Mechanisms Mediating Brain Plasticity: IGF1 and Adult Hippocampal Neurogenesis

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This review addresses the role of serum insulin-like growth factor 1 (IGF1) as one mechanism of adult neural plasticity, specifically, its regulation of hippocampal neurogenesis among other plasticity-related processes. It is suggested that IGF has been reused advantageously both for the control of energy expenditure as a function of the organism's activity and to protect, repair, and plastically modulate the brain. Moreover, because as the main source of IGF1 in the adult organism is outside the brain and its presence in this organ is a function of the activity, IGF1 becomes an ideal factor to induce plastic/neuroprotective functions as a function of the organism's activity. The link for this point of view comes from the original function of IGF1 during ontogeny/phylogeny, the promotion of cell survival and control of neural cell numbers, whereas one of the IGF1 functions in the adult brain is the control of hippocampal neurogenesis. The investigation of the IGF1 role as mediator of exercise effects suggests that many but not all the effects of physical activity are mediated by IGF1. These investigations have contributed to delimit the role of IGF1 as mediator of exercise actions, but at the same time are unveiling new roles for serum IGF1 inside the brain.

Keywords: physical/cognitive activity; insulin-like growth factor 1; cognitive reserve; neural plasticity; newborn immature neurons

Every single cell or tissue has the capability to change some of its molecular, morphological, and functional features to cope with an ever-changing world. Specifically, neural plasticity is the capacity of reorganization of the neural tissue during the entire lifespan of the individual (Garcia-Segura 2009). The cerebral capability for plastic changes ranges from modifications at the morphological level (number, location, and function of synaptic intercellular contacts; the length of neuronal dendrites; the function of glial cells and processes; neuron size or shape), at the level of the functional properties of these cells (modifications in the receptive fields of neurons), or changes in the organization of the neural tissue such as regional blood flow or cellular replacement (the ability of some brain regions to generate newborn cells able to differentiate, mature, and work integrated in a preexisting circuit in the same way the existing cells do, with or without new roles).

An important aspect of neural plasticity is the modulation by physical and cognitive activity. If neural plasticity is the ability of the brain to change faced with a changing environment or endogen milieu, and embrace from synaptic plasticity to neuronal replacement, this neural plasticity in turn has flexible limits, so the neural tissue has the ability to change the margins and general properties of the plasticity itself, what is called metaplasticity (see below). Moreover, when neural plasticity is achieved in time by means of physical and cognitive activities, that is, the individual's experience, the brain would gain resilience to neurodegeneration by means of new neural resources. These resources confer capabilities to cope with new and highly complex situations, what is called cognitive reserve (Carro and Torres-Aleman 2006; Katzman and others 1988). The component of neural plasticity consisting of neuronal replacement is therefore called neurogenic reserve (Kempermann 2008).

Both forms of brain plasticity, changes in cell shape and cellular replacement, contribute to the functional plasticity of the nervous tissue (Garcia-Segura 2009). Nevertheless, what makes the brain a particularly different tissue regarding the capability for change is the metaplasticity. The concept of metaplasticity was first raised to account for the synaptic metaplasticity, as the ability of variation in the way synapses exhibit functional synaptic plasticity (Abraham and Bear 1996; Deisseroth and others 1995). Accordingly, the concept of neural

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metaplasticity has been coined for "both morphological synaptic plasticity, neuronal and glial replacement, and the associated changes in angiogenesis, over long timescales and depending on the biological context and on the previous history of plasticity" (Garcia-Segura 2009).

Neural plasticity has an adaptive purpose, because a higher capacity of adaptation of the brain to challenging environments is an evolutionary advantage considering the function of the brain, compared with the function and the necessity of plastic adaptation of the lung or kidney, for example. Besides, by controlling metaplasticity (adapting the threshold for brain plasticity during life to the precise homeostatic needs of each moment [Garcia-Segura 2009]), the organisms would gain an additional adaptive handicap. This knowledge might be very useful to recover the operation when it becomes lost after disease and/or aging, or even to promote this capacity when it is insufficient to cope with the insult-induced damages.

Plasticity in the adult brain has long been recognized and reported. A huge number of tasks and brain areas able to experience adaptability and/or reorganization have been identified, the cerebral cortex, hippocampus, hypothalamus, or cerebellum being good examples. In this way, the topographical map of the monkey somatosensory cortex was one of the first long-lasting plastic systems to be described (Merzenich and others 1983; Wall and others 1983; for a recent review, see Navarro and others 2007), the plasticity in the hypothalamus is closely related with everyday functioning of the neuroendocrine system (Gahr 2004; Langle and others 2002), the hippocampus-dependent spatial memory-associated synaptic plasticity is an extensively investigated model of neural plasticity (for a recent review, see Bast 2007), and the cerebellum has long been recognized as one of the best models for activity-dependent plasticity (Jorntell and Hansel 2006). Recently, neural stem cells and neurogenesis in the adult brain have also been suggested as one powerful and interesting system for neural plasticity (Parent 2007), because neuronal replacement is the most drastic aspect of brain reorganization in adult vertebrates (Garcia-Segura 2009).

Therefore, investigation of all these mechanisms of brain physiology (plasticity, metaplasticity, and cognitive reserve) will help us to understand key aspects of both neuroprotection and neurodegeneration.

Mechanisms Mediating Neural Plasticity in the Adult Brain

The mechanistic comprehension of the molecular and cellular changes of the adult brain to environmental changes, lesions, or aging, is necessary not only for the understanding of the brain function, but also for the design of novel therapies. We know that the main actors leading the neural plasticity processes are the formation of new neurons and new glia, the factors secreted by these cells, the axonal sprouting and dendritogenesis, and the formation of new synapses. All these actors are regulated through distinct and specific gene expression patterns. It is beyond the scope of this review to list extensively the literature about the mechanisms of brain plasticity. We will focus on some of the main mechanisms mediating the physical/cognitive activity-induced plasticity, because the organism's activity is the main factor driving the changes underlying the cognitive reserve. It is relevant to note that much of the information about molecules mediating plasticity has been obtained by analyzing the damaged or lesioned brain, as well as neurodegenerative diseases. Many, but not all, proteins involved in brain plasticity are activated only after the brain homeostasis becomes compromised after neural damage or neurodegenerative diseases (reviewed by Nithianantharajah and Hannan 2006; Wieloch and Nikolich 2006). The data about the functioning of plasticity genes and molecules point to different properties of reparative versus protective plasticity. However, many other molecules are directly involved in all plastic events, pointing to basic mechanisms operating to mediate the adaptability of the brain.

