolactin release as well as some aspects of active maternal care (Leko et al., 2017b). However, our knowledge is limited as to the function of IGF-1 related to the control of hormonal and behavioral changes in mothers despite the large number of established neuronal functions related to the maternal brain. Therefore, we will be discussing the IGF-1 system of the brain in a way that potential maternal implications will also be considered.

2. The IGF-1 system

IGF-1 is a small protein consisting of 70 amino acids. It is released from the liver to the circulation as a hormone while it is also expressed in various organs to have paracrine actions (Fig. 1). Its bioavailability depends on a variety of binding proteins. IGF-1 exerts its actions via the IGF-1 receptor (IGF-1R), which belongs to the growth factor receptors possessing tyrosine-kinase activity.

2.1. Signal transduction of IGF-1 receptor (IGF-1R)

The signal transduction of IGF-1R consists of 2 major pathways. The beta chain of the receptor can directly phosphorylate the adaptor protein insulin receptor substrate-1, which in turn phosphorylates the regulatory subunit of phosphoinositide 3-kinase thereby activating the enzyme to convert PIP2 to PIP3 (Giovannone et al., 2000). PIP3 binds to 2 other kinases, Akt and PDK1. Their downstream substrates include mammalian target of rapamycin, which stimulates cell growth: ribosome production and protein synthesis, and inhibits pro-apoptotic effects of Bcl-2-associated death promoter (Bad) and glycogen synthase

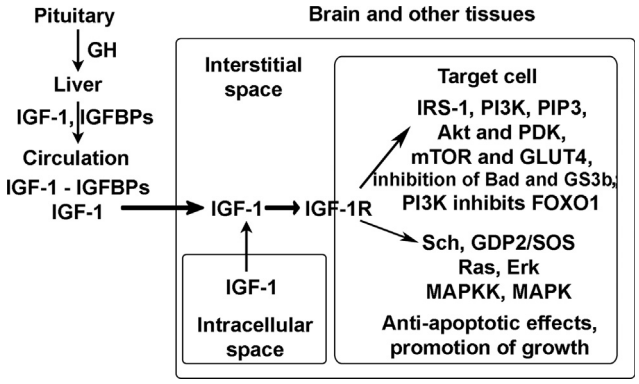

Fig. 1. The regulation of IGF-1 action. IGF-1 is produced by the liver in response to growth hormone (GH) secreted by the pituitary. IGF binding proteins (IGFBPs) and acid labile subunit (ALS) are also secreted by the liver. The majority of IGF-1 in the circulation is in tertiary complexes formed by IGF-1, IGFBP-3 and 5 and ALS. Free IGF-1 as well as IGF-1 in binary complexes formed by IGF-1 and IGFBPs can leave the circulation and enter the extravascular or interstitial space to combine with the locally released pool of IGF-1 and IGFBPs. IGF-1 can bind to IGF-1 receptor (IGF-1R) and activate the IGF-1 it to initiate its 2 major signal transduction pathways via adaptor proteins insulin receptor substrate 1 (IRS-1) and Shc.

3b, while the latter also contributes to glycogen storage (Wrigley et al., 2017). In addition, the pathway induces the GLUT4 glucose transporter and translocates it to the plasmamembrane thereby enhancing glucose uptake of neurons (Bondy and Cheng, 2004; Czech and Corvera, 1999). Phosphoinositide 3-kinase also inactivates FOXO1 transcription factor to inhibit the synthesis of additional pro-apoptotic genes (Yin et al., 2013). Phosphorylation of another adaptor protein, Sch, by the beta chain of the IGF-1R recruits the GDP2/SOS complex thereby activating the small G-protein Ras, which initiates the MAP kinase pathway. This pathway promotes growth and mitosis of cells and also has anti-apoptotic properties (Hakuno and Takahashi, 2018).

2.2. IGF binding proteins (IGFBPs) and their regulations

While insulin is released by regulated secretion, IGFs are probably exclusively released by constitutive secretion, and their bioavailability is regulated by complex extracellular reactions mediated by additional proteins, which, therefore, also belong to the IGF system (Fig. 1). There are 6 different IGF binding proteins (IGFBPs), which can bind IGF-1 and IGF-2 (but not insulin) with high affinity and are important in the regulation of their effective concentrations in the extracellular space (Jones and Clemmons, 1995), although some of them could have IGF-independent actions as well (Wheatcroft and Kearney, 2009). IGFBP-1-5 bind IGF-1 with higher affinity than IGF-2 while IGFBP-6 seems to preferentially bind IGF-2 (Forbes et al., 2012; Headey et al., 2004). Two of the IGFBPs, IGFBP-3 and 5 require a third protein, acid labile subunit (ALS) to bind IGFs (Twigg and Baxter, 1998). Since the tertiary complexes bind IGF-1 with the highest affinity, in the blood, where over 99% of IGF-1 is bound to IGFBPs, 80–90% of IGF-1 is bound to IGFBP-3 and about 10% to IGFBP-5 (Martin and Baxter, 1992). Because of the large size of ALS (85 kDa), the tertiary complexes cannot leave the circulation and represent a huge reservoir of IGF-1. Thus, in the transgenic mice without functional ALS, IGF-1 levels are very markedly reduced but lead to only mild deficits in IGF-1 actions (Boisclair et al., 2001; Ueki et al., 2000). In turn, binary complexes of IGF-1 and IGFBP-1,2,4, of which IGFBP-2 is the most abundant in the circulation, can cross the vascular epithelial border and deliver IGF-1 to the interstitial space (Binoux and Hossenlopp, 1988). The affinity of IGF-1 is higher to IGFBPs than to IGF-1R, therefore, IGFBPs are able to sequester IGF-1 and prevent it from activating the IGF-1R. Consequently, overexpression of IGFBPs typically reduces the effects of IGF-1 while in transgenic mice with reduced IGFBPs, the actions of free excess IGF-1 dominate. However, IGFBPs also stabilize IGF-1 (in plasma, the half-life of unbound IGF-1 is about 12 min, which is increased to over 12 h after binding to IGFBPs), which can increase its bioavailability in the long term (Boisclair et al., 2001). There are regulations to provoke release of IGF-1 from the complexes locally. The ability of IGFBPs to bind IGFs may be regulated by phosphorylation, glycosylation, binding to the extracellular matrix and proteolysis (Firth and Baxter, 2002; Yu et al., 1998). IGFBP-2,3,5 and 6 have been shown to interact with glycosaminoglycans, which decreases their affinity for IGF-1 thereby increasing the concentration of free IGF-1 (Fowlkes et al., 1997). However, proteolysis seems to be the most efficient regulatory process to release IGF-1 from IGFBPs (Fig. 2). There are proteases, including pregnancy-associated plasma proteins (PAPP-A and A2) named after their original discovery in the plasma of pregnant women, which are able to digest IGFBPs into an N-terminal (NT) of IGFBPs and a C-terminal (CT) protein. These IGFBP fragments cannot efficiently bind IGFs, thereby, the proteolysis releases IGF-1 from the complex (Bunn and Fowlkes, 2003). Decrease in the otherwise markedly increased serum PAPP-A level derived from the placenta during pregnancy has been used as a biochemical screening marker of Down syndrome (Bonno et al., 1994; Oxvig, 2015; Wald et al., 1992) long before it was recognized that PAPP-A is a protease almost exclusively selective for IGFBP-4 (IGFBP-2 and 5 are the only other, significantly weaker substrates) (Byun et al., 2001; Hjortebjerg, 2018; Lawrence et al., 1999).

