The Insulin-Like Growth Factor (IGF) Receptor Type 1 (IGF1R) as an Essential Component of the Signalling Network Regulating Neurogenesis

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Abstract The insulin-like growth factor receptor type 1 (IGF1R) signalling pathway is activated in the mammalian nervous system from early developmental stages. Its major effect on developing neural cells is to promote their growth and survival. This pathway can integrate its action with signalling pathways of growth and morphogenetic factors that induce cell fate specification and selective expansion of specified neural cell subsets. This suggests that during developmental and adult neurogenesis cellular responses to many signalling factors, including ligands of Notch, sonic hedgehog, fibroblast growth factor family members, ligands of the epidermal growth factor receptor, bone morphogenetic proteins and Wingless and Int-1, may be modified by co-activation of the IGF1R. Modulation of cell migration is another possible role that IGF1R activation may play in neurogenesis. Here, I briefly overview neurogenesis and discuss a role for IGF1R-mediated signalling in the developing and mature nervous system with emphasis on crosstalk between the signalling pathways of the IGF1R and other factors regulating neural cell development and migration. Studies on neural as well as on non-neural cells are highlighted because it may be interesting to test in neurogenic paradigms some of the models based on the information obtained in studies on non-neural cell types.

Introduction

Neurogenesis is regulated by a complex network of growth factors and morphogens. Effects of discreet signalling factors on early patterning of the nervous system and on neural cell growth and differentiation are well-documented, but their combinatorial effects are only now starting to be elucidated. Since factors regulating neurogenesis may activate overlapping signalling pathways, the outcome of their combined action may be different from a simple sum of cellular responses elicited by each particular factor. Various modes of interaction between signalling pathways are conceivable, such as competition for a limited pool of a secondary messenger, a cumulative effect of two pathways if they converge on a component that cannot be fully activated by either of them, etc.

A well-recognised function of insulin-like growth factor (IGF)-I is to regulate cellular mass in various tissues by controlling both cell size and number. Complete genetic ablation of IGF-I results in a ~50% decrease in body size [1, 2]. Studies on mice with genetically manipulated expression of IGF system proteins (including IGF-I, IGF-II, IGF receptor type 1(IGF1R) and IGF-binding proteins) selectively in the nervous system revealed that the development of all neural cell lineages is highly dependent on the IGF1R signalling because a consistent finding in those studies was brain size reduction in mice with IGF1R signalling deficiency (by up to 70% in IGF1R knockouts) and brain overgrowth in mice with exaggerated IGF1R activation [3, 4].

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Correct morphogenesis of the nervous system requires a tightly regulated localised and transient expression of signalling factors. The peculiarity of the IGF1R pathway is that it is activated early in the primordial central nervous system (CNS) and its activity is maintained, with some regional variation, throughout development into adulthood. Therefore, there are many instances during developmental neurogenesis or during the regenerative and adaptive responses of the adult CNS when the IGF1R and receptors for growth and morphogenetic factors with more localised distribution in the CNS are co-activated. This raises interest to the molecular events where the IGF1R and these pathways converge.

IGF1R Signalling in Neural Cells

IGF1R Signalling Complex Assembly

The IGF1R, whose ligands include IGF-I, IGF-II and insulin at a concentration in excess of 100 nM, is a receptor tyrosine kinase. It consists of covalently linked two α- and two β-subunits. Ligand binding to the α-subunits of the IGF1R induces tyrosine kinase activity in the β-subunits by the phosphorylation of three tyrosine residues within the receptor autocatalytic domain. This leads to the phosphorylation of other tyrosine residues in the IGF1R β-subunit and subsequent formation of the signalling complex by docking and tyrosine phosphorylation of several intracellular proteins, including insulin receptor substrates (IRS) and Src homology domain-containing adaptor proteins [5–8]. At least three IRS isoforms, IRS-1, IRS-2 and IRS-4, are expressed in the nervous system [9] and may play different roles in neural cell activation and development [10]. The activation of the two major signalling cascades, the phosphatidylinositol-3 (PI3) kinase/Akt and the Ras/Raf/mitogen-activated protein kinase (MAPK) pathways, resulting from the IGF1R signalling complex formation is well documented in neural cells.

Neuroprotective Pathways of the IGF1R

The serine threonine kinase Akt mediates pro-survival effects of the IGF1R signalling pathway by targeting a number of proteins regulating tissue growth, such as the glycogen synthase kinase 3 (GSK3), the mammalian target of rapamycin (mTOR) and proteins belonging to a subclass of forkhead transcription factors (FoxO) [11, 12] (Fig. 1). Akt activation is coupled with IGF1R ligation by the activation of PI3 kinase. PI3 kinase is activated by recruitment to the IGF1R signalling complex and generates phosphatidylinositol 3,4,5-triphosphate at the plasma membrane. This forms a binding site for the pleckstrin
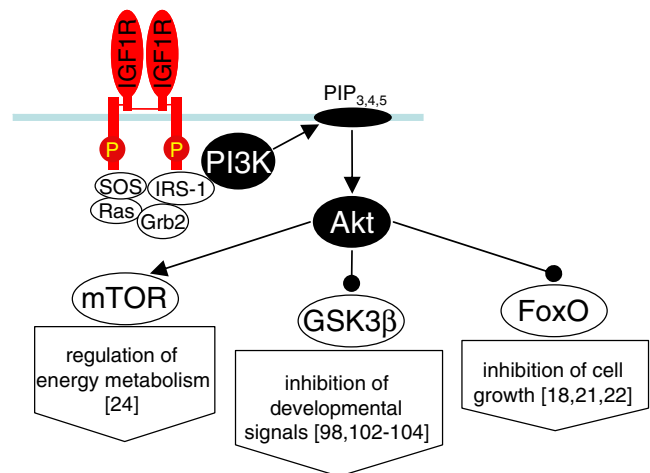

Fig. 1 Neuroprotective signalling by IGF1R. Three signalling pathways mediating cytoprotective effect of IGF1R signalling with a confirmed role in developing and mature neural cells are shown. IGF1R activation leads to the activation of Akt, which phosphorylates mTOR, GSK3β and FoxO, master regulators of pathways controlling cell growth. Positive regulation is shown as an *arrowhead*, negative as a *black circle*. References to the reports investigating a role of these pathways in neuroprotection mediated by IGF1R activation are given in *brackets*. $PIP_{3,4,5}$ phosphatidylinositol 3,4,5-triphosphate

homology domain of Akt, which is activated following translocation to the plasma membrane. The PI3 kinase/Akt pathway is coupled to the IGF1R in neural cells [13] and may be developmentally regulated in neurogenesis [14].

The serine/threonine kinase GSK3 induces inhibitory phosphorylation of several proteins in pathways promoting cell growth and proliferation, including β-catenin and N-myc [15]. Akt was phosphorylated in response to IGF1R activation and inhibited GSK3β in different types of neurons [16–18]. In the study of Johnson-Farley et al. [16], IGF-I and brain-derived neurotrophic factor exhibited an additive effect on the activation of the PI3 kinase/Akt pathway that was translated into the additive effect on the inhibition of GSK. The authors explained the additive effect of the two growth factors by spatial segregation of their signalling pathways, suggesting a possible mode of interaction between signalling pathways in general.