An increasing number of molecules and genes have been involved in activity-induced plasticity. The growth factor cascade, including insulin-like growth factor 1 (IGF1), brain-derived neurotrophic factor (BDNF), and vascular endothelial growth factor (VEGF), requires a preeminent mention (Cotman and others 2007). Growth factors are necessary mediators of the effects of physical activity and environmental enrichment in brain plasticity. IGF1 is a key factor in the neurobiology of exercise, because it shows brain area–specific, temporal rank–sensitive, and behavioral task–dependent features (Llorens-Martin and others 2008) in response to exercise (we will deal more deeply with IGF1 in the next section). In the same way, neurotrophins like BDNF and NGF have been directly involved in the plasticity induced after environmental enrichment in several brain regions including hippocampus (Ickes and others 2000; Pham and others 1999; Torasdotter and others 1998; Young and others 1999). Neurotrophins are activity-dependent regulators of adult brain plasticity through its actions on the canonical tyrosine kinase Trk receptors. The BDNF-TrkB signaling at glutamatergic synapses (reviewed by Soule and others 2006) promotes synaptic consolidation by an Arc (activity-regulated cytoskeleton–associated protein)–dependent mechanism concomitantly with a number of BDNF-regulated genes involved in LTP or spine morphogenesis like Ca^{2+}/calmodulin–dependent protein kinase II (α-CaMKII). BDNF controls protein synthesis probably

through stimulation of translation by means of TrkB-coupled PI3k-dependent phosphorylation of 4E-BP, a binding protein that controls the availability of eIF4E (the eukaryotic initiation factor 4E), a rate-limiting step for translation of most mRNAs, and also by means of ERK/MAPK-dependent phosphorylation of eIF4E (Soule and others 2006).

As for VEGF, its activation is linked to recruitment of immune cells like T cells and activated microglia (Ziv and others 2006) concomitantly with neuronal replacement-mediated plasticity. The actions of the growth factors in brain plasticity are both reparative and protective. The former function can be induced by common activators, for example, erythropoietin (EPO). EPO stimulates angiogenesis, neurogenesis, and is neuroprotective probably because it increases the levels of BDNF and VEGF (Wang and others 2004). In a similar way, glial-derived neurotrophic factor (GDNF) mediates the beneficial effect of enrichment on motor function (Young and others 1999), and *g-csf* (granulocyte-colony stimulating factor) is a lesion-inducible gene that promotes neurogenesis (Schneider and others 2005).

Another aspect closely related with enrichment-associated plasticity is the modulation of the synaptic strength. An enriched environment induces increased expression of synaptophysin and PSD-95 (postsynaptic density protein 95 kDa; Nithianantharajah and others 2004). The neurotrophin BDNF induces the expression of the vesicle proteins synaptophysin and synaptobrevin at nerve terminals facilitating vesicle docking. The increase in the density of docked vesicles facilitates high-frequency tetanic stimulation contributing to the modulation of LTP (Lu and Chow 1999), and PSD-95 participates on dendritic spine maturation through a mechanism dependent on a spine-resident actin-binding protein, drebrin A. Drebrin A is responsible for recruiting F-actin and PSD-95 in filopodia, resulting in spine formation (Sekino and others 2007). Another molecule activated after enrichment is DARPP-32 (the dopamine and cAMP-regulated phosphoprotein of 32 kDa). DARPP-32 is a protein phosphatase inhibitor highly expressed in medium-sized spiny neurons that participates in the integration of synaptic signals (reviewed by Le Novere and others 2008).

Experience-driven changes in brain include both modifications of the synaptic connectivity of the circuits in a local synapse-specific manner (Malinow and Malenka 2002), and the induction of activity-dependent gene expression (reviewed in Flavell and Greenberg 2008). This neuronal activity-regulated gene expression consists of both the activation of immediate early genes and activity-regulated neurotrophin genes like *bdnf*. *c-fos* is an immediate early gene up-regulated in response to many physiological stimuli (Morgan and others 1987). Induction of *c-fos* is critical for the adaptive responses to experience, including synaptic plasticity, learning, and memory (Fleischmann and others 2003). The links between some of the factors summarized here have been long recognized, as, for example, between c-fos and CREB (Flavell and Greenberg 2008). Increased phosphorylation of CREB has been described in the effects of enrichment on neuroprotection and plasticity (Young and others 1999). *Homer* is another immediate early gene involved in neural plasticity (Andreasson and Kaufmann 2002) and closely related with the organism's activity, because of the coupling of its activation with the cellular activity during both the resting and the active periods (Marrone and others 2008).

Other classical plasticity-associated groups of molecules like the NMDA- and AMPA-receptor subunits show modified expression after enrichment (Naka and others 2005; Tang and others 2001). Both LTP and LTD require the activation of NMDARs (*N*-methyl-D-aspartate receptors). In turn, influx of Ca^{2+} via NMDARs triggers expression of AMPARs (α-amino-3-hydroxy-5 methylisoxazole-4-proprionic acid receptors). AMPARs are mainly responsible for the basal excitatory postsynaptic potential (EPSP). NMDARs are regulated by the Src-family of protein kinases and phosphatases. Nevertheless, electrical activity increases locally the number of NMDA receptor binding sites and decreases $GABA_A$ receptor subunits. This neurotransmitter excitation in turn promotes axonal sprouting and neural plasticity (Ben-Ari and Represa 1990).