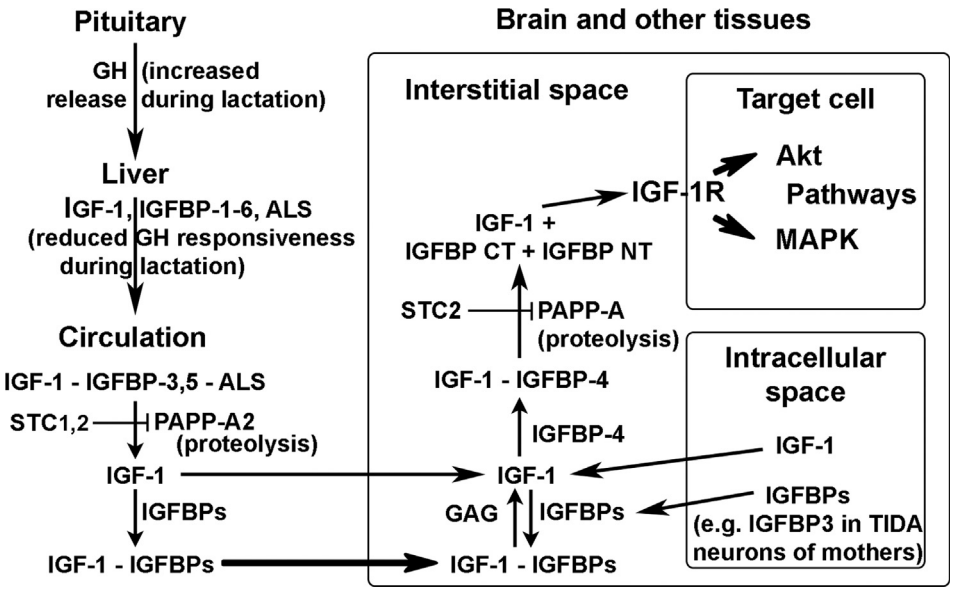

Fig. 2. A model of the regulation of IGF-1 availability. IGF-1 is produced by the liver in response to growth hormone (GH) secreted by the pituitary, processes, which are altered during lactation. The majority of IGF-1 in the circulation is in tertiary complexes formed by IGF-1, IGFBP-3 and 5 and ALS. Free IGF-1 as well as IGF-1 in binary complexes formed by IGF-1 and IGFBPs can leave the circulation and enter the extravascular or interstitial space to combine with the locally released pool of IGF-1 and IGFBPs. Proteolysis of IGFBPs e.g. by pregnancy-associated plasma proteins (PAPPs) inhibited by stanniocalcins (STCs), and also their binding to extracellular matrix proteins releases IGF-1, which can activate the IGF-1 receptor and its 2 major signal transduction systems using Akt and MAPK.

The homodimer of PAPP-A is present in a 500 kDa heterotetramer complex with eosinophil major basic protein (proMBP), which inhibits its protease activity (Gyrup et al., 2007). Since in non-pregnant individuals, the concentration of PAPP-A is much higher in the interstitial space bound to cell surfaces than in the circulation (Espelund et al., 2017), IGFBP-4 typically contributes to the release of IGF-1 rather than reducing its bioavailability as other IGFBPs do (Ning et al., 2008). Therefore, IGF-1 actions are diminished in the IGFBP-4 KO mice in sharp contrast to mice lacking all other IGFBPs (Hjortebjerg, 2018). Recently, a structurally related (46% sequence homology) other extracellular protease, also synthesized in a number of organs and also present in the plasma of pregnant women, PAPP-A2 was discovered and characterized: it is selective for IGFBP-3 and 5 (Overgaard et al., 2001). PAPP-A2 KO mice or patients with PAPP-A2 deficiency have increased total but reduced free IGF-1 (Andrew et al., 2018). Thus, the main function of PAPP-A2 could be to allow IGFs to leave the circulation (Fujimoto et al., 2017). The activity of these proteases can be regulated by a new class of proteins, stanniocalcins (STC). STCs are named after the corpuscle of Stannius, an endocrine gland associated with the kidney of fish where they participate in calcium homeostasis (Wagner et al., 1986), an ability probably lost in mammals. Instead, STCs are widely expressed in different organs (Yeung et al., 2012), STC1 can bind to several different proteases including PAPP-A to inhibit their activity (Kloverpris et al., 2015) while STC2 has similar, but more specific action as it blocks the activity of PAPP-A and PAPP-A2 (Jepsen et al., 2015). IGF-1 actions are increased in the absence of STC2 (Chang et al., 2008) without any change in plasma IGF-1 level suggesting locally restricted actions of the protease inhibitors. Given the importance of STCs and the relative scarcity of available information, more data on the role of STCs in the regulation of IGF-1 action is expected in the future.

2.3. Alternative forms and degradation products of IGF-1

IGF-1 has an alternatively spliced form discovered in muscle and therefore called Mechano growth factor (MGF). It is induced in muscle (and bone and tendon) following muscle stress and damage and results in muscle cell proliferation (Dai et al., 2010; Rigamonti et al., 2009). MGF was found in neurogenic areas of the brain and its levels declined with age. MGF overexpression significantly increased the number of proliferative cells in the dentate gyrus of the hippocampus and subventricular zone but did not alter the distribution of adult newborn neurons at post-mitotic stages (Tang et al., 2017). In addition, MGF was also found to be neuroprotective after brain ischemia (Dluzniewska et al., 2005), for dopaminergic neurons in the midbrain (Quesada et al., 2009) and for motoneurons (Aperghis et al., 2004). Despite these data on some effects of MGF, its regulation and functions remain elusive.

Finally, IGF-1 can be enzymatically split into a smaller protein, des-(1-3) IGF-1 and its N-terminal tripeptide glycine-proline-glutamate (GPE) (Yamamoto and Murphy, 1995). The protein product des-(1-3) IGF-1 can activate the IGF-1R but cannot bind to IGFBPs. Thus, it contributes to the active pool of IGF-1 and is also a useful experimental tool for the investigation of the effects of IGF-1. GPE, and its derivative *cyclo*-glycyl-proline (cGP), an endogenous diketopiperazine are also affecting IGF-1 actions although they cannot bind to the IGF-1R. Rather, they are able to enhance the bioavailability of IGFs by competitive binding to IGFBPs (Guan et al., 2014). Given the relatively poor central uptake of IGF-1 and its mitogenic potential limiting its clinical translation, the smaller peptide derivatives and their synthetic analogues (e.g. *cyclo*-L-glycyl-L-2-allylproline or NNZ-2591) offer useful experimental and possibly therapeutic tools in the future (Guan et al., 2013).

3. Expression, secretion and brain functions of the IGF-1 system

3.1. Regulation of the IGF-1 system by growth hormone (GH)

The originally discovered function of IGF-1 was its growth-promoting action as part of the growth hormone (GH) system (Murphy et al., 1987). GH releasing hormone (GHRH) cells, located in the arcuate nucleus of the hypothalamus, release GHRH into the blood vessels of the median eminence, which stimulates the synthesis and secretion of GH from the pituitary into the circulation. While GH itself has a number of direct actions in different organs including the mammary gland (Trott et al., 2008), most if its effects are exerted via IGF-1 released from the liver in response to GH (Chia, 2014). IGF-1 also participates in the negative feedback stabilizing GH levels by inhibiting GHRH neurons and also by stimulating somatostatin neurons located in the periventricular hypothalamic nucleus (Berelowitz et al., 1981; Sato and Frohman, 1993; Uchiyama et al., 1994), which in turn secrete the GH inhibitory hormone somatostatin into the median eminence to inhibit the secretion of GH from the pituitary (Morisset, 2017). In addition to IGF-1, the majority of IGFBP1-6 and ALS in the circulation are also synthesized by the liver (Boisclair et al., 2001). Of them, GH can stimulate most effectively the synthesis and secretion of IGFBP-3 and ALS (Baxter and Dai, 1994).