In dephosphorylated form, FoxO transcription factors are translocated to the nucleus where they induce the expression of proteins inhibiting cell cycle progression, such as the cyclin D kinase (cdk) inhibitor p27[kip1] and the retinoblastoma-related protein p107. They also inhibit the expression of cyclin D and upregulate eLF4E binding protein 1, a global transcriptional repressor sequestering eIF4E [19]. Akt-mediated FoxO protein phosphorylation followed by their nuclear exclusion and transcriptional inactivation [20] has been implicated in a neuroprotective effect of IGF1R activation [18, 21, 22].

mTOR is activated by Akt-mediated phosphorylation. mTOR activates p70 ribosomal S6 protein, a positive

regulator of protein translation [23]. mTOR mediates effects of IGF-I and other growth factors on cell growth, but little experimental evidence is available to appreciate the significance of IGF1R/mTOR axis in neural cells. In cortical neurons, the mTOR pathway, in response to activation by IGF-I or insulin, induced the expression of the monocarboxylate transporter 2 [24], suggesting a role for this pathway in the regulation of neuronal energy metabolism.

Another downstream target of the IGF1R signalling cascade is the upstream binding factor 1 (UBF1), an important regulator of cell size. Cell size largely depends on protein biosynthesis, which, in turn, depends on the biosynthesis of ribosomes. UBF1 transcriptionally activates RNA polymerase I, a limiting factor in ribosome biosynthesis. UBF1 gene expression is activated by the nuclear translocation of IRS-1 in response to IGF-I stimulation (reviewed in reference [1]).

MAPK in IGF1R Signalling

The activation of Ras by the son-of-sevenless recruited to the IGF1R signalling complex is the major mechanism of MAPK activation in response to IGF-I. Additional mechanisms, such as the transactivation of G-proteins [25] or Src kinase activation [26], have also been shown. Which particular pathways link the Ras/Raf/MAPK to IGF1R activation in neural cells is not fully understood, but the activation of MAPK in response to IGF1R ligation has been clearly demonstrated in several, but not all, types of neural cells. This pathway was activated by the IGF1R in adult rat hippocampal neural stem and progenitor cells (NSPC) [27] and, to a lesser extent, in postmitotic neurons from embryonic rat hippocampus [16, 28]. No MAPK activation, however, was found in astrocytes of transgenic mice overexpressing IGF-I [13]. The involvement of the MAPK pathway in downstream signal transduction from activated IGF1R moderately increased in cells of oligodendroglial lineage as they matured [14], but an anti-apoptotic response of neonatal rat oligodendrocyte precursors (OPC) to IGF-I was independent of this pathway [29]. Extracellular response kinase inhibition may be required for an anti-apoptotic effect of IGF-I on neural cells [30]. The available experimental evidence suggests that the efficacy of IGF1R coupling to the Ras/Raf/MAPK signalling pathway varies between different neural cell subsets.

Anatomical Basis of Neurogenesis and a Role of Signalling Factors

Two models have been proposed to account for the patterning activity of morphogenetic factors produced in organising centres of the developing nervous system (Fig. 2). In one of them, different cellular identities are induced along the concentration gradient of a signalling factor secreted at one end of undifferentiated tissue mass. This mechanism, for example, accounts for the dorsoventral patterning of the spinal cord by sonic hedgehog (Shh) secreted from the notochord [31]. An alternative possibility is that a morphogenetic factor produced by a restricted group of cells regulates cell fate specification within the surrounding area. Such a mechanism may account for the patterning of the telencephalon [32, 33]. The patterning molecules impart positional information to neural progenitors by inducing specific sets of transcription factors in them [34, 35]. Patterns of transcription factor expression demarcate boundaries of neuroepithelial domains, which are particularly distinct at the embryonic stage of development (before E12.5 in mice). Several signalling molecules have been implicated in early CNS patterning on the basis of their expression in organising centres and ability to form concentration gradients, as well as on the basis of developmental abnormalities associated with their deficiency or ectopic expression. They include ligands of Notch, Shh, fibroblast growth factor (FGF) family members, ligands of the epidermal growth factor (EGF) receptor (EGFR), bone morphogenetic proteins (BMP) and Wingless and Int-1 (Wnt; Fig. 3a).

The pool of NSPC is reduced as development progresses, but a subset of self-renewing multipotential progenitors persists into adulthood residing at restricted anatomical locations of the mature CNS adult neurogenic zones [36]. The best characterised area of adult neurogenesis is in the subventricular zone (SVZ) [37–39]. Newly born neuroblasts tangentially migrate from the SVZ to the
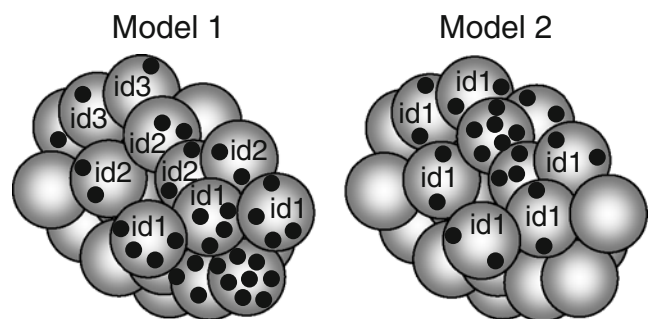

Fig. 2 Early CNS patterning. Two models of early tissue patterning are schematically represented. In *model 1*, a signalling factor (*black circles*) secreted at one end of the tissue mass forms a concentration gradient. Cells (*grey circles*) along this gradient are exposed to different concentrations of the signalling factor. The set of transcription factors which a given cell will express depends on what concentration of the signalling factor it is exposed to. This will define its cellular identity (id1, id2, etc.). In *model 2*, a signalling factor is produced in a restricted area and induces a particular cellular identity in surrounding cells [31–33]
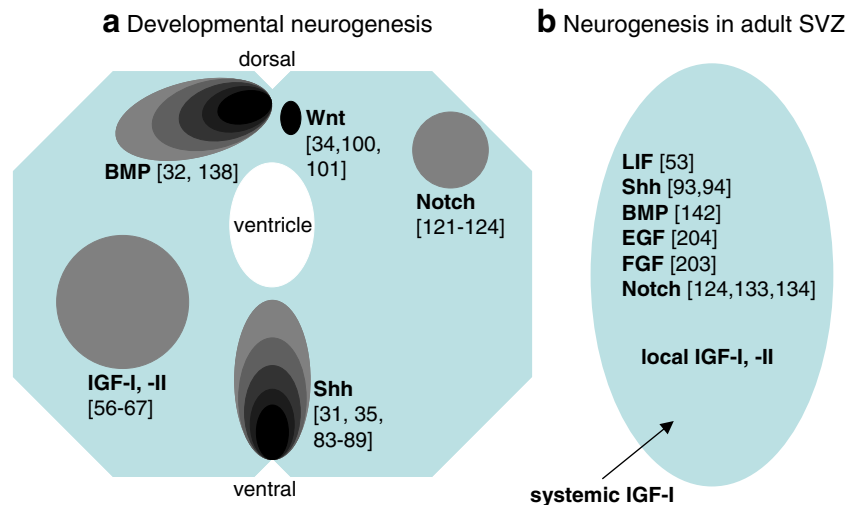
a Developmental neurogenesis   **b** Neurogenesis in adult SVZ

Fig. 3 Signalling factors regulating neurogenesis. **a** Typical modes of signalling factor expression in the developing CNS are schematically represented. These include a concentration gradient of BMP, which mediates patterning of dorsal midline, local production of Wnt, which mediates the induction of dorsal identities, secretion of Notch ligands, which maintains multipotential progenitors in undifferentiated state, a

concentration gradient of the ventralising morphogen Shh and tonic expression of IGF1R ligands throughout the developing CNS. **b** Signalling factors expressed in the adult SVZ are shown. IGF1R activation in the adult SVZ is maintained by local secretion and systemic delivery of its ligands. References to selected reports are shown in *brackets*

olfactory bulb (OB) to become interneurons [40–42]. In addition, a platelet-derived growth factor (PDGF) receptor α (PDGFRα)-expressing subset of astrocyte-like glial fibrillary acidic protein$^+$ type B cells in SVZ may give rise to NG2 chondroitin sulphate-positive OPC that migrate into the brain parenchyma [43, 44] to become myelinating oligodendrocytes [45]. The expression of Sox2 and Pax6 may define subsets specified for glial and neuronal fate, respectively, in the human SVZ [46]. Additional areas of adult neurogenesis include the subgranular layer of the dentate gyrus (SGZ) in the hippocampus [47] and cerebellum [48, 49] where neurogenesis may continue until puberty [50]. Self-renewing cell populations are also present in the normal CNS parenchyma and include pyramidal cells in the rat pyriform cortex [51], O4$^+$ OPC and multipotential A2B5$^+$ cells [44, 52].