One family of molecules strongly involved in plasticity is the cell-adhesion molecules (CAMs), including NCAM, L1-CAM, cadherins, neuroligins, and integrins (reviewed by Gerrow and El-Husseini 2006). A number of these plasticity-related genes have been involved with activity in gene expression profile studies (Rampon and others 2000). For example, the expression of integrin α4 (Pinkstaff and others 1999), but also PSD-95, and proteins involved in synaptogenesis like the GTPase RhoA (Tashiro and Yuste 2004), the cytoskeletal protein dynactin (Martin and others 1999), and the actin-binding cortactin (Naisbitt and others 1999), are all increased by physical/cognitive activity. Synapsin I and II are neuron-specific phosphoproteins associated with the membranes of synaptic vesicles, involved in the formation and maintenance of synaptic contacts (Ferreira and Rapoport 2002). Synapsins are up-regulated by physical activity (Griesbach and others 2007, 2008).

In the same way, the family of molecules involved in the equilibrium between anabolic/catabolic processes appears relevant for the plastic capabilities of the brain, as, for example, growth-promoting factors like GAP-43 and growth-inhibitory factors like aggrecan, versican, or brevican. In the same way, statins (HMGCoA reductase inhibitors) and phosphodiesterase-5 inhibitors stimulate angiogenesis and synaptogenesis after stroke (Chang and others 2003; Zhang and others 2005; reviewed by Wieloch and Nikolich 2006).

Finally, hormones have been suggested as one preferential mechanism to control this neural plasticity. Moreover, hormones can modulate even metaplasticity, by "adapting the threshold for brain plasticity during life to the precise homeostatic needs of each moment" (Garcia-Segura 2009).

As for metaplasticity, two main mechanisms have been described. The alteration to the threshold between net depression and potentiation in synaptic strength has been described as one possible mechanism in hippocampal neurons (Bach and others 1995; Mayford and others 1995). Another more general mechanism has also been suggested in the way of events involving the mean activity of a great population of synapses (Bienenstock and others 1982). The former is a synapse-specific mechanism relying on the properties of calcium-calmodulin–dependent kinase II (revised by Deisseroth and others 1995). The molecular mechanisms underlying these changes in synaptic features have been traced to NMDA receptor–dependent synaptic plasticity (Bortolotto and others 1994) and rises in postsynaptic $[Ca^{2+}]$ (reviewed by Abraham and Bear 1996).

In this way, it is noteworthy that the physical activity is a physiological stimulus providing the brain with peripheral trophic support. IGF1 is a critical mediator for the beneficial effects of physical activity on brain function, and in this way the mediator mechanisms including IGF1 form part of the phenotypic expression of the exercise-driven genome (Booth and others 2002). Circulating IGF1 is a growth factor mostly produced by the liver (Butler and LeRoith 2001), although body growth does not depend on it since serum IGF1-deficient animals (LID) show normal body size (Yakar and others 1999). However, LID mice show not only specific metabolic defects as expected based on previous observations (for example, insulin-resistance developed in aging), but also a wide range of neurological complications (Trejo and others 2004, 2007, 2008), pointing to crucial roles of blood-borne IGF1 on brain function. Therefore, because IGF1 is one of the more interesting factors mediating neural plasticity and metaplasticity, we will discuss this factor more extensively in the next section.

The Role of IGF1 on the Adult Brain

IGF1 is an important modulator of brain function (Torres-Aleman 1999), both during development through the classical role of promoting neuronal survival and in the adult life through a number of pleiotropic actions ranging from neuroprotection to neural plasticity (Torres Aleman 2005). IGF1 modulates neural plasticity through the regulation of the level of activity of neural circuitries and the strength of the synapses. The control of such actions relies on the amount of neurotransmitter released by the neurons participating in those circuitries, the abundance of postsynaptic neurotransmitter receptors, and the intrinsic excitability of postsynaptic neurons (Torres Aleman 2005). Besides, recently IGF1 has also been implicated in the control of hippocampal LTP and learning, and synaptic plasticity through its trophic effects on central glutamatergic synapses (Trejo and others 2007), and in the regulation of the other major aspect of brain plasticity, namely neuronal replacement (Trejo and others 2001, 2008). Nevertheless, IGF1 might play also activity-independent roles, because the blockade of the serum IGF1 is able to alter the memory of tasks not modulated by exercise (LLorens-Martin M, and others, 2008, unpublished data).

In this way, the IGF1 actions on the brain are a relevant part of the mechanisms operating the cognitive reserve, that is, the ability of the brain to increase its functional resources in direct proportion to its activity (Richards and Deary 2005). Synaptic plasticity is one main actor to display such cognitive reserve, and in this context, the role of IGF1 on both synaptic plasticity and hippocampal neuronal replacement appears especially relevant. In this way, serum IGF1 is needed in the adult brain for both basal hippocampal neurogenesis and exercise-induced increases of neurogenesis (Trejo and others 2001), but also for synaptic plasticity and cognition.

The processes related to synaptic plasticity modulated by the IGF1 have been reviewed extensively elsewhere (Aberg and others 2006; Davila and others 2007; Torres-Aleman 1999), consisting of a wide list of specific actions in the brain including modulation of neurotransmitter actions (Jones and Clemmons 1995; Seto and others 2002), a critical role in glucose metabolism and nutrient homeostasis (Taguchi and White 2008), the modulation of cerebral blood flow (Gillespie and others 1997), and arteriolar and vessel densities (reviewed by Aberg and others 2006). IGF1 increases astrocyte intercellular gap junctional communication (Aberg and others 2003), it promotes and maintains dendritic arborization (Cheng and others 2003), regulates the rate of neurogenesis in a dose-dependent manner (see below), and increases oligodendrogenesis (Aberg and others 2007). Many of these aspects have been reported responding to IGF1 after experience- or activity-induced events, like physical exercise, enriched environment, learning, and memory. All these actions, together with the above-mentioned evidence about the role of IGF1 modulating diverse membrane channels, many neurotransmitter receptors, and neurotransmitter release, point to a control of critical aspects of neuronal excitability and, therefore, of the neuronal integrative capacities (Davila and others 2007). Nevertheless, the actions of IGF1 on neural precursor/stem cells range from a shortening of the length of the cell cycle in neuron progenitors to influence on the

growth of all neural cell types (reviewed by Ye and D'Ercole 2006).