Although IGFs, IGFBPs, and ALS are typically synthesized in the

liver, they are also produced in local tissues. In most cases, the relative contributions of locally expressed IGF-1 and IFGBPs compared to that derived from the circulation remain elusive (Jones and Clemmons, 1995; Wheatcroft and Kearney, 2009). IGF-1 and IGFBP production in organs other than the liver may not be regulated by GH, although the role of systemic or locally produced GH cannot be excluded from the regulation of local IGF-1 synthesis and should be investigated individually in each organ (Harvey, 2010). Particularly in the brain, the effects of GH was not significant on the local IGF-1 synthesis investigated by administering GH to hypophysectomized rats (Murphy et al., 1987) even though GH receptors are present in the brain based on immunolabeling and in situ hybridization histochemistry (Lobie et al., 1993) as well as by visualization of its signal transduction (Furigo et al., 2017). GH itself, has also been shown to be synthesized in different regions of the brain including hypothalamus and hippocampus (Harvey, 2010; Tang et al., 2011). Although the role of locally synthesized GH is not very well known, in the hippocampus, a significant increase in GH but not in IGF-1 expression was found following kainic acid treatment suggesting a neuroprotective function of the locally produced GH independent of IGF-1 (Arellanes-Licea et al., 2018).

3.2. The expression of IGF-1 and its receptor in the brain

In the present chapter, we describe the presence and distribution of members of the IGF-1 system in the normal brain. Pathological or transgenic overexpression related to normal function may be mentioned occasionally, however, the well-established induction of the IGF-1 system in brain tumors (Dmitrenko et al., 2011) is beyond the scope of the present review. The synthesis of IGF-1 and its receptor has been demonstrated in different brain regions, and also in different cell types including neurons, astrocytes and oligodendrocytes (Wrigley et al., 2017). In contrast, IGF-2 is mostly expressed in mesenchymal cell types, the meninges and the choroid plexus (Werner and LeRoith, 2014). The abundance of IGF-1 was the highest in the developing olfactory bulb, cerebellum, hippocampal, and midbrain regions (Aguado et al., 1993; Bach et al., 1991; Bartlett et al., 1991) while also present in the hypothalamus (Niblock et al., 1998; Yamaguchi et al., 1990). IGF-1R has a generally similar widespread distribution pattern in the brain with occasional differences from that of IGF-1 at higher magnification suggesting expression in different types of neurons in the same brain area (Bondy et al., 1992). An electron microscopic study revealed that IGF-1R is present both pre- as well as postsynaptic structures of neurons (Garcia-Segura et al., 1997). There is a marked change in the expression level of IGF-1 but less so for IGF-1R during ontogeny as the amount of expressed IGF-1 increases until the end of the second postnatal week in rats and decreases thereafter (Bondy et al., 1990). Since IGF-1R level remains high in adulthood, it has been suggested that IGF-1 of plasma origin can act on these receptors physiologically. Indeed, IGF-1 was shown to cross the blood brain barrier (Reinhardt and Bondy, 1994) via a receptor-mediated transport process (Fernandez and Torres-Aleman, 2012; Werner and LeRoith, 2014). It is not known whether IGF-1, complexed with IGFBPs without ALS, can enter the brain parenchyma from the circulation as it does in other tissues. In turn, it was shown that neuronal activity drives localized blood-brain-barrier transport of serum IGF-1 into the CNS (Nishijima et al., 2010). The entry of peripheral IGF-1 may have several different functions discussed later. In addition, IGF-1 may inhibit its own expression and the expression of IGF-1R in all types of brain cells (Trueba-Saiz et al., 2016).

3.3. The expression of IGFBPs and their regulators in the brain

IGFBPs are also expressed in the brain although not uniformly. IGFBP-2, 4 and 5 have been shown to be present to the largest extent (Werner and LeRoith, 2014) while IGFBP-1 is probably not expressed in the brain (Han et al., 1996). IGFBP-2 gene expression is localized in astroglia, with a distribution similar to that of IGF-1 in sensory relay centers but not in other parts of the brain. Similarly to IGF-1, IGFBP-2 expression is greatly reduced throughout the brain by the third week after birth in rats (Lee et al., 1993). Neuronal expression of IGFBP-2 may also be induced following injury of the brain, to a larger extent than other IGFBPs (Beilharz et al., 1998). IGFBP-2 is mostly expressed in astrocytes but not in microglia where IGFBP-2 was not detected (Fletcher et al., 2013) as opposed to IGF-1, which is induced in microglia following brain injury (Beilharz et al., 1998; Woods et al., 1998). The mechanism of induction may be via depolarization involving NMDA receptor (Holmin et al., 2001). IGFBP-3 has a highly restricted expression pattern in the brain, which explains why its expression can be overlooked when large brain areas are investigated under basal conditions (Shimasaki et al., 1989). However, a study focusing on the effect of hypoxia described IGFBP-3 expression in the cerebral cortex and thalamus (Lee et al., 1999). In the hypothalamus, where a more detailed mapping was performed, it is expressed in the medial preoptic area, the paraventricular and arcuate nuclei (Leko et al., 2017b). The ontogenic development of IGFBP-3 has not been described yet. However, 2 microarray studies suggested that IGFBP-3 may be induced in the hypothalamus during maternal care (Dobolyi, 2009; Driessen et al., 2014; Gammie et al., 2016; Leko et al., 2017b). The increased mRNA level of IGFBP-3 was confirmed using qRT-PCR in the hypothalamus, and subsequent in situ hybridization histochemistry revealed that IGFBP-3 is induced in the medial preoptic area and the arcuate nucleus but not in the paraventricular nucleus in mother rats (Leko et al., 2017b). While the potential function of this activation of IGFBP-3 will be discussed later in the present review, it should be noted that our knowledge is limited as to the mechanism of the induction of IGFBP-3. It is clearly possible that hormonal changes, such as altered estrogen, or prolactin levels are responsible for the induction but direct neuronal inputs from the pups cannot be excluded either.

IGFBP-4 is abundantly expressed in the cerebral cortex and hippocampus, mostly in large projection neurons but not in the diencephalon (Stenvers et al., 1994). IGFBP-4 may also be expressed in choroid plexus and meninges, the basal ganglia, the cerebellum and a few hindbrain structures including the inferior olive (Brar and Chernausek, 1993; Kang et al., 2008).

IGFBP-5 gene expression is also highly abundant during brain development and demonstrates significant spatiotemporal correlation with IGF-1 (Cheng et al., 1996), but exhibits a neuroanatomical distribution that is distinct from IGFBP-2 (Green et al., 1994) and IGFBP-4 (Stenvers et al., 1994). Colocalization in some brain regions and paralocalization with IGF-1 in other sites suggests the potential for autocrine and paracrine interaction between the binding protein and IGF-1 in different settings (Bondy and Lee, 1993). The relationship between brain IGF-1 and IGFBP-5 was further supported by the finding that IGF-1 regulates the expression level of IGFBP-5 in the brain (Ye and D'Ercole, 1998). Altogether, it is unfortunate for neuroendocrinological studies of IGFBP-2 and 5 that these proteins, although present in the hypothalamus based on figures of in situ hybridized sections, was not analyzed in this part of the brain in the original papers focusing on their more abundant level in the olfactory bulb, cortex, hippocampus and thalamus (Bondy and Lee, 1993; Lee et al., 1993).