Adult neurogenic zones have some features characteristic for the developing CNS, such as the basal lamina, proximity to the vascular bed and polarised niche cells, but there is no evidence of organising centre formation in them. Many proteins regulating developmental neurogenesis are expressed in the adult brain and have been shown to play a role in adult neurogenesis (Fig. 3b). They include leukaemia inhibitory factor (LIF), which stimulates growth of primitive NSPC in early embryogenesis (before E8.5 in mice) [53], and Numb/Numblike, a protein with a cell fate-determining function in the developing CNS [54]. The expression of such proteins in the adult CNS may be regulated by external stimuli, with LIF expression in the adult SVZ in response to hypoxic conditions being one of such examples [55].

IGF1R in Neurogenesis

The IGF1R and its ligands IGF-I and IGF-II are widely expressed in the developing CNS starting from early embryogenesis and continue to be expressed, with some variation in intensity, during CNS development and into adulthood; cells of all three neural lineages have been shown to express the IGF1R and secrete its ligands [56–67]. IGF-I, produced locally or delivered to the CNS from the circulation, induces a constitutive level of IGF1R-mediated signalling in the adult CNS, which is important for brain functions and adult neurogenesis [68]. This level can increase in response to a pathological process in the CNS [69] or as a result of adaptive response to exercise and correlates with increased hippocampal neurogenesis [70]. Secretion of IGF1R ligands in organising centres or its expression in a graded manner is not characteristic for the developing mammalian CNS whose patterning, by contrast to the neurogenesis in *Xenopus laevis* [71–73], is not known to depend on IGF1R activation.

Cell differentiation involves transcriptional activation of genes encoding proteins that mediate functions of mature cells of a given lineage. IGF1R signalling may play a role in terminal differentiation of oligodendrocytes because IGF-I induces the expression of the gene for myelin oligodendrocyte glycoprotein in OPC [74–76] and has been found to synergise with transferrin in the induction of myelin basic protein gene expression [77]. A pro-survival effect of IGF-I may complicate interpretation of experiments addressing its role in neural cell differentiation.

The recently emerged hypothesis that cellular proteins involved in the regulation of apoptosis, such as caspases, FoxO3a, mTOR and p53, may also be involved in the differentiation of neural cells [78–80] suggests a novel conceptual framework for understanding the role of cytoprotective factors, in particular IGF1R ligands, in neural cell differentiation. In this regard, recent reports on hypermyelination of the CNS in mice constitutively over-expressing active Akt in OPC [81] and the involvement of mTOR in the induction of genes for several myelin components in maturing OPC [82] are particularly interesting because, as said above, the Akt/mTOR axis is a target of the IGF1R signalling.

A role for the IGF1R signalling in the epigenetic control of gene expression in the brain [13] suggests a possible mode of co-operation between the IGF1R and signalling factors regulating neurogenesis. Epigenetic effects involve covalent modification of histone proteins by acetylation, phosphorylation and methylation. By promoting such modifications, IGF-I may loosen the structure of the nucleosome, making it more accessible to transcription factors induced by other signalling factors.

Some of the signalling factors with a patterning function in the developing CNS can also control the size of specific CNS structures because they may regulate survival and proliferation of the cell subsets whose fate they specify. It is incompletely understood how these pathways can integrate their action with the signalling pathway of the IGF1R, a global regulator of tissue mass, but some points of convergence between them have been elucidated and are discussed below.

Modulation of Signalling Pathways Regulating Neurogenesis by IGF1R

Shh

In the developing CNS, Shh is secreted in a spatially restricted manner from the ventral midline and displays a concentration gradient decreasing dorsal-ward (Fig. 3a). This morphogen defines ventral identities in the neural tube [83–85] and in the embryonic forebrain [35, 86–89]. Shh produced by Purkinje neurons in the neonatal cerebellum is a sole mitogen-expanding cerebellar granule cell precursors (reviewed in [90]), and in adulthood its activity is required for neurogenesis in the hippocampus [91, 92] and SVZ [93, 94] (Fig. 3b).

Shh has a mitogenic and pro-survival effect on subsets of those neuronal cells which it specifies. As well as its patterning activity, the growth-promoting effect of Shh is mediated by transcription factors of the Gli family [35, 95], which are unique for this signalling pathway. Unlike the anti-apoptotic response to IGF1R activation, the effect of

Shh on cell survival does not involve a direct activation of the PI3 kinase/Akt pathway [96], a GSK3β inhibitor. Moreover, GSK3β itself can negatively regulate Shh-induced cell proliferation by inactivating N-*myc*, a proto-oncogene that is a direct transcriptional target of Shh and mediates its mitogenic effect [97, 98] (Fig. 4). Therefore, the effect of Shh may be dependent on co-operation with other factors that can activate the PI3 kinase/Akt pathway and thereby inhibit GSK3β, such as IGF1R ligands [90]. As discussed below, in addition to Shh, the IGF1R/PI3 kinase/Akt/GSK3β axis may regulate signalling pathways of several other morphogens. In addition, the interaction between Shh and IGF1R pathways may be bi-directional as suggested by the ability of Shh to stabilise IRS-1 by interfering with its mTOR-mediated degradation [99].

Wnt

Wnt is secreted by the dorsal midline and adjacent non-neural cells and is involved in dorsal telencephalon patterning (reviewed in [34, 100]; Fig. 3a); deficiency of this pathway leads to underdevelopment of dorsally derived structures of the brain, such as the hippocampus [101]. The major cellular receptor for Wnt is Frizzled, a seven-pass transmembrane protein, which functions in combination with a co-receptor, a single-pass transmembrane protein belonging to the family of low-density lipoproteins.