All these effects are mediated by the IGF-I receptor (IGF-IR), a member of the growth factor tyrosine kinase receptor family that signals through the PI3k-Akt pathway and the MAPK cascade (LeRoith and Roberts 1993). IGF-I actions are regulated, in turn, by IGF-binding proteins (Jones and Clemmons 1995).

Nevertheless, IGF1 plays roles related to the right operation of basic energy regulatory loops, besides the actions related to cognition and brain plasticity (reviewed by Fernandez and others 2007). It is important to note that both the IGF1 actions on metabolism/homeostasis and the actions on brain plasticity are mediated by the same receptor and the above-mentioned common signal transduction pathways.

The open debate about the roles of the IGF1 from different sources is far from being settled. The role of peripheral IGF1 has been recently strengthened by evidence demonstrating that although serum IGF1-deficient mice show a strong brain phenotype (Lopez-Lopez and others 2004; Trejo and others 2007, 2008), forebrain-specific deletion of IGF1 displays only minor detectable brain changes (Davila and others 2007). This evidence shows that serum IGF1 influences different aspects of learning, memory, and behavior. This "body-to-brain" signaling via peripheral IGF1 will contribute to the suggested importance of the "endocrine milieu" in higher brain function (Fernandez and others 2007).

In view of all this, we can conclude that one of the most outstanding features of neural plasticity and metaplasticity involving IGF1 is the adult hippocampal neurogenesis that we will deal in the next section.

Adult Hippocampal Neurogenesis

The regeneration of the central nervous system and the neuronal replacement in the brain has long been considered nonexistent or negligible (Ramón y Cajal 1913). Although this statement still appears valid for the majority of brain regions, we know now that there exist at least two constitutive neurogenic regions in the adult brain (Ortega-Perez and others 2007), the subventricular layer of the lateral ventricles (generating cells that populate the olfactory bulbs) and the subgranular zone of the hippocampal dentate gyrus (generating granule neurons that populate the granule cell layer). There also exists some sparse evidence about potentially neurogenic areas along the walls of the third and fourth ventricles. Finally, reactive neurogenesis has been suggested after lesion-induced neuron loss in the cerebral cortex, striatum, and pyramidal cell layers of the hippocampus.

It is noteworthy that the neurogenic regions in the adult brain have been found along the complete vertebrate phylogeny. Electric (Zupanc 2006) fishes, amphibia (Beazley and others 1998), reptiles (Lopez-Garcia and others 1988), birds (Nottebohm 2002), and mammals (Kempermann 2008), including primates (Gould and others 1999) and humans (Eriksson and others 1998) all have adult neurogenesis. However, the adult neurogenesis is not understood at present as a phylogenetic atavism, but rather as a challenging feature of adult brains (for a review, see Kempermann 2008).

Abundant literature has accumulated in recent years about the pattern of molecular development of this cell population. Granule neurons specifically express the transcription factor Prox1. The life cycle of the new neuron (reviewed by Duan and others 2008) begins as a precursor cell actively proliferating and expressing Mash1, Id3, Hes5, and Notch1 (Pleasure and others 2000). They also express NeuroD1 at the first steps of differentiation, subsequently also coexpressing neurogenin1 and neurogenin2. This first step has three successive stages called type I, type II, and type III cell, during which the cells also express GFAP, Nestin, and Sox2, respond to the mitogenic action of Sonic hedgehog (Lai and others 2003), to EGF, bFGF, and LIF, and are sensitive to tonic GABAergic activation. After this period, they begin to express doublecortin (DCX) and PSA-NCAM, a stage while it is called immature neuron. As the differentiation process progresses, NeuroD1 expression begins to disappear in favor of the expression of NeuroD2. The immature neuron can migrate a short distance and progressively differentiate into a growing axon leading to the hilus and a growing dendritic tree leading to the dentate molecular layer. During this stage, the cells respond to the regulatory/modulator actions of IGF1 (Llorens-Martin and others 2008), VEGF (During and Cao 2006), and BDNF (Schmidt and Duman 2007; Vaynman and Gomez-Pinilla 2006). After two to three weeks of age the afferent perforant axons from enthorrinal cortex, as well as commissural axons from hilar mossy cells, begin to make contact with the growing dendrites, signaling the last step in the maturation of the newborn neurons. During this stage, the cells express calretinin and then calbindin, and NeuN, and gain sensitivity to glutamatergic and GABAergic innervation. This maturation pattern replicates the ontogenetic pattern of a mature granule neuron (Esposito and others 2005). However, this process is strongly regulated not only because the final purpose of adult neurogenesis is to raise new mature granule neurons, but also because the immature neurons may play some roles. We know much, but not enough, about the function of the new neurons in the adult brain. We do know that newborn neurons are functional (van Praag and others 2002), and their axons establish synapses with