IGFBP-6 has an expression largely restricted to the trigeminal ganglia in early postnatal age (Naeve et al., 2000). After postnatal day 21, however, its expression increases in primarily GABA-ergic neurons of the forebrain, as well as in the cerebellum, and hindbrain and spinal cord areas associated with sensorimotor function of the cerebellum (Naeve et al., 2000).

The brain distribution of other components of the IGF-1 system, such as ALS, PAPPs, STCs have not been investigated in detail. The expression of STC has been reported in neurons both in basal conditions (Franzen et al., 2000) and following brain injury (Zhang et al., 2000). The Allen Mouse Brain Atlas suggests that PAPP-A2 is expressed in the thalamus, midbrain and cerebellum (Atlas, 2004). It is obvious that given the recent expansion of the IGF system, and their likely

involvement in neuronal processes, their distribution awaits further, more detailed investigations.

3.4. The presence of the IGF-1 system in the pituitary

The distribution of the IGF-1 system in the pituitary is also relevant to its neuroendocrine functions. In the pituitary, IGF-1 mRNA is expressed by nonendocrine folliculo-stellate cells (Bach and Bondy, 1992) and also by somatotrophs (Honda et al., 1998) regulated by GH (Honda et al., 2003) and corticotrophs (Eppler et al., 2007). In the latter cell types, the presence of IGF-1 was demonstrated in adrenocorticotropin-containing vesicles at the ultrastructural level suggesting co-release of the hormones (Eppler et al., 2007). IGFBP-2, -4, and -5 were abundant in the neural lobe (Bach and Bondy, 1992). In the anterior lobe, IGFBP-5 was the most abundant while other types of IGFBPs were not present or only diffusely present with low abundance in scattered cells (Bach and Bondy, 1992). IGFBP-5 was also expressed in precursors of hormone-secreting cells suggesting its developmental function (Holley et al., 2002). Other IGFBPs may also participate in developmental processes as they change their expression level postnatally (Gonzalez-Parra et al., 2001). IGF-1 receptor mRNA was abundant and homogeneously distributed in the anterior lobe overlapping with somatotrophs and corticotrophs (Honda et al., 1998) while lower levels of IGF-1R was present in other cell types, too, suggesting the possibility that IGF-1 may be able to affect different types of secretory neurons in the pituitary (Bach and Bondy, 1992; Eppler et al., 2007). IGF-1R was located in the plasmamembrane of somatotrophs and corticotrophs suggesting functional receptors (Eppler et al., 2007). Functional studies demonstrated that IGF-1 suppresses GH expression (Uchiyama et al., 1994) but stimulates the expression of proopiomelanocortin (Honda et al., 2003). In the absence of IGF-1, GH cells had reduced size but increased GH mRNA levels while IGF-1 increased prolactin expression and plasma levels (Stefaneanu et al., 1999).

3.5. The effect of IGF-1 on the size of the body and brain

IGF-1 has a profound role in the growth of the organism as best demonstrated by human data implicating mutations in several members of the IGF system in the length of the stature (Marouli et al., 2010). Data from transgenic mice altering the function of different members of the IGF system are also consistent with the effect of IGF system on the size of the animals. However, developmental roles of IGF-1 are generally not the topic of the present review, therefore, we refer to excellent reviews in the field (Aberg, 2003; O'Kusky and Ye, 2012). Most importantly, individuals with mutations or partial deletion in the IGF-1R exhibit reduced postnatal growth resistant to IGF-1 treatment while mice with reduced IGF-1 actions (IGF-1 KO, IGF-1R KO, PAPP-A2 KO, STC2 KO or overexpression of binding proteins) have reduced body size. In turn, overexpression of IGF-1 or STC2 in mice leads to increased body size. A similar action is also evident as far as the brain is concerned because mice overexpressing IGF-1 possess with enlarged brains while overexpressing IGFBPs reduced brain size, in some cases to disproportionally small even as compared to the body size (Chang et al., 2008; Liu et al., 1993; Modric et al., 2001; Murphy, 2000; Trejo et al., 2005).

3.6. The effect of IGF-1 on adult neuroplasticity

IGF-1 is involved in different forms of neuroplasticity in adult animals (Wrigley et al., 2017). Since its expression declines postnatally but remains the highest in the dentate gyrus and the subventricular zone (Bondy and Cheng, 2004; Bondy et al., 1990), it has been suggested that IGF-1 plays a role in adult neurogenesis characteristic of these brain regions (Lepousez et al., 2015). Hippocampal progenitor cells indeed possess IGF-1R, through which adult neurogenesis is promoted in the dentate gyrus (Aberg et al., 2006; Carlson and Saatman, 2018; Pardo et al., 2016).

IGF-1 may also be involved in the neuroplastic regulation of dendritic spines. For example, IGF-1 was shown to mediate the exercise-induced increase in the density of dendritic spines (Trejo et al., 2008) as anti-IGF-1 antibody treatment prevented the running-induced increase in spine density on basal dendrites of CA1 pyramidal cells (Glasper et al., 2010). Furthermore, IGF-1 increased glutamatergic neurotransmission by enhancing the expression of components of voltage-gated calcium channels and/or AMPA and NMDA glutamate receptors (Blair et al., 1999). IGF-1 was also necessary to long-term potentiation (LTP) of synaptic strength in the hippocampus and medial prefrontal cortex (Burgdorf et al., 2015). In general, IGF-1 has a tendency to enhance excitatory neurotransmission (Dyer et al., 2016).

Apart from the above discussed physiological neuroplasticity, IGF-1 may also be involved in the neural regeneration of the injured brain. Overexpression of IGF-1 protected against neuron loss and behavioral effect of traumatic brain injury, multiple sclerosis, amyotrophic lateral sclerosis, and stroke. Potential mechanisms of neuroprotective effect of IGF-1 include anti-apoptotic property, promoting remyelinization, neurite outgrowth, and dendritic arborization as well as its ability to increase the transport of glucose thereby alleviating local hypoglycemia resulted from the injury (Russo et al., 2004). However, as these brain injuries are not the topic of the present paper, we refer to excellent reviews in the field (Aberg et al., 2006; Costales and Kolevzon, 2016; O'Kusky and Ye, 2012).

3.7. The effect of IGF-1 on aging and cognitive functions

Pituitary secretion of GH as well plasma IGF-1 levels decline with age (Junnila et al., 2013). IGF-1 action may also be reduced in the brain as the density of IGF-1R decreases with age in the hippocampus (Sonntag et al., 1999). Furthermore, higher IGF-1 levels were correlated with better perceptual motor performance, information processing and fluid intelligence (Aleman et al., 2001), and general cognitive functions (Rollero et al., 1998) although not in all studies (Papadakis et al., 1996). Mice studies also suggested that IGF-1 can ameliorate age-related deficits in memory assessed by object recognition and Morris water-maze (Markowska et al., 1998). In agreement with these findings, mice with reduced IGF-1 actions showed impaired memory, e.g. astrocyte-specific knockout of IGF-1R induced impairments in working memory (Logan et al., 2018). Different neuroprotective mechanisms including increased blood flow, glucose utilization, neurogenesis, and NMDA receptor density have been suggested (Wrigley et al., 2017). In addition to direct protective effects on neurons, the effect of IGF-1 could also be mediated by anti-inflammatory actions on astrocytes and microglia (Labandeira-Garcia et al., 2017). Furthermore, IGF-1 seems to be protective in Alzheimer's disease, too. IGF-1 contributes to the clearance of Abeta plaques (Bates et al., 2009; Piriz et al., 2010). In turn, blockade of the IGF-1R led to the appearance of amyloid plaques and cognitive decline (Carro et al., 2006) while IGF-1 administration has been shown to improve memory in patients with Alzheimer's disease (Zemva and Schubert, 2014).