GSK3β negatively regulates the canonical Wnt signalling pathway in neural progenitors by the inactivation of its relatively specific component β-catenin [102–104] (Fig. 4). In the absence of Wnt stimulation, β-catenin associates with a complex of axin and adenomatous polyposis coli (APC) gene product, which pre-phosphorylates β-catenin, making it susceptible to the phosphorylation by GSK3β. GSK3β-mediated phosphorylation reduces the pool of β-catenin available for signalling by targeting it to degradation. When released from the axin/APC complex in response to Wnt stimulation, β-catenin becomes resistant to GSK3β-mediated phosphorylation and translocates to the nucleus where it forms a complex with members of the T cell factor (TCF)/lymphoid enhancer factor (LEF) family of DNA-binding proteins, which activates transcriptional targets of the Wnt signalling pathway. Wnt has also been shown to inhibit GSK3β [105], but significance of this inhibition in developing mammalian neural cells has not yet been confirmed. A role of the IGF1R/PI3 kinase/Akt/GSK3β axis in the activation of the canonical Wnt signalling in developing neural cells is incompletely understood, but insulin- or IGF-I-induced GSK3β inhibition, mediated by the PI3 kinase/Akt pathway, has been shown to stabilise β-catenin in cancer cell lines and in normal epithelial cells and fibroblasts and can induce the expression of Wnt target genes [106–108].
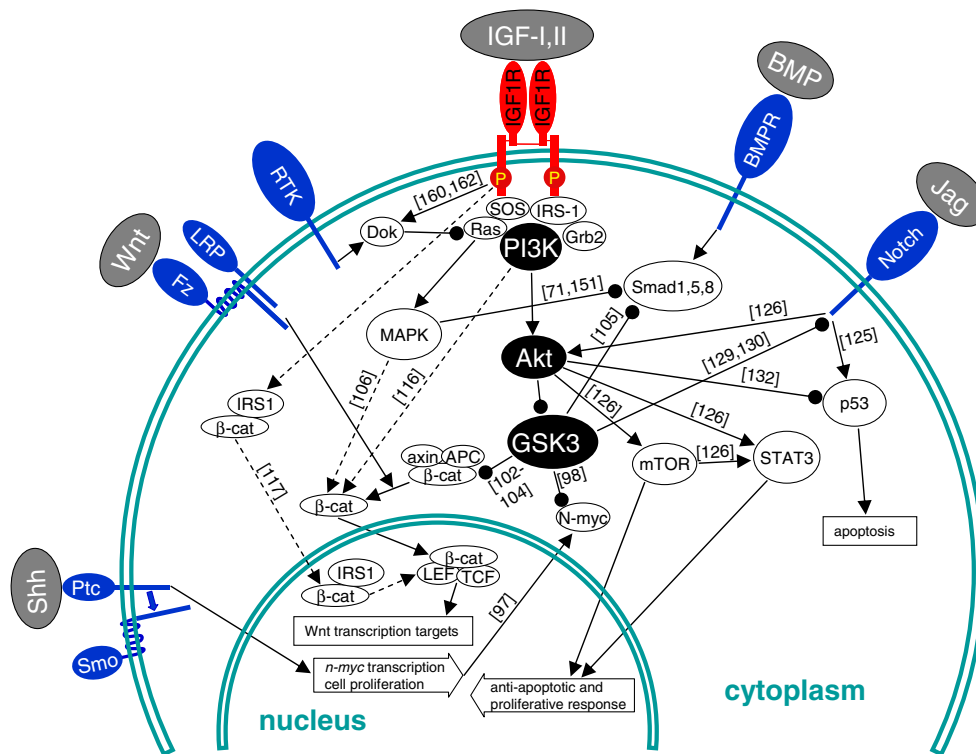
Fig. 4 Convergence of the IGF1R pathway with signalling pathways implicated in neurogenesis. Schematic representation of interactions mediating integration of IGF1R signals into the pathways of signalling factors regulating neural cell growth and development. *Solid arrows* show pathways confirmed in neural cells; *dash arrows* show pathways demonstrated in non-neural cells only. Positive regulation is shown as an *arrowhead*, negative as a *black circle*. References to the reports confirming a given interaction between signalling pathways are given in *brackets*. Well-established interactions are shown unreferenced. The IGF1R/PI3K/Akt/GSK3β axis positively regulates signalling pathways activated by Wnt, BMP, Shh and Notch ligands. *β-cat* β-catenin; *Ptc* patched, Shh receptor; *Smo* Ptc inhibitor, which dissociates upon Shh binding; *Fz* frizzled, Wnt receptor; *Lpr* Fz co-receptor; *Jag* Jagged, Notch ligand; *RTK* a receptor tyrosine kinase

Activation of the canonical Wnt signalling pathway has diverse effects on developing neural cells ranging from the maintenance of self-renewing multipotential pool of progenitors to the induction of neuronal fate specification [109–113]. Whether progenitor cells proliferate or undergo neuronal specification in response to Wnt signal may be mediated by cell-autonomous mechanisms [114], as well as by modulation of cellular response to Wnt by growth factors that can activate the IGF1R/PI3 kinase/Akt/GSK3β axis. The latter possibility is suggested by the ability of FGF2 to divert NSPC overexpressing β-catenin from differentiation to self-renewal, which correlated with the nuclear translocation of β-catenin and GSK3β inhibition [115], but whether IGF-I can have a similar effect remains to be seen.

Studies on non-neural cells indicate that some of Wnt target genes are transcriptionally activated by the IGF1R independently of GSK3β inhibition via mechanisms that involve an Akt-independent action of PI3 kinase [116] or the Ras/Raf/MAPK pathway [106]. Another GSK3β-indepenent mode of co-operation between the IGF1R and Wnt pathways involves formation of a complex between IRS-1 phosphorylated by IGF1R activation and β-catenin.

This complex was translocated to the nucleus and activated the cyclin D1 promoter in mouse embryonic fibroblasts [117] (Fig. 4).

It has been suggested that the competition for a limited pool of β-catenin between FoxO proteins and the transcription factor complex of the Wnt signalling pathway TCF/LEF constitutes a regulatory mechanism inhibiting the cell-growth-promoting Wnt signalling under conditions of cellular stress when FoxO proteins become activated [116, 118, 119]. Via this mechanism, factors causing cellular stress, for example at sites of CNS pathology [120], may compromise Wnt-dependent maintenance of NSPC. One could hypothesise that the IGF1R signalling pathway, via one of the above-said mechanisms, might promote Wnt target gene expression at the expense of FoxO-mediated transcriptional inhibition in NSPC, thereby rescuing their Wnt-dependent self-renewal at sites affected by a pathological process.

Notch

A well-documented function of the Notch receptor signalling pathway is to maintain the pool of NSPC by promoting

their symmetrical division and preventing their neuronal differentiation [121–124]. This pathway also regulates neural cell death, and its activation has been shown to either promote [125] or inhibit [126, 127] apoptosis in different subsets of neural cells. Similar diversity of cellular responses to Notch activation has been reported in non-neural cells [128]. There are little published data on the role of GSK3 in Notch signalling pathway in neural cells. In non-neural cell lines, however, Notch has been shown to be a substrate of inhibitory phosphorylation by both isoforms of GSK3, α and β [129, 130], suggesting that Notch signalling, in similarity to the pathways of Shh and Wnt, may be influenced by the IGF1R/PI3 kinase/Akt/GSK3β axis (Fig. 4).

Notch and IGF1R pathways may also co-operate at levels other than GSK3β activation. The pro-apoptotic effect of Notch signalling on some of the NSPC subsets may be dependent on the activation of p53 and its transcriptional targets *Bax* and *Noxa* [125]. The p53-dependent pathway of cell death may be inhibited by IGF1R activation, as demonstrated in studies on transformed cells [131] and primary neurons [132], indicating that Notch and IGF1R signalling may have opposite effects on p53-mediated apoptosis. Furthermore, Akt-dependent activation of mTOR may also mediate the anti-apoptotic effect of Notch signalling [126]. This identifies p53 and mTOR as potential points of convergence between Notch and IGF1R signalling (Fig. 4).

The expression of Notch1 and its ligands in the postnatal mouse SVZ [133, 134] (Fig. 3b), the ability of adult NSPC to respond to Notch stimulation [126] and the reduced number of NSPC in neurogenic zones of adult Notch1-deficient mice [124] point to the importance of this pathway for adult neurogenesis. This suggests that the interplay between the Notch and IGF1R signalling pathways may play a role in the regenerative response in the postnatal CNS.