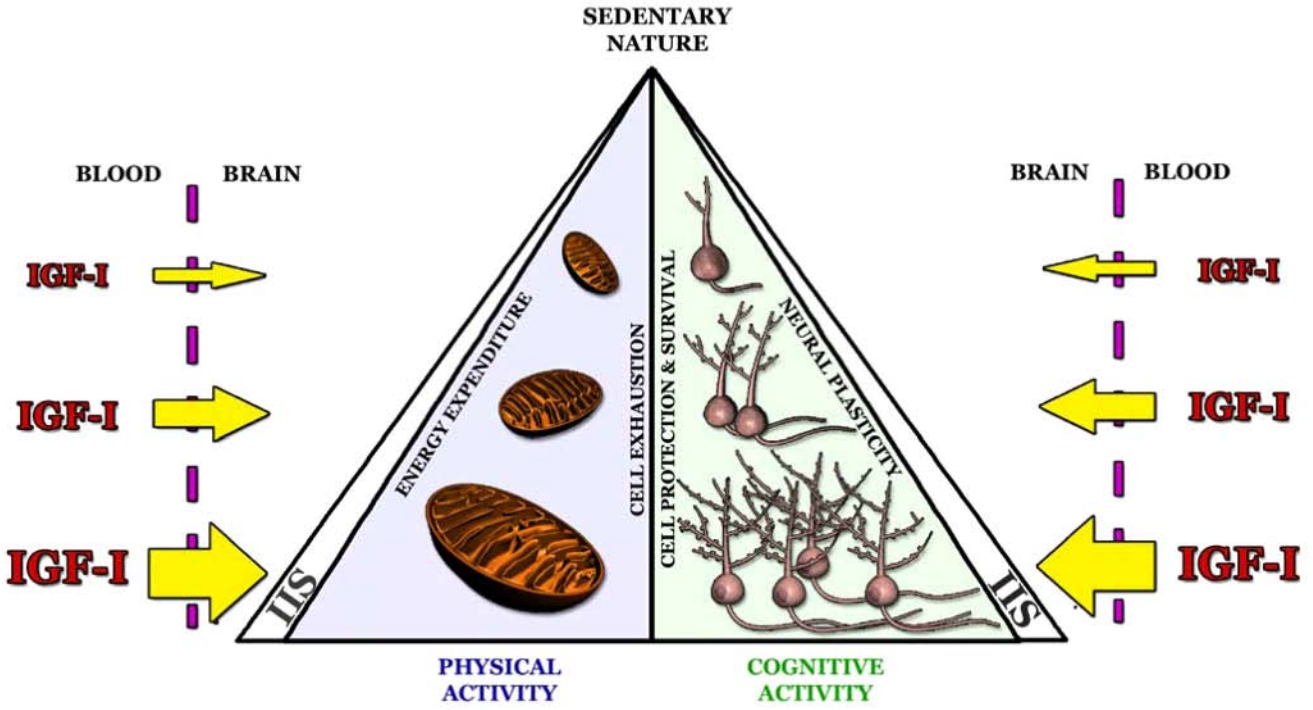

Figure 1. Serum insulin-like growth factor 1 (IGF1) entrance into the brain as a function of the organism's activity. Serum IGF1 appears to act as a sensor for the intensity of physical and cognitive activity. Increasing levels of activity influence brain function through increasing levels of serum IGF1 signaling into the brain. This variable signaling can be achieved through variable levels of either blood IGF1 concentration, by modulating IGF1 entrance into the brain, the levels and function of IGF binding proteins inside the brain, or finally, by modulating the differential sensibility of brain regions to capture the incoming IGF1 and the response of the canonical signaling transduction pathways. Whatever the way, IGF1 contributes to sustain the function of the neural tissue through the modulation of the energy expenditure (causing cell exhaustion) and, at the same time, through the modulation of neural plasticity (and also neuroprotection). The higher the activity, more resources are required to process the information and more plasticity will be needed, and more cell exhaustion is generated and more neuroprotection will be useful.

hilar interneurons, mossy cells, and CA3 pyramidal cells and release glutamate as their main neurotransmitter (Toni and others 2008). However, controversial literature has accumulated recently about the function of these neurons after different manipulations to eliminate or reduce the basal rate of hippocampal neurogenesis. We will deal in the next section with this issue considering its relation to behavior and neural plasticity.

We can reasonably conclude that the formation of new cell subpopulations with new connections inside a mature neural circuit with a strict regulatory system is an outstanding form of plasticity. Indeed, because every new cell and connection of this subpopulation can, in addition, suffer the other plastic processes described in the previous sections, such as modulation of dendritic arborization and synaptic plasticity, the metaplasticity of the hippocampal neurogenesis can reach the maximum.

Next we will revise the most recent ideas about how IGF1 can modulate neural plasticity through its actions on adult hippocampal neurogenesis.

IGF1 and Adult Hippocampal Neurogenesis, Mediators of Neural Plasticity

IGF1 is involved, as mentioned above, in the control of the energy metabolism, in the control of the cell survival and the cell number, and, in addition, in the adult with the induction of neuroprotection, the modulation of cognition, and the regulation of the adult hippocampal neurogenesis. These functions, together with the fact that IGF1 is synthesized in adult organisms mostly outside the brain, make serum IGF1 an ideal signaling factor of the organic activity for the brain. The organism's activity (physical and cognitive) is the main trigger of neural plasticity, and the higher the activity, the higher the necessity for adaptive changes in the properties and functioning of the neural cells to cope with a challenging environment. Therefore, it is not surprising that IGF1 is a main factor signaling physical activity to the brain by inducing this plasticity (Fig. 1). It is tempting to speculate about the phylogenetic mechanism that made IGF1 and its actions on hippocampal neurogenesis one of the ways of induction of neural plasticity in the adult brain as a response to the increase in physical activity.