Based on the growth-promoting, cognition-enhancing and neuroprotective actions of IGF-1, it was assumed that IGF-1 action would delay aging and prolong the lifespan of the animals. However, heterozygous IGF-1R KO mice (homozygous KO die after birth due to lung failure) had a longer lifespan than wild type littermates probably due to better resistance to oxidative stress (Holzenberger et al., 2003; Kappeler et al., 2008) while an overrepresentation of heterozygous mutations in the IGF-1R gene associated with high serum IGF-1 levels and reduced activity of the IGF-1R was identified among human centenarians (Suh et al., 2008).

3.8. Interaction of IGF-1 with the reproductive neuroendocrine system

IGF-1, as an effector of the GH axis inhibits the synthesis and

Table 1
The established neuronal functions of IGF-1 and their related potential roles in mothers.

	Established role of IGF-1	Maternal action/alteration with potential role of IGF-1 elevated during pregnancy and diminished after parturition
Size of the body	Increase of the size of the body (Aberg, 2003; Marouli et al., 2010; O'Kusky and Ye, 2012)	Increase of the size of newborn offspring (Bowman et al., 1991; Elhddad and Lashen, 2013; Gargosky et al., 1990; Monaghan et al., 2004; Tarantal and Gargosky, 1995)
Size of the brain	Defect in the IGF system causes reduced brain size (Chang et al., 2008; Liu et al., 1993;Modric et al., 2001;Murphy, 2000; Trejo et al., 2005)	There is a temporal reduction in the size of female brain during pregnancy (Hillerer et al., 2014; Hoekzema et al., 2017; Oatridge et al., 2002)
Adult neurogenesis	Promotes neurogenesis in the dentate gyrus (Carlson and Saatman, 2018; Lepousez et al., 2015; Pardo et al., 2016; Wrigley et al., 2017)	Reduced neurogenesis in the early postpartum period (Leuner et al., 2007; Leuner and Sabihi, 2016; Pawluski and Galea, 2007). We suggest a so far not reported role of IGF-1 in maternal neurogenesis
Dendritic morphology	Increases synaptic strength and the density of dendritic spines (Glasper et al., 2010; Trejo et al., 2008)	Cellular morphological changes e.g. in hippocampus and hypothalamus (Grattan, 2015; Leuner and Gould, 2010; Pawluski et al., 2016; Theodosis and Poulain, 2001). We suggest a so far not reported role of IGF-1 in mothers
Cognitive functions	Increases cognitive functions and memory in old animals (Aleman et al., 2001; Bates et al., 2009; Carro et al., 2006; Labandeira-Garcia et al., 2017; Logan et al., 2018; Markowska et al, 1998; Papadakis et al., 1996; Piriz et al., 2010)	Elevated memory and cognition in early pregnancy, their impairment in late pregnancy and the first week of lactation, elevated executive functions in long term (Albin-Brooks et al., 2017; Cost et al., 2014; Kinsley et al., 1999; Leuner and Gould, 2010). We suggest a so far not reported role of IGF-1
Reproductive hormones	Promotes puberty via action on GnRH neurons, decline in IGF-1 causes subfertility with reduced luteinizing hormone (Divall et al., 2010; Froment et al., 2002; Frystyk et al., 1999; Pazos et al., 1999; Rodriguez et al., 2013; Sun et al., 2011; Wolfe et al., 2014)	Reduced postpartum IGF-1 (Rhoads et al., 2004) could contribute to lactational anestrus. We suggest a so far not reported role of IGF-1 in the control of lactational anoestrus
Prolactin release	Promote the development and survival of dopaminergic neurons (Ayadi et al., 2016; Hereñú et al., 2007; Kim et al., 2014; Li et al., 2017; Quesada et al., 2007)	Prolonged IGF-1 treatment reduced suckling-induced prolactin release and maternal motivation (Leko et al., 2017a,b)
Depression	Antidepressants increase IGF-1 level, IGF-1 may be protective against depression (Basta-Kaim et al., 2014; Burgdorf et al., 2015; Duman et al., 2009; Hoshaw et al., 2005; Khawaja et al., 2004; Mitschelen et al., 2011; Park et al., 2011; Schilling et al., 2011; Trojan et al., 2016)	We propose that postpartum reduction in IGF-1 level could contribute to the vulnerability of mothers to depression

secretion of GH with a negative feedback action. In addition, it has also been suggested to affect the gonadotropin-releasing hormone (GnRH) neurons (Wolfe et al., 2014). IGF-1 expression in the hypothalamus is enhanced during puberty while IGF-1 administration results in precocious puberty (Hiney et al., 1996). Most importantly, intracerebroventricular infusion of an antibody to IGF-1 in rats delayed the onset of puberty (Pazos et al., 1999), which was also found in mice lacking IGF-1R in GnRH neurons (Divall et al., 2010). Physiologically, IGF-1 may mediate the effect of fasting on puberty as IGF-1 levels are reduced following fasting even if not as fast as insulin levels (Frystyk et al., 1999) while IGFBP-3 levels increased thereby further limiting the bioavailability of IGF-1 (Powolny et al., 2008). In addition to puberty, IGF-1 may also play a role in the female cycling and fertility. Since the IGF system is also present in the gonads, one should be cautious when interpreting subfertility of mice with altered brain IGF-1 actions. For example, IGF-1 KO mice are infertile due to gonadal effects (Liu et al., 1993). However, mice overexpressing IGFBPs are often subfertile and also demonstrate reduced luteinizing hormone (LH) levels (Froment et al., 2002). Even more importantly, a decline of brain IGF-1 was shown to contribute to impaired estrous cycling in older rats as long-term IGF-1 gene therapy in the mediobasal hypothalamus of middle-aged female rats extended regular cyclicity and preserved ovarian structure (Rodriguez et al., 2013). To perform these actions, IGF-1 could act directly on the GnRH neurons as they possess IGF-1R (Miller and Gore, 2001). Indeed, IGF-1 increased GnRH neuronal activation in vivo (Sun et al., 2011) and GnRH release from GnRH neurons in vitro (Anderson et al., 1999). However, an indirect action via kisspeptin neurons is also possible (Hiney et al., 2009). Furthermore, it is likely that prolonged exposure to IGF-1 is necessary for these actions as short exposure to IGF-1 did not affect GnRH neurons (Weiss et al., 2006). Altogether, the effects of IGF-1 on GnRH neurons increase estrogen levels. Therefore, it is particularly interesting that many of the actions of IGF-1 are exerted in conjunction with estrogen. A concerted action of IGF-1 and estradiol underlies sex differences in mood regulation by exercise (Munive et al., 2016). Antagonism of brain IGF-1 receptors blocked the effect of estradiol on memory and the level of synaptic proteins in the hippocampus (Nelson et al., 2014). In turn, blockade of estrogen receptor prevented the effect of IGF-1 on adult neurogenesis (Takeuchi et al., 2015). Furthermore, estradiol promoted the differentiation of embryonic stem cells into dopamine neurons via cross-talk between IGF-1 and estrogen receptor beta (Li et al., 2017). Midbrain dopaminergic neurons possess both estrogen and IGF-1 receptors (Quesada et al., 2007), and it was proposed that IGF-1 and estrogen may interact at the level of Akt during their signal transduction (Dyer et al., 2016). The effect of IGF-1 on other neuroendocrine systems is less well established but cannot be excluded. One candidate is the prolactin system, which is regulated by dopaminergic neurons in the mediobasal hypothalamus (Grattan, 2015) as dopamine neurons may be affected by IGF-1 (Ayadi et al., 2016; Hereñú et al., 2007; Kim et al., 2014; Rodriguez-Perez et al., 2016).