BMP

BMPs, members of the transforming growth factor beta superfamily, have diverse effects on NSPC including specification of neuronal or astroglial identities, cell proliferation, mitotic cycle arrest and apoptosis [135, 136]. They inhibit oligodendroglial specification at all developmental stages [135]. BMPs expressed in the signalling centre located along the dorsomedial edge of the cortical primordium [137] mediate patterning of the medial–lateral axis of the telencephalon [34, 138] (Fig. 3a). They also promote development of the choroid plexus [32] and specify dorsal identities in the hindbrain [139]. Adult neurogenesis in the SVZ [140] and hippocampus [141] may be in part regulated by a balance between BMPs, which are

secreted by endothelial cells [142], and their inhibitor Noggin (Fig. 3b).

The type of cellular response to BMPs is determined by intensity of activation, different signalling capabilities of their receptors BMPR1 and BMPR2 [143] and convergence of their signalling pathways with signals delivered by other receptors, such as the receptors for LIF and, most importantly for this discussion, receptor tyrosine kinases [136]. Adding to this complexity is the appreciation that, dependent on the developmental stage of neural cells, the interaction of BMPs with such co-activating signals can be either co-operation or antagonism. For example, neural plate specification in the ectoderm in early gestation was dependent on the FGFR-mediated inhibition of BMP signalling [144], but a combination of BMP2 and FGF2 activities was required for specification of identities characteristic for choroid plexus and neural crest [145].

There are several events in the signalling pathways of the BMPRs and IGF1R where negative or positive interactions between these pathways are possible, and some of these interactions have been confirmed experimentally in neural cells. Intracellular signal from activated BMP receptors is transmitted in neural cells via the canonical pathway that involves activating phosphorylation of the signalling proteins Smad1, Smad5 and Smad8, which then associate with common-partner Smads and translocate to the nucleus where they function as transcription factors [146]. Non-canonical BMP signalling and its functional significance in developing neural cells have also been shown. The non-canonical pathways include the activation of STAT3 by S^{727} phosphorylation, which may be mTOR dependent [147] and a pathway leading to p38MAPK activation [148]. In addition, the activation of mTOR mediated by the PI3 kinase/Akt pathway in response to BMP-2 has been demonstrated in cancer cells [149], but its significance in developing mammalian neural cells has not been elucidated.

As first shown by Kretzschmar et al. [150], BMP-activated Smad1 can be inactivated by phosphorylation with MAPK at the linker region, a location different from the BMPR phosphorylation site. Functional significance of this inhibitory phosphorylation was confirmed in studies on the *Xenopus* embryo and suggested an explanation to the known ability of FGF2 and IGF-I to promote neurogenesis in this developmental paradigm by inhibiting the effect of BMP [71, 151]. To complicate the prediction of the effect that IGF1R signalling may have on cellular response to BMP in mammalian neural cells, a second phosphorylation event mediated by GSK3β, in addition to phosphorylation by MAPK, has been found to be required for targeting Smad1 to degradation [105]. Thus, IGF1R activation has the potential to inhibit Smad1 by activating MAPK cascade as well as the potential to protect this signalling molecule

from inactivation via the IGF1R/PI3 kinase/Akt/GSK3β axis (Fig. 4).

MAPK-dependent Smad1 inhibition may play a role in mammalian neurogenesis because in the rat spinal cord the inhibition of BMP signalling via MAPK-dependent Smad1 phosphorylation mediated one of the ventralising effects of FGF2, the Shh-independent induction of oligodendroglial differentiation [152]. In the adult rat hippocampus, IGF-I promoted induction of oligodendroglial differentiation via a mechanism that also involved inhibition of BMP signalling [75]. A role of Smad1 phosphorylation was not reported in that study, but an increased expression of extracellular (Noggin) and cytoplasmic (Smad6) inhibitors of BMP signalling was demonstrated. Furthermore, the expression of the lipid phosphatase and tensin homolog deleted from chromosome 10 (PTEN), an inhibitor of PI3 kinase, in adult NSPC in response to BMP stimulation suggests a possible mechanism whereby a signal from BMPR may antagonise the IGF1R pathway [142].

Possible modes of interaction between BMP and IGF1R signalling are suggested by examples of crosstalk between these pathways during histogenesis of non-neural tissues. BMP-2 and BMP-9, which have no mitogenic effect on chondrocytes, may indirectly stimulate their proliferation by enhancing binding of IGF-I, which is a mitogen for these cells [153]. Furthermore, BMP-2 and IGF-I signalling pathways had a synergistic effect on the osteogenic differentiation of human mesenchymal [154, 155] and bone marrow [156] stem cells, with protein kinase D, MAPK and PI3 kinase identified as points of convergence between them.

Receptor Tyrosine Kinases

The IGF1R signalling complex contains components that are shared with other receptor tyrosine kinases regulating neural cell development, including FGFR family members, EGFR and PDGFRα. These shared components may mediate crosstalk between receptor tyrosine kinases. The Grb2-associated binder family adapter proteins may be interesting in this regard because they provide a major link between activated receptor tyrosine kinases and downstream signalling and play non-redundant functions in mammalian neurogenesis [157–159]. Furthermore, the downstream of tyrosine kinase (Dok) family adaptor proteins p62Dok-1 and p56Dok-2 have the potential to cross-inhibit activation of the IGF1R and other receptor tyrosine kinases (Fig. 4). When tyrosine phosphorylated by EGFR [160, 161], PDGFR [162] or IGF1R, Dok adaptors can inhibit the MAPK pathway, an effect that depends on their ability to bind several signalling proteins, most importantly RAS GTPase activating protein, and to modulate the activity of their binding partners [160, 162–167].

Neuronal cells in the adult hippocampus express p62Dok-1 with a pattern similar to their IGF1R expression [168].

FGFRs At least 18 members of the FGF family play a role in neurogenesis [169], and at least three members of the FGFR family, FGFR1-3, mediate their effects ([170, 171]; reviewed in reference [144]). The analysis of FGFR signalling in neural cells is complicated because FGFRs activate different sets of downstream signalling molecules [172]; their expression is developmentally regulated [173–176]; they display different ligand binding affinities to a given FGF [169, 175, 177] and elicit different cellular responses in neural cells [173].

Examples of FGF-mediated early CNS patterning include specification of neuronal identities at the junction between the midbrain and hindbrain by FGF8, FGF17 and FGF18 (reviewed in [178]), anterior–posterior patterning of the telencephalon by FGF8 [34, 179, 180], medial–lateral patterning of the dorsal telencephalon by FGF7 [181], patterning of cerebellar structures by FGF8 and FGF17 [182], laminar patterning of the developing neocortex by FGF18 [183], ventral forebrain specification [184] and the Shh-independent specification of oligodendrocytes in the dorsal neural tube (reviewed in [185]). Those FGFs that induce cell fate specification of developing neural cells may also promote subsequent expansion of the cell subsets they have specified. FGF2 is, perhaps, more widely expressed in the embryonic nervous system than FGFs with patterning activity [186], and its expression continues in the adult CNS [187, 188]. Its wide distribution resembles that of the IGF1R and its ligands. In addition, reduced size of progenitor pool resulting from FGF2 deficiency [188–192] and its well-recognised role as a growth factor for NSPC in vitro suggest that FGF2 may function as an NSPC growth and maintenance factor in embryonic and mature CNS.