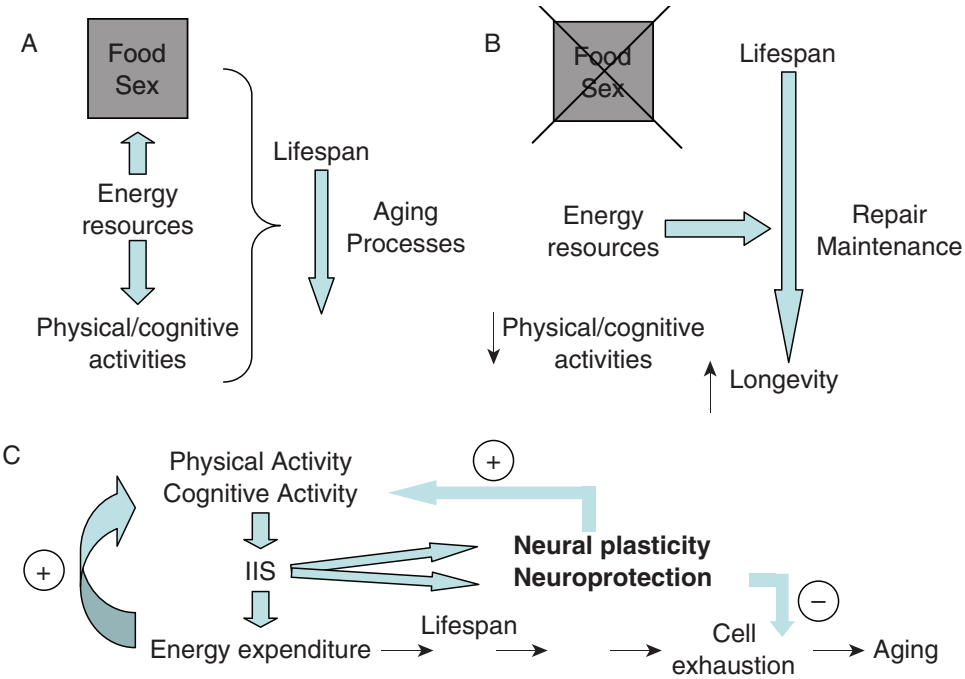

Figure 2. A connection between the success of reproduction, diet consumption, aging/longevity, and neural performance exists by means of a trade-off between activity versus maintenance and repair, and an associated mechanistic link: the common signaling pathways. Processes in A represent the situation of an organism using its energy resources to ensure food or sex. This situation along lifespan implies normal aging. Processes in B represent the situation of an organism when the success of reproduction is not ensured: Energy resources can be reallocated to repair and maintenance leading to increased longevity. Under normal conditions, both processes are compensated through the action of one family of molecules mediating the two mechanisms in a regulatory loop (C): Insulin and insulin-like signaling pathways (IIS) mediate in both the energy expenditure associated with physical/cognitive activities required for lifespan performance (this implies a specific rate of cell exhaustion and aging), and brain plasticity and neuroprotection (as a mechanism to compensate cell exhaustion and brain aging). If reproduction is jeopardized, energy resources can be used for different processes and cell exhaustion decreases, diminishing the requirement of plasticity and neuroprotection.

The energy regulatory mechanisms are highly conserved through phylogeny. These mechanisms consistently support the organism's activity through catabolic pathways that ultimately promote toxicity, and finally, aging. The higher the activity of an organism, the faster it accumulates oxygen reactive species and toxicity. The lifespan of the organisms is in this way linked to the activity of the individual. However, this is a strongly regulated process. When successful reproduction of the organism is jeopardized (for example, during a period of food shortage), the signaling pathways sustaining metabolism become down-regulated to minimize the exhaustion of the organism, intending to augment the possibilities of reproduction by extending the lifespan waiting best times (Kirkwood and Shanley 2005). This is the probable reason because dietary restriction increases lifespan (Prolla and Mattson 2001). Insulin and IGF1 signaling are directly involved in the metabolic regulatory mechanisms throughout phylogeny. Therefore, it is not surprising that experimental reduction of the insulin and IGF1 signaling also extend lifespan (Kenyon 2001; Fig. 2). The gene sequences encoding IGF peptides are highly conserved among vertebrate species, and IGFs are found in species whose ancestors diverged 550 million years ago (LeRoith and Roberts 1993). Recently, a number of studies also point to a decreased aging in models of reduced or silent insulin and IGF1 signaling, due to diminished neurotoxicity, as demonstrated measuring proteotoxicity in non-neural tissue of invertebrate organisms (reviewed in Cohen and Dillin 2008).

However, abundant literature has long demonstrated the neuroprotective actions of IGF1 in adult brains (reviewed by Aberg and others 2006) together with roles in cognition (Trejo and others 2007). Therefore, it is not surprising either that experimental reduction of the IGF1 signaling induced a strong brain phenotype including decreased synaptic plasticity, impaired learning and memory, and alterations in anxiety (Ding and others 2006; Llorens-Martin and others 2008; Svensson and others 2006; Trejo and others 2007). It is noteworthy that some of the mouse models of genetic silencing or blockade of insulin-like signaling course with impaired cognition besides extended lifespan (for example, brain-specific knockout of IRS2; Taguchi and others 2007; Martín and others, 2008, unpublished data) whereas other models have not been behaviorally analyzed.

This controversy unavoidably leads to the conclusion that the aging mechanisms are not exactly the