4. Possible maternal alterations and functions of IGF-1

4.1. GH resistance of IGF-1 release

There are 2 conditions, fasting, and lactation when GH loses its ability to secrete IGF-1 from the liver (Beauloye et al., 2002; Escalada et al., 1997), a state termed "GH resistance" (Donaghy and Baxter, 1996), which is likely a consequence of the reduction in the abundance of GH receptors in hepatocytes (Kobayashi et al., 1999) resulting in reduced IGF-1 levels in the circulation (Arellanes-Licea et al., 2018; Barber et al., 1992). Based on positive correlations between plasma IGF-1 concentrations and hepatic IGF-1 mRNA levels, the peripartum drop in plasma IGF-1 may be a consequence of reduced production of IGF-1 in liver (Wook Kim et al., 2004). It is not established yet if the effect of lactation on the general uncoupling of IGF-1 release from GH is exerted via the negative energy balance created by milk production or is mediated by a different mechanism. A possible mechanism may involve a feedback inhibitor of action induced by cytokines, suppressors of cytokine signaling (SOCS)-2, which inhibits IGF-1 synthesis by reducing STAT5b, a central element of the signal transduction of GH (Waters, 2003). In that regards, it is interesting to mention that estrogens can

induce SOCS2, which may be the mechanisms how estrogens suppress growth (Leung et al., 2003).

4.2. The involvement of IGF-1 in the control of maternal brain size changes

The size of the female brain as well as the grey matter volume decreases in relation to pregnancy in a reversible process (Hoekzema et al., 2017; Oatridge et al., 2002). The mechanism of this process is not known yet. Apart from maternal hormones, such as estrogen or prolactin, the role of growth factors including vascular endothelial growth factor and placental growth factor have been suggested (Hillerer et al., 2014). It is surprising that the IGF system has not been hypothesized so far as a factor in the process as we believe it is a plausible candidate (Table 1).

4.3. Maternal influence on the size of the offspring via the IGF-1 system

A maternally relevant developmental function of IGF-1 is the one the mothers convey to the growth of their offspring during pregnancy. IGF-1 as well as IGFBP-1 and 3 are increased both in mothers during pregnancy as well as in the fetus (Gargosky et al., 1990; Monaghan et al., 2004; Tarantal and Gargosky, 1995). Maternal increases of the IGF system result from placental GH secreted by the syncytiotrophoblast (McIntyre et al., 2009). Since IGF-1 cannot cross the placenta (Wang et al., 1991), it has been a debate for decades if the effect of IGF-1 on the development of the fetus is exerted by maternal IGF-1 or IGF-1 of the fetus (Elhddad and Lashen, 2013). However, IGF-1 level of the fetus correlates better with the size of the newborn, it was suggested that fetal IGF-1 has a direct role in the growth of the fetus (Bowman et al., 1991) while the maternal increase in the IGF-1 level during pregnancy has only an indirect role, e.g. by stimulating amino acid uptake by the placenta (Karl, 1995).

Mothers might continue to influence the development of their offspring via IGF-1 after parturition. Apart from the effect of the nutritional value of milk, it was also shown to contain IGF-1 as well as *cyclo*-glycyl-proline (cGP), the derivative of IGF-1 known to increase free IGF-1 by inhibiting its binding to IGFBPs (Guan et al., 2014). IGF-1 content in the milk was demonstrated to contribute to the novelty recognition of the developing offspring (Singh-Mallah et al., 2016). IGF-1 was also found necessary for the visual input-driven development of the visual cortex, which was inhibited with IGF-1R antagonists (Ciucci et al., 2007). Thus, apart from the direct transfer of IGF-1 through milk, it would be also interesting to examine if maternal inputs, e.g. the suckling stimulus can induce elevated IGF-1 level in the pups.

4.4. The suggested role of IGF-1 in neuroplastic changes in mothers

The most profound neuroplastic changes of the adult mammalian brain are expected in relation to maternal adaptations to ensure the survival of the offspring (Barba-Muller et al., 2018; Hillerer et al., 2014). As far as adult neurogenesis, it has been reported that cell proliferation in the dentate gyrus is reduced during early postpartum period in the rat (Leuner et al., 2007; Leuner and Sabihi, 2016; Pawluski and Galea, 2007). This is a period when IGF-1, known to enhance cell proliferation, has a generally low serum level. Therefore, it is plausible that the decreased postpartum IGF-1 could contribute to the reduction of cell proliferation in the postpartum period.

Other forms of neuronal plasticity, such as synaptic and dendritic morphology, gene expressional changes also take place in the brain maternal circuitry during pregnancy and the postpartum period (Pawluski et al., 2016; Pereira, 2016). For example, the pattern of hypothalamic input is altered in mothers, which contributes to the hyporesponsiveness of the hypothalamic-pituitaryadrenal axis, oxytocin and prolactin secretion (Cservenak et al., 2017; Cservenak et al., 2013; Douglas et al., 1998). The cellular morphological changes are best described for the oxytocin neurons in mothers (El Majdoubi et al., 1996; Theodosis and Poulain, 2001) but morphological changes have been reported in other brain regions, e.g. the hippocampus (Leuner and Gould, 2010; Pawluski and Galea, 2006) and the auditory cortex (Elyada and Mizrahi, 2015) as well. Neuroplastic changes have also been reported for dopaminergic cells of the arcuate nucleus, a cell type responsible for prolactin release from the pituitary (Grattan, 2015). In addition, extensive gene and protein expressional changes in mothers have also been reported in the cerebral cortex and the hypothalamus (Gammie et al., 2016; Udvari et al., 2017; Volgyi et al., 2017). Based on the extensive maternal alterations of the brain, we propose the hypothesis that IGF-1 may participate in some of the maternal neuroplastic changes.

4.5. IGF-1 might contribute to cognitive changes in mothers

It has been a debate on how the cognitive abilities of mothers change during pregnancy and lactation. Overall evidence suggests that spatial cognition and reference memory are increased during early pregnancy but impaired in late pregnancy and during the first week of lactation in rats when a dam has to stay a lot in the nest (Darnaudery et al., 2007; Hillerer et al., 2014) while spatial memory as well as executive functions are elevated later on to boost the ability of the mother to forage and protect the young (Albin-Brooks et al., 2017; Cost et al., 2014; Kinsley et al., 1999; Leuner and Gould, 2010). It has not been examined how IGF-1 increasing gradually during pregnancy and then declining in the postpartum period may contribute to the cognitive changes of mothers. In turn, mothers, especially multiparous mothers have been shown have increased possibility for Alzheimer's disease (Jang et al., 2018), in which the role of the IGF system has not been investigated yet, either.