The ability of some of the FGFs to induce cell fate specification is in apparent disagreement with the ability of FGF2 to maintain a pool of self-renewing neural progenitors by promoting their symmetrical division. Amongst other possible explanations, which I do not discuss here, a plausible suggestion is that co-activation with other factors may bias the FGFR-induced cellular response either toward cell fate specification or toward self-renewing cell division. IGF1R ligands might play a role of such a factor for the following reasons. On the one hand, patterning activity of FGFs does not depend on IGF1R co-activation because there is no loss of particular structures in the IGF1R-signalling-deficient CNS. On the other hand, a mitogenic effect of FGFs on developing neural cells strongly depends on the co-activation of the IGF1R [193, 194]. Changing local availability of IGF1R ligands suggests a hypothetical mechanism to account for modulation of the cellular response to FGFs: cell fate specification occurs in the

absence of IGF1R activation whereas a co-activation of IGF1R and FGFRs is mitogenic.

What is the molecular basis of interaction between the FGFRs and IGF1R signalling pathways? A direct promotion of mitotic cycle progression in FGF-stimulated neural cells by the co-activation of the IGF1R has been clearly demonstrated. The mitotic cycle restriction points regulating transition from G1 to S phase are possible convergence points of growth factor signalling pathways. Accelerated transition through G1 phase of the mitotic cycle in response to IGF1R activation has been observed in various cell types including embryonic [195] and adult neural progenitors [196]. The formation of the early G1 complex containing cyclin D1, cdk4 and the cdk inhibitor $p27^{kip1}$ is required for the cell to pass the restriction points and proceed to S phase [197, 198]. IGF-I applied on its own was unable to induce early G1 complex formation in primary OPC, but the formation of this complex in response to FGF2 was enhanced by co-stimulation with IGF-I and so was the association of cyclin E with cdk4 in late G1, which was required for progression of the cell to peak S phase [199].

Furthermore, FGFR activation can prevent apoptotic death of non-dividing neural cells, with the PI3 kinase/Akt signalling pathway playing a role in this neuroprotection [200]. The interaction between neuroprotective signalling pathways has been addressed in a number of recent reports [16, 28, 201, 202]. Johnson-Farley et al. demonstrated that FGF2 and IGF-I co-treatment had a cumulative effect on the phosphorylation of Akt in cultured hippocampal neurons, which partially correlated with the increased survival of cells co-treated with both growth factors in comparison with cells treated with FGF2 alone [28].

EGFR and PDGFRα Two other receptor tyrosine kinases, EGFR and PDGFRα, play an important role in neurogenesis. EGF promotes expansion of NSPC clones whose multipotentiality may be restricted in comparison with FGF-responsive clones because they emerge at a later developmental stage [203], and in the adult SVZ they have the morphology of transit amplifying progenitor cells and neuroblasts [204]. EGF-responsive precursors may be biassed to the astroglial lineage [192] or to the oligodendroglial lineage, as suggested by the ability of EGF to expand pre-progenitors positive for the polysialylated form of the neural cell adhesion molecule (PSA-NCAM), a subset in the rat neonatal neocortex that gives rise to OPC [205, 206]. EGFR ligands may also have a patterning activity because they are expressed in organising centres of the embryonic CNS [181].

A combination of IGF-I and EGF exerts a far more potent growth-promoting effect on the PSA-NCAM⁺ pre-progenitors than either factor alone [206] suggesting a possibility of co-operation between their signalling pathways. The molecular basis of this co-operation in neural cells is largely unknown. In mammary epithelial cells, in which a synergistic effect of IGF-I and EGF on cell proliferation was also observed, IGF1R and EGF promoted Akt phosphorylation via different signalling pathways and only stimulation through EGFR induced the activation of the Ras/Raf/MAPK cascade [207].

PDGFRα is expressed in distinct neuroepithelial domains specified by transcription factors Olig1 and Olig2 [208] in the embryonic spinal cord, hindbrain and ventral telencephalon. Early OPC transiently express high levels of PDGFRα, and its ligand, PDGFAA, is a growth factor for them [209]. PDGFRα expression and PDGFAA responsiveness rapidly decrease to zero as these cells mature to become OPC, through the stage of the PSA-NCAM⁺ pre-progenitors [206, 209].

A combination of PDGFAA and FGF2 was mitogenic for the multipotential A2B5⁺ progenitors from the adult rat corpus callosum and IGF-I enhanced the effect of these growth factors. The more mature O4⁺ OPC from the same source proliferated only when IGF-I was applied in addition to the other two growth factors [74] suggesting that the dependency of PDGFAA- and FGF2-responsive progenitors on IGF1R signalling may increase as they mature.

IGF1R and Developmental Changes in Neural Cell Motility

Molecular Basis of Neural Cell Motility

The motility of developing neural cells changes according to the requirements of a given developmental stage. In order to ensure correct positioning of a progenitor cell within a concentration gradient of a signalling factor, this cell has to remain immotile up to a strictly defined developmental stage when it leaves the boundaries of the neuroepithelial domain and migrates, radially or tangentially, to its final destination [210]. Neural cell migration is usually guided by phenotypically distinct tissues including radial glia of the embryonic CNS [211], Bergman glia, which mediates final layering of the cerebellum shortly after birth, and the rostral migratory stream [41] of the adult brain. Normal mature brain parenchyma, however, is permissive for neural cell migration too [212, 213]. The transition between motile and sessile phenotype in developing neural cells is regulated by changes in the ligand binding affinities of adherence junctions and focal adhesions, two types of multiprotein complexes on their cytoplasmic membrane [214, 215].

The function of adherence junctions is to mediate intercellular adhesion. Increased ligand binding affinity of adherence junctions is often associated with decreased cell motility. Cadherins are adhesion molecules in adherence

junctions. Their multiple isoforms are expressed in neural cells [216–220]; their expression is developmentally regulated and correlates with regional cell specification [221–223]. Correlation between increased cadherin activity in neural cells and decreased cell motility has been shown [217, 224].

The function of cadherins as cell adhesion molecules is mediated by homophilic interaction between calcium-binding repeats of two cadherin molecules on the cytoplasmic membranes of apposing cells. Cadherin cytoplasmic domains are linked to the cytoskeleton and a number of intracellular proteins. For example, one of the most common cadherin isoforms expressed in neural cells, E-cadherin, is associated with α-, β- and γ-catenins [225]. Functional regulation of adherence junctions involves modulation of cadherin expression and their interaction with the cytoskeleton rather than conformation-dependent affinity modulation [226]. Redistribution of intracellular pool of β-catenin to adherence junctions stabilises E-cadherin, thereby increasing ligand binding affinity of adherence junctions. Since, as said above, β-catenin is also involved in the Wnt canonical signalling pathway, it may play an important role in the co-ordination of neural cell development and their motility [111].

Focal adhesions mediate binding of cells to the extracellular matrix (ECM). Their ligand-biding components are β integrins, heterodimers formed by several combinations of a limited number of α- and β-subunit. The ectodomains of β integrins bind to ECM proteins, such as laminins, fibronectin, collagen, etc., and their cytoplasmic domains are associated with a variety of cytoskeletal, adaptor and signalling molecules constituting focal adhesions. Focal adhesions link the actin cytoskeleton to the ECM and transmit signals generated by β integrin ligand occupancy. Cell migration fully depends on oscillating changes in β integrin ligand-binding affinity, which are translated, via a number of intermediate interactions, into dynamic remodelling of the cytoskeleton. NSPC express several sub-classes of β integrins that are functionally important for their maintenance and survival [227–229]. The expression of these molecules is developmentally regulated, as for example shown in cells of the oligodendroglial lineage, which express β_1, β_3 or β_5 integrin subunits at different stages of maturation, with a positive correlation between the expression of β_1 and motile phenotype [230].