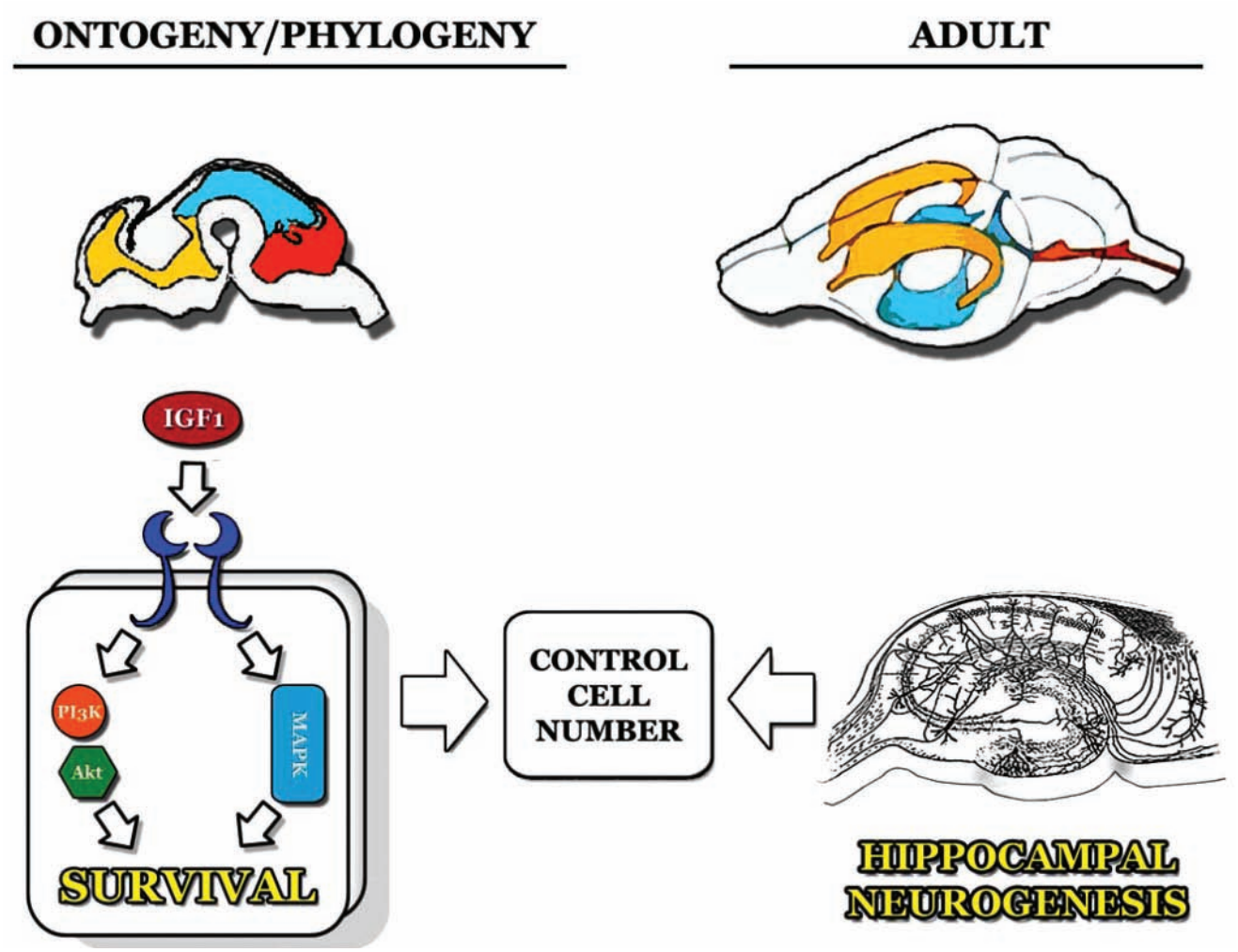

Figure 3. Advantageous reuse of insulin-like growth factor (IGF) functions. The signaling transduction pathway of IGF is highly conserved through phylogeny, and it is maintained during brain development and in the adult organism. The cell survival and the control of neural cell numbers appear as a main consequence of IGF signaling, both in lower organisms and neural development. In adult brain, IGF1 also plays a role in controlling neuron number and survival, together with roles in plasticity. Consequently, it is not surprising that an outstanding role of IGF1 in controlling cell survival and differentiation takes place in hippocampal neurogenesis that constitutes a recapitulation of ontogenetic events inside adult mature circuits.

same in different tissues, and more important, that inside the brain, cellular exhaustion as measured by neurotoxicity might be dissociated in some unknown way from normal neuronal functioning and plasticity as measured by the animal's behavior and neuroprotection-associated parameters. The simplest explanation for this discrepancy might be that the IGF1-signaling system has been phylogenetically adapted to serve two apparently opposite functions, namely the maintenance of energetic consumption (leading to cell exhaustion and aging) and neuroprotection and brain plasticity (assuring cognition processes in normal conditions). Both actions are linked by the organism's activity. If the activity of the animal is reduced to reallocate resources due to jeopardized reproduction or food shortage (see above), IGF1 signaling is reduced, both because a diminished activity implies a decreased demand for information processing and memory storage, and because a reduced activity increases lifespan by reducing cell exhaustion. IGF1 signaling is the mediator of both kinds of actions mediated by common signal transduction pathways, as mentioned above. In this way, IGF1 becomes the ideal humoral factor to translate the stimuli of exercise to several organs, especially brain. Some of the actions of IGF1 in the adult brain (survival and control of cell numbers) resemble those ones during development and those ones the IGF family plays in lower organisms, while some other functions are specific (Fig. 3). The particular roles IGF1 play in each case will be regulated depending on the cell state, time, and the brain region, and therefore, a specific and complex coupling

of the IGF1 signaling pathways to downstream regulatory loops must exist.

Such a functional adaptation of IGF1 roles makes special sense in relating to adult hippocampal neurogenesis, because neuronal replacement is probably the most relevant aspect of neural plasticity and metaplasticity induced by the organism's activity. This argument relies on the functional role of the adult hippocampal neurogenesis, although this function is still far to be fully understood. Controversial evidence has been reported in the recent years. The works by Shors and others (2001, 2002), Santarelli and others (2003), Meshi and others (2006), Saxe and others (2006), Trejo and others (2008), Zhang and others (2008), Dupret and others (2008), and Imayoshi and others (2008) have reported contradictory results. Summarizing, spatial learning and memory (at least in the most complex forms) appears impaired in many models of decreased neurogenesis, whereas the effect on fear conditioning (especially the contextual forms) depends completely on the approach considered. Other behaviors are still not corroborated by different works. It is noteworthy that the anxiolytic effects of environmental enrichment appeared not dependent on neurogenesis, but those of physical exercise were dependent. Considering all this evidence, we can assume a functional role of the new neurons participating in spatial learning and memory and some forms of anxiety-related behaviors strongly supported. Therefore, taking into account the changeable morphological and electrophysiological characteristics of the newborn neurons, it is reasonable to think that the adult hippocampal neurogenesis has a major role in the neural plasticity related to learning and memory.

Little is known about how these cells perform the role of participating in learning and memory. It is beyond the scope of this review to tackle this issue, but it will serve to state that several theoretical models of the operation of these immature neurons exist (recently reviewed by Kempermann 2008). The hypothesis by Aimone and others (2006) establishes that the new neurons might work by helping to distinguish the temporal pattern of two separate events. The rate of new and complex information entering the brain along time might be a distinguishing criterion between low- and high-demanding processes of neural plasticity. For the former, a less complex environment could be coped with by plasticity processes without modifying the cell numbers. On the contrary, higher demanding environments might need variations in the number of neurons to accomplish the task of establishing temporal patterns between separate events, at least for hippocampus-dependent tasks. We could say that high-challenging environments might need plastic resources beyond the capacity of the existing cells, recruiting resources involving the newborn dentate neurons. Besides, this rate of entering information is one of the factors supporting the notion of neurogenic/cognitive reserve, because the faster the entering information accumulates, the higher the plastic changes would be. Therefore, adult hippocampal neurogenesis can be envisaged as a mechanism allowing the brain to respond to different degrees of environmental challenge by modulating the plastic capability to the change itself, what is called metaplasticity (Garcia-Segura 2009).