4.6. The effect of IGF-1 on prolactin secretion in mothers

Prolonged infusion of IGF-1 into the cerebral ventricle using osmotic minipumps in the postpartum period markedly inhibited prolactin release. The peak of suckling-induced prolactin level reduced about 60% in the presence of IGF-1 as opposed to controls and the weight gain of suckled pups was also significantly lower (Leko et al., 2017a). The high IGF-1 level is not a natural situation for the mothers in the postpartum period because, interestingly, serum IGF-1 levels are about 70% reduced during early lactation as compared to late pregnancy (Rhoads et al., 2004), as are IGFBP-3 and ALS levels, too (Holman and Baxter, 1996; Kim et al., 2006). During lactation, GH mRNA level is reduced in the pituitary (Arellanes-Licea et al., 2018), still, suckling can evoke a marked GH release (Terry et al., 1977; Wehrenberg and Gaillard, 1989), which results in some temporal increase in IGF-1 level: IGF-1 level is doubled at its peak at 30 min following the onset of suckling as compared to basal postpartum levels (Leko et al., 2017a). This relatively small increase following suckling and the generally low IGF-1 levels during lactation (Barber et al., 1992) are probably due to the GH unresponsiveness of the liver IGF-1 production. The state of GH resistance during lactation is characterized with a generally low IGF-1 level and elevated GH levels (Beauloye et al., 2002; Escalada et al., 1997). The elevated GH levels are due to its suckling-induced release and possibly also to the low IGF-1 level, which minimizes the negative feedback action on GH secretion. While suckling-induced GH release is required for proper lactation (Madon et al., 1986), the smaller increases in serum IGF-1 level following suckling may also be necessary to maintain increased blood flow to the mammary gland and milk synthesis (Prosser and Davis, 1992; Prosser et al., 1996), and to allow prolactin release from the pituitary lactotrophs (Fruchtman et al., 2002; Hikake et al., 2009; Stefaneanu et al., 1999).

Although experimental evidence is available for the inhibition of prolactin release by IGF-1 during the postpartum period, it is very possible that such inhibitory influence is present during pregnancy as well, when serum IGF-1 levels are elevated (Gargosky et al., 1990). In

rats, prolactin secretion is absent from about the 10th day of pregnancy, primarily due to placenta-derived prolactin (Grattan, 2015). It is, however, conceivable that elevated IGF-1 may also contribute to the cessation of pituitary prolactin secretion at the level of the hypothalamus.

The mechanism how IGF-1 inhibits prolactin release may be via stimulation of the tuberoinfundibular dopaminergic neurons located in the mediobasal hypothalamus. These neurons release dopamine into the median eminence to inhibit prolactin release from the pituitary as the major hypothalamic regulatory cells of prolactin secretion (Grattan, 2015). IGF-1 has been shown to promote the development and survival of different neuronal cell types, described in chapter 8, including dopaminergic neurons (Ayadi et al., 2016; Kim et al., 2014; Rodriguez-Perez et al., 2016). In fact, IGF-1 gene therapy in defected female rats reversed their hypothalamic dopamine dysfunction and hyperprolactinemia (Hereñú et al., 2007) probably via IGF-1R known to be present in the arcuate nucleus (Garcia-Segura et al., 1997). It has also been demonstrated that the expression of tyrosine hydroxylase (TH), the rate-limiting enzyme of dopamine synthesis (Tekin et al., 2014), is increased by the prolonged IGH-1 treatment in vivo in the arcuate nucleus of mothers (but not in the A13 cell group of the zona incerta), as well as in vitro in mediobasal hypothalamic primary cell culture (Leko et al., 2017b). Furthermore, phosphorylation of TH was also increased by IGF-1 at the 31 Ser site (Leko et al., 2017b) known to increase the activity of TH (Haycock et al., 1992). The TH site of phosphorylation was specific as phosphorylation at 40 Ser was not enhanced by IGF-1 treatment.

IGF-1 may also exert some neuroendocrine actions at the level of the pituitary, too. While inhibiting GH secretion as part of a negative feedback loop, it was shown to have a trophic action on lactotroph cells (Hikake et al., 2009; Stefaneanu et al., 1999) suggesting that elevated prolactin release requires IGF-1 action. Such action of IGF-1 may be particularly important during pregnancy when the mothers must prepare for lactation in the postpartum period. IGF-1 actually also contributes to the development of the mammary epithelial cells as well (Trott et al., 2008).

4.7. The effect of IGF-1 on maternal behavior

In addition to reducing prolactin release, prolonged IGF-1 treatment also inhibited maternal motivation as demonstrated by increased pup retrieval latency in mother rats while other components of maternal care, such as kyphosis, nursing, and licking of the pups did not change (Leko et al., 2017b). When endogenous IGF-1 level was increased by prolonged treatment with NBI-31772, a drug releasing IGF-1 from its binding proteins (Malberg et al., 2007), rather than applying exogenous IGF-1, a similar effect was seen albeit retrieval time of only the first pup was significantly increased (Leko et al., 2017b). The behavioral effect of IGF-1 may not be an indirect result of reduced prolactin level as preventing prolactin secretion with the D2 dopaminergic receptor agonist bromocriptine did not increase pup retrieval latency (Bridges and Ronsheim, 1990; Olah et al., 2018). Rather, this effect of IGF-1 could be exerted via neurons in the preoptic area, known to control maternal responsiveness (Dobolyi et al., 2014; Wu et al., 2014), which inhibit maternal behaviors. One such candidate is the melatonin-concentrating hormone (MCH) neurons in the preoptic area whose activation reduces maternal responsiveness (Benedetto et al., 2014; Rondini et al., 2010).

4.8. Other potential actions of IGF-1 on maternal adaptation of the brain

Apart from prolactin secretion and the appearance of maternal behaviors, parenting includes a variety of additional neuroendocrine, metabolic, and psychological adaptations of the brain including among other things lactational anoestrus, increased food intake, increased body temperature, stress hyporesponsiveness, oxytocin release, etc. (Bridges, 2015), in which IGF-1 could be involved. The role of IGF-1 is plausible if IGF-1 has already been implicated in the particular brain function. Thus, postpartum decrease in IGF-1 level could be involved in lactational anoestrus given the above described role of IGF-1 in facilitating the GnRH neurons. Similarly, IGF-1 is known to play a role in food intake control (Fujita et al., 2017; Todd et al., 2007) suggesting its involvement in the increased maternal food intake. IGF-1 has also been suggested to elevate body temperature as pharmacological or genetic inhibition of IGF-1R enhanced the reduction of temperature and of energy expenditure during calorie restriction (Cintron-Colon et al., 2017). Lactating mothers are in a relative calorie restricted state but still have an increased body temperature probably due to increased metabolism (Eliason and Fewell, 1997; Gamo et al., 2016; Gellen et al., 2017). Therefore, further elevation of their body temperature is not advantageous, which is in agreement with the relatively low IGF-1 levels in the postpartum period.

4.9. A proposed model on the elimination of IGF-1 from key maternal brain regions during lactation

IGF-1 serum level is markedly reduced during lactation as compared to pregnancy as discussed above. In the light of the inhibitory action of IGF-1 on lactation and maternal behavior, this reduction makes sense not only to allow increased GH levels with a reduction of feedback inhibition but also to prevent the inhibitory actions of IGF-1 on hypothalamic maternal centers. However, the presence of some IGF-1 in the serum may be required to support mammary gland epithelial cells as well as lactotrophs in the pituitary (Hikake et al., 2009; Stefaneanu et al., 1999). However, some of this IGF-1 reaches the brain as IGF-1 can penetrate the blood brain barrier (Fernandez and Torres-Aleman, 2012; Werner and LeRoith, 2014). Based on the induction of IGFBP-3 in the preoptic area and the arcuate nucleus of lactating mother rats, we suggest that IGFBP-3 can locally sequester IGF-1 from the extracellular space of these brain regions allowing fully developed maternal behavior and maximal prolactin release following suckling (Fig. 3). Such induction of IGFBPs have been reported before as IGFBP-5 was shown to be upregulated in the visual cortex following monocular deprivation preventing IGF-1 from contributing to the formation of normal ocular dominance columns (Tropea et al., 2006) while IGFBP-2 and 3 are induced by brain injuries (Fletcher et al., 2013; Lee et al., 1999). Although it is not known at present if maternally induced IGFBP-3 is present in the interstitial space of the hypothalamus and in what form. There is, however, example of extravascular IGF-1-IGFBP-3-ALS tertiary complex, e.g. in the follicular fluid of the ovary (Hughes et al., 1997).