Cell migration through solid tissues is a common biological processes studied in many paradigms including embryogenesis, haematopoiesis, inflammation, tumour metastasis, etc. Metastasis of some tumours strongly depends on the activation of receptor tyrosine kinases, which can induce separation of transformed cells from an epithelial monolayer and stimulate their motility and invasion of tissue parenchyma. IGF-I is amongst the most potent scattering factors for breast cancer cells [231] and can also modify migratory behaviour of other transformed and untransformed cells, such as glioblastoma [232] and cardiac fibroblasts [233]. The activation of the receptor tyrosine kinases of FGFR family [234], PDGFRα [235, 236] and IGF1R [237–239] has been shown to stimulate migration of neural cells at different developmental stages. Molecular events underlying the ability of receptor tyrosine kinases to promote cell migration have been elucidated in transformed cells, but their nature in neural cells is largely unknown.

Disruption of Intercellular Adhesion by IGF1R Activation

Invasive growth of transformed cells and epithelial-to-mesenchymal transition in response to IGF1R activation is thought to result from disintegration of adherence junctions caused by phosphorylation of β-catenin and its translocation from the E-cadherin-bound pool to the nucleus [240]. This mechanism, however, is not uniformly confirmed [241]. A possibility of cross-signalling between the IGF1R and adherence junctions is suggested by the formation of multimolecular complexes containing components of the IGF1R signalling pathway together with adherence junction components in a number of cell types, including mouse embryonic stem cells [117, 242]. Reorganisation of α-actinin mediated by the PI3 kinase/Akt pathway may also promote disintegration of adherence junction in response to IGF1R activation [231] (Fig. 5; Table 1).

Little is known about reorganisation of adherence junctions in response to IGF1R activation in neural cells, but a role of the PI3 kinase/Akt pathway in the regulation of neural cell motility has been indirectly suggested by the phenotype of mice with genetically ablated expression of PTEN, a natural inhibitor of the PI3 kinase/Akt pathway whose effect is mediated by degradation of phospholipids generated by PI3 kinase. Its hereditary deficiencies manifest by increased cancer incidence and aberrant tissue development [239, 243, 244].

Aberrant layering was a common finding in mice with genetically ablated PTEN. This includes the overgrown and displastic cerebellum in mice with conditional PTEN inactivation in precursors of cells populating the vermis of the cerebellum [244], the impaired ability of PTEN-deficient Bergmann glia to guide migration of granular cells inward from the Purkinje cell layer [243] and accumulation of Purkinje cells, in which PTEN was selectively inactivated, in clusters above the fourth ventricle instead of migrating to the cerebellar surface [244]. These results point to a possibility that the PI3 kinase pathway is involved in the regulation of neural cell migration without, however, excluding contribution of other PTEN-dependent pathways [245–247] to the observed effects.
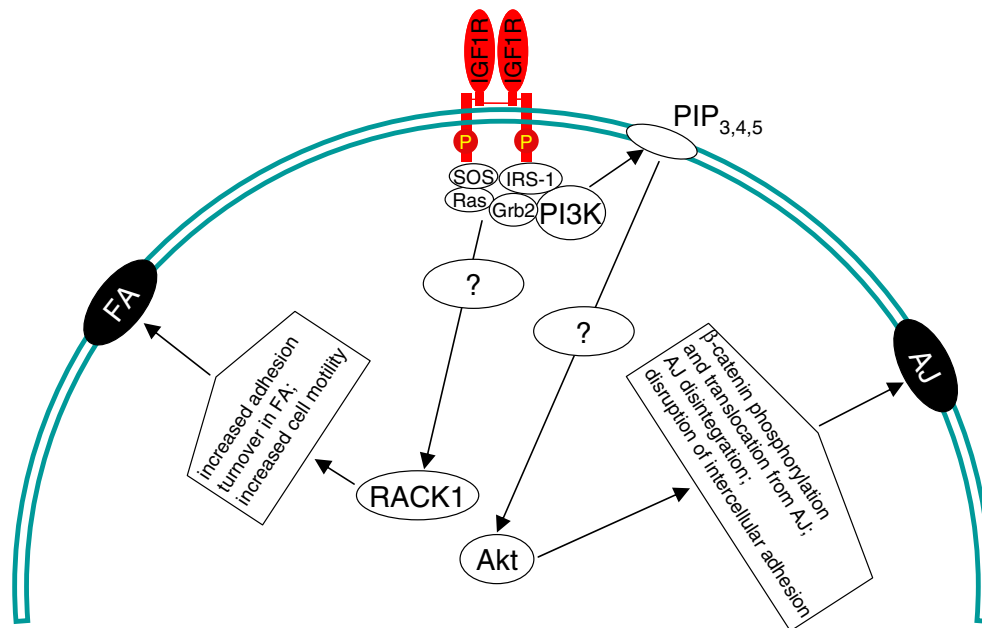
Fig. 5 Pathways mediating increased cell motility in response to IGF1R activation. Schematic representation of possible pathways transmitting the signal from the activated IGF1R to focal adhesions (*FA*) and adherence junctions (*AJ*), multiprotein cytoplasmic membrane complexes mediating cell adhesion and motility. Disruption of AJ followed by increased cell motility may result from Akt-mediated β-catenin phosphorylation. The scaffolding protein RACK1, which shuttles signalling proteins between different cellular compartments, may play a role in the increased adhesion turnover in FA in response to IGF1R activation. Disintegration of AJ and oscillating changes of β-integrin ligand binding affinity in FA are required for increased cell motility

IGF1R Activation and Neural Cell Migration

Modulation of β Integrin Activity by IGF1R β integrins play a role in modulation of cell migration induced by IGF1R activation. For example, a migratory response of smooth muscle cells to IGF1R activation was dependent on the interaction of their $\alpha_v\beta_3$ integrin with vitronectin [248]. The migration-promoting effect of IGF1R activation requires that the activation of IGF1R pathway components and β integrin ligand occupancy are spatially and temporally co-ordinated and is mediated mainly by the PI3 kinase/Akt pathway [249].

Changes in the activation status of focal adhesion components have been shown to occur in response to IGF1R activation. This includes changes in the phosphorylation status of focal adhesion kinase (FAK) in transformed epithelial cells, which are indicative of adhesion turnover in focal adhesions [250, 251], and tyrosine phosphorylation of several other focal adhesion components, which correlated with lamellipodia motility, in fibroblast [252] and neural [253] cell lines. Furthermore, α_V integrin was redistributed from adhesion junctions to focal adhesions in response to IGF-I stimulation in transformed epithelial cells, suggesting a mechanisms to account for the increased migration of these cells in response to this stimulation [251] (Fig. 5; Table 1). Modulation of β integrin activity and changes in focal adhesions induced

by IGF1R activation in developing neural cells remain to be assessed.

Adaptor Proteins Mediate Association of IGF1R Signalling with Focal Adhesions One of the proteins supporting structural integrity of focal adhesions and facilitating their functions is the receptor for activated C kinase (RACK)1, a scaffolding protein [254] whose major function is to regulate cellular responses by targeting signalling molecules to specific intracellular locations. Protein kinase C (PKC) family members and other signalling molecules, including β-integrin cytoplasmic domains [255], have been identified as RACK1 binding partners (reviewed in [256]). RACK1 is required for targeting PKC isoforms [257], Src [258] and ERK [259] to focal adhesions and for their participation in adhesion dynamics and cell migration.

Elucidating the mechanism to account for the crosstalk between IGF1R activation and focal adhesion dynamics, two research groups identified independently that IGF1R binds to RACK1 [260, 261]. This has led to the hypothesis that RACK1 mediates association of IGF1R signalling cascade with focal adhesions. In the MCF-7 breast carcinoma cell line, translocation of the complex formed by IGF1R and RACK1 to focal adhesions was dependent on β_1 integrin binding to ECM, an event which induced release of RACK1 from an inhibitory action of the serine threonine phosphatase, the protein phosphatase 2A (PP2A).

Table 1 Effects of IGF1R activation on cell adhesion and migration

Status of the IGF1R	Status of the structures mediating cell adhesion and migration	Experimental evidence	Cells	Ref
No activation	Formation of a multimolecular complex including components of IGF1R signalling pathway and adherence junctions (AJ)	Association between IGF1R, E-cadherin and β-catenin	Human mammary carcinoma Mouse embryonic stem cells	[242]
		Association between IRS-1, E-cadherin and β-catenin	Cell lines from colorectal carcinoma	[240]
		Association between IRS-1 and β-catenin	Mouse embryonic fibroblasts	[117]
		Association between α_v integrins, IGF1R, E-cadherin and α-catenin	Human colon carcinoma	[251]
	Formation of a multimolecular complex including components of IGF1R signalling pathway and focal adhesions (FA)	Association between FAK and the IGF1R signalling complex	Human mammary carcinoma	[250]
Activation	Disintegration of AJ	Translocation of IGF1R and E-cadherin to the cytoplasm	Rat bladder carcinoma Mouse embryonic stem cells	[242]
		Degradation of E-cadherin in the cytoplasm	Rat bladder carcinoma	[242]
		Dissociation of E-cadherin and β-catenin	Human colorectal carcinoma	[240]
		PI3 kinase-dependent displacement of α-actinin from AJ	Human mammary carcinoma	[231]
	Transcription activation by β-catenin	Nuclear translocation of β-catenin from the plasma membrane and TCF-3 from the cytoplasm increased transcription of the β-catenin pathway genes	Rat bladder carcinoma	[242]
		β-catenin stabilisation in response to IGF-I	Human colorectal carcinoma	[240]
		IRS-1-dependent nuclear translocation of β-catenin	Mouse embryonic fibroblasts	[117]
	Increased adhesion turnover in FA	FAK dephosphorylation, which correlated with increased adhesion to vitronectin and was dependent on SHP-2	Human mammary carcinoma	[250]
		Increased ligand binding affinity of $\alpha_v\beta_3$ integrin	Human smooth muscle cells	[248]
		PI3K/Akt pathway-dependent increase in cell migration on vitronectin	Human mammary carcinoma	[249]
	Translocation of α_v integrins from AJ to FA	Redistribution of α_v integrins from cell–cell contacts to cell–ECM sites	Human colon carcinoma	[251]
	Involvement of scaffolding proteins in providing a link between IGF1R and FA	β_1 integrin ligand occupancy induced release of RACK1 from an inhibitory action of PP2A and RACK1-mediated translocation of IGF1R to FA	Human mammary carcinoma	[262, 264]

RACK1-mediated translocation of IGF1R to focal adhesions resulting from PP2A dissociation led to increased cell migration [262]. In a cardiomyocyte cell line, however, modulation of cell migration by IGF1R signalling was RACK1 independent [263]. The authors identified a tyrosine residue in the RACK1 molecule that was critical for its ability to associate IGF1R activation with the function of focal adhesions [264].

Little is known about a role of RACK1 as a link between IGF1R activation and reorganisation of focal adhesions in neural cells. The importance of this scaffolding protein for neuronal functions, however, has been shown. RACK1 binding partners in this cell lineage include proteins involved in localised protein synthesis [265] and receptors for neurotransmitters [266]. RACK1 is widely expressed in the developing and mature CNS, with regional variations in expression levels, and forms concentration gradients, suggesting its involvement in CNS patterning [267]. RACK1-mediated translocation of a Na^+/H^+ exchanger to focal adhesions in neurons has been shown [268], implicating this adaptor in functions of focal adhesions in cells of the neural lineage.

Modulation of Cellular Responses to IGF-I by β Integrin Activation Co-operation between the IGF1R and β integrin signalling pathways is bi-directional because β integrins activated by ligation with ECM components can modify cellular response to IGF-I. A growth-promoting effect of IGF-I was enhanced by ligation of $\alpha_5\beta_1$ integrin with fibronectin in chondrocytes [269] and by co-activation of a vitronectin receptor in transformed and non-transformed epithelial cells [270]. Co-activation of $\alpha_V\beta_3$ integrin in IGF-I-stimulated smooth muscle cells enhanced their proliferative response via a mechanism that involved an increase in the duration of IGF1R phosphorylation [271, 272]. Combinatorial effects of short-range signals delivered to NSPC by adhesive interactions with the components of the basal lamina and signals from activated growth factor receptors have been proposed to play an important role in NSPC maintenance within neurogenic zones [227–229, 273]. IGF1R might be an important component in such regulatory signalling networks.

IGF1R and Cellular Responses that Involve Cytoplasmic Membrane Remodelling

Accumulating evidence suggests that IGF1R signalling may promote outgrowth of cytoplasmic membrane extensions in neurons and glial cells. The importance of this effect for neurogenesis and functions of the CNS is suggested by recent studies. The IGF-I and IGF-II have been shown to be expressed in a graded manner in a developing mouse OB and mediate mapping of its neuronal connectivity by directing growth of neuronal processes [274]. The exercise-induced induction of dendritic spine outgrowth in specific subsets of hippocampal neurons depends on IGF-I [275].

Cytoplasmic membrane remodelling in neural cells is regulated by a variety of signals, including attractive and repulsive guidance cues, in many cases without the induction of new gene expression. The effects of the IGF1R activation on cytoplasmic membrane remodelling are likely to be in conjunction with these guidance molecules. Analysis of signalling pathways mediating stimulatory effects of IGF-I on the outgrowth of cytoplasmic membrane derivatives showed that the Ras/Raf/MAPK and PI3 kinase/Akt pathways mediated axon outgrowth in corticospinal motor neurons [276] and exocytosis of plasmalemmal precursor vesicle during growth cone extension [277]. Transcription-independent cytoskeleton remodelling mediated by the Rho family GTPases was involved in such effects of IGF-I as the induction of neurite outgrowth in SH-SY5Y neuroblastoma [278] and the establishment of polarity and initiation of axonal outgrowth in hippocampal neurons [279].

Conclusion

IGF1R signalling pathway plays a non-redundant role in neural cell development. Its major biological function in the nervous system is to promote increase in cellular mass via a variety of mechanisms which involve suppression of pathways inhibiting cell growth, such as FoxO transcription factors and GSK3β, stimulation of mitotic cycle progression by enhancing G_1 to S phase transition in cells proliferating in response to other mitogens and promoting growth of cytoplasmic derivatives in neural cells. IGF1R signalling may be involved in the combinatorial regulation of neurogenesis at different developmental stages by cumulative or antagonistic interactions with pathways of several signalling factors, including receptor tyrosine kinases, Shh, BMP, Notch and Wnt. The Akt-mediated inactivation of GSK3β has emerged as a common mechanism integrating the action of the IGF1R with other signalling pathways. A role of the IGF1R pathway in the developmental regulation of neural cell motility is suggested by its well-documented effects on migration in a number of transformed and non-transformed cells, including mouse embryonic stem cells. It may be interesting to investigate changes in adherence junctions and focal adhesions induced by IGF1R activation in neural cells and implications that such changes may have for the regulation of neural cell migration during development and in CNS pathology. A better understanding of molecular basis to account for co-operation between IGF1R and other

signalling pathways in neural cells may lead to identification of new targets for neuroprotective and neuroregenerative therapy, as well as to the development of new approaches to promote engraftment and dissemination of NSPC transplanted in the CNS, thereby increasing their therapeutic efficiency.

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