Based on the recently elaborated mechanisms how the activity of IGFBPs can be regulated by proteolysis and phosphorylation (detailed in Section 2.2), it is likely that additional mechanisms may also be involved in the maternal regulation of the IGF system. However, our knowledge is limited at present and further studies should determine where ALS, PAPP, SRC are expressed in the maternal hypothalamus and whether some of these proteins are induced in mothers and how they affect maternal IGF-1 actions.

4.10. Potential role of IGF-1 in brain diseases in relation to mothers

Depression is much more frequent in the postpartum period (10–15%) than in the general population (~1%) suggesting that adaptation of the brain to motherhood creates a vulnerable period to the development of depression. Although the mechanisms of maladaptations are not known at present, we suggest that IGF-1 may be a candidate. It has been established in recent years that IGF-1 may be protective against depression. Single as well as prolonged IGF-1 treatment caused anti-depression like behaviors in rodents as assessed using the forced-swim and the sucrose preference tests (Burgdorf et al., 2015; Duman et al., 2009; Hoshaw et al., 2005; Park et al., 2011). In a prenatal rat stress model of depression, and also for a lipopolysaccharide-induced depression model, intracerebroventricular administration of IGF-1 reversed the symptoms of depression-like behaviors in the

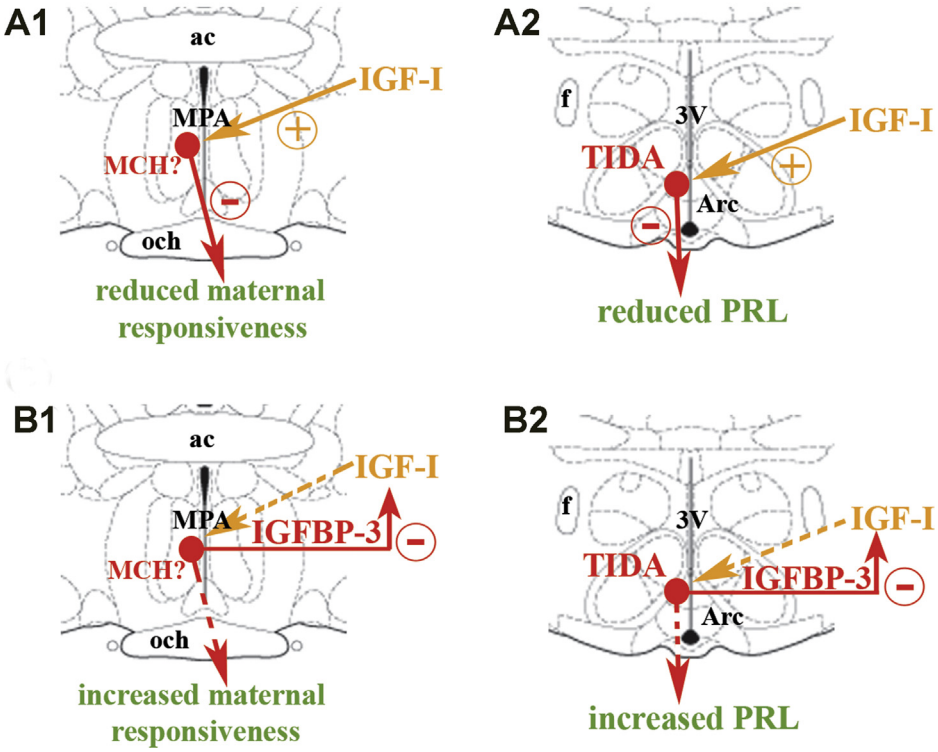

Fig. 3. A model showing how the IGF-1 – IGFBP-3 system may regulate maternal responsiveness and prolactin release. A: In non-maternal animals, IGFBP-3 is absent in the preoptic area and the arcuate nucleus, responsible for the control of maternal responsiveness and prolactin release, respectively. Thereby, IGF-1 (high concentration at the end of pregnancy) can exert its action on neurons inhibiting maternal responsiveness (possibly MCH neurons, see A1) and dopaminergic neurons (A2) inhibiting prolactin release. B: In lactating mothers, local neurons (possibly MCH and DA neurons themselves), produce IGFBP-3 to sequester IGF-1, thereby neutralizing its effects. This promotes maternal responsiveness and prolactin secretion due to the release of the executive processes from tonic inhibition. Abbreviations: ac – anterior commissure, Arc – arcuate nucleus, f – fornix, MPA – medial preoptic area, och – optic chiasm, 3V – third ventricle. The figure is a modification from a previously published article (Leko et al., 2017b).

stressed animals (Basta-Kaim et al., 2014; Park et al., 2011). Interestingly, in the latter case, the GPE tripeptide derivative of IGF-1 was also effective.

In addition, treatment with antidepressants elevated IGF-1 level in the cerebrospinal fluid of human patients (Schilling et al., 2011) as well as in the rat brain (Khawaja et al., 2004). In a prenatal rat stress model of depression, decreased IGF-1 expression, dysregulation in the IGFBP network, and diminished IGF-1R expression was found in the olfactory bulb while antidepressants normalized most of the changes in the IGF-1 system (Trojan et al., 2016). In turn, long-term deficiency of IGF-1 induced depressive behavior in adult mice further confirming the involvement of IGF-1 in depression (Mitschelen et al., 2011). Some of these effects of IGF-1 could be mediated by brain-derived neurotrophic factor (BDNF) also involved in depression (Ding et al., 2006). Altogether, IGF-1 is considered a therapeutic possibility for the treatment of depression. Because of potential side effects including hypoglycemia (Clemmons et al., 2005), an intranasal application has been suggested (Paslakis et al., 2012).

We propose here that a marked reduction in the IGF-1 level following parturition could contribute to the vulnerability of mothers to depression in the postpartum period as a protective factor is removed from the brain at about the time of parturition. In fact, the necessity of IGF-1 in other brain regions provides a possible explanation why the preoptic area and the arcuate nucleus were protected from IGF-1 action by the local induction of IGFBP-3 instead of a general decrease in the penetration of IGF-1 through the blood-brain barrier, which would prevent peripheral IGF-1 from reaching the whole brain. Interestingly, anyway, some activity-dependent brain entry mechanism of IGF-1 has been identified (Nishijima et al., 2010). Nevertheless, it would be interesting to explore the alterations of all members of the IGF system including binding proteins and their proteases and how they are affected by depression and in particular postpartum depression.

5. Conclusion

A great deal of information was collected on the biochemistry and function of the IGF system, including regulations of the bioavailability of IGF-1 as well as its actions on a variety of cell types. Our understanding of the IGF system of the central nervous system lags behind to that of the peripheral organs even though IGF-1 is likely to play important roles in the brain, too. A lot of the recent studies on the brain IGF-1 system focused on neuropsychiatric and neurodegenerative diseases where IGF-1 and its derivatives have great potential. However, the endogenous physiological mechanisms, in which IGF-1 plays a part, should also be addressed. One example is the maternal adaptation of the brain, in which IGF-1 is likely involved based on its well established role in neuroplasticity. Some recent studies indeed suggest the involvement of IGF-1 in the regulation of lactation and the control of maternal behaviors.

6. Declarations of interest

None.

Acknowledgements

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