A different model postulates, on the other hand, that the key point for understanding the role of adult hippocampal neurogenesis is rather the homeostatic mechanisms by which an increasing number of new neurons making new connections are able to stabilize new memories into a preexisting circuit (reviewed by Meltzer and others 2005), which is a counterintuitive concept. In this way, a compensatory mechanism between an increased number of firing newborn neurons and the excitability of CA3 pyramidal neurons might exist. This process is called synaptic scaling, a good example of these homeostatic systems. Growth factors like IGF1 might contribute to establish and maintain the balance of these features of the synaptic connections, because of its above mentioned specific actions on the interneuronal connectivity. For example, it has been recently shown that IGF1 plays a role in balancing the excitatory/inhibitory signals in the dentate gyrus (as measured by the VGlut1/GAD6 ratio of synaptic buttons in the inner molecular layer [Trejo and others 2008]), with relevant consequences for the hippocampus-dependent behavior.

It is obvious that the signaling of the organism's activity to the brain is both humoral regarding physical activity, and also directly neural during physical and cognitive activities, because every physical activity implies a cognitive activity unavoidably associated. In this way, it is noteworthy that the adult hippocampal neurogenesis is highly sensitive to neural activity, probably through an intricate neural plexus populating the subgranular zone (SGZ) where both the dentate precursors reside and the immature neurons differentiate. Much evidence supports these interactions between neural activity and the SGZ, being the GABAergic input and some other transmitter systems, prominent actors of this neurogenesis-activity link (for a recent review, see Ge, Pradhan, and others 2007). In this way, recent evidence points to the ambient GABA levels inside the dentate gyrus as a sensor of the dynamic neuronal network activity (Ge, Yang, and others 2007), and GABA signaling might be considered the final step where the different mechanisms indicating activity meets to inform both precursors and immature neurons. An extensive plexus of connections inside the dentate gyrus endorses this possibility, together with the fact that many of the processes in the vicinity of the SGZ penetrate this layer and run in close proximity to

the soma and processes of the immature newborn neurons, such as, for example, the distal parts of the mossy cell dendritic processes ending in the SGZ close to the newborn granule cells (Hontecillas-Prieto, L, and Trejo, JL, 2008, unpublished results). A putative connection and the functional meaning of these contacts must still be demonstrated.

Therefore, both serum IGF1 and the SGZ plexus act as activity sensors for the brain, with the response being an increase in neural plasticity and neuronal replacement. The link becomes reinforced because serum IGF1, in turn, influences the AHN rate. Nevertheless, other factors contribute to neural plasticity as a response to activity, such as the cyclic/stationary hormonal changes (Garcia-Segura 2009) or variations of interindividual social interaction (Adamec and others 2005; Korzan and Summers 2007). Whatever the origin, the activity-induced actions in the brain can be mediated by a number of molecules. Mounting evidence supports an emerging point of view about the convergence and the synergy between IGF1, BDNF, and VEGF in mediating the exercise effects (Cotman and others 2007), as a part of a growth factors cascade in which all growth factors are necessary but not sufficient (reviewed by Llorens-Martin and others 2008).

It is relevant to note that the involvement of the adult hippocampal neurogenesis as an activity-sensitive mechanism of neural plasticity is not definitely circumscribed to the function of the future mature neurons. The specific function of the immature neurons is still a matter of intense debate. One point of view established that the fate of the new neurons born in the adult dentate gyrus was the maturation and insertion into a neural circuit, to perform the same roles of the older granule neurons (Van Praag and others 2002). Several recent reports have supported a complementary, not exclusive point of view. According to this view, the immature neurons would also have an additional role while maturing, because of the specific electrical properties they display (Ge, Yang, and others 2007; Schmidt-Hieber and others 2004; Song and others 2002; Wang and others 2000; and for a recent review, see Ge, Pradhan, and others 2007). Besides, the number of immature neurons exhibited controllable plasticity by the physical/cognitive activity (Llorens-Martin and others 2006, 2007). The fact that the immature neurons may play some role before completing maturation, and that such a role may be relevant for the hippocampal function (Kempermann 2008), has prompted us to describe this way of working as "functional immaturity," better than the old view of immature functioning. It is the survival and growth of this immature subpopulation of newborn cells that might be influenced by activity-induced serum IGF1 signaling. Further investigations are still needed to demonstrate this issue. Some insights into the response of the immature neuron subpopulation to levels of activity have been made recently. Environmental enrichment increases adult neurogenesis (Brown and others 2003; Kempermann and others 2002), and it has been reported that the enrichment-induced increase in the number of immature neurons is not a consequence of a generalized increment in cell survival, but an action on cell populations of a specific age (Llorens-Martin and others 2007). Besides, enrichment increases the number of new neurons responding to reexposure to the same environment but not to a different experience (Tashiro and others 2007). This evidence points first to a critical period during an immature stage of new neurons sensitive to activity and experience when increases in the survival can occur, and second, to the capability of the dentate gyrus to change neural representations of the experience as a function of previous ones. This is the way through which experience might exert a long-term influence on learning- and memory-related dentate gyrus functioning (Tashiro and others 2007). In this way, serum IGF1 may serve as an activity sensor mediating the effects of the exercise in a maturation stage-dependent manner, because the blockade of serum IGF1 in both sedentary and exercised animals modulates the number of immature granule neurons, depending on the differentiation stage of the newborn cells (LLorens-Martín M, and others, 2008, unpublished data).

The complexity of the mediation of physical activity effects by IGF1 and adult hippocampal neurogenesis has begun to be unveiled only in the last years. Although the exercise-induced effects of serum IGF1 on neurogenesis have long been demonstrated (Trejo and others 2001), recent work has shown that serum IGF1 has a direct role in cognition (Trejo and others 2007), and at the same time reveals that some long-term behavioral effects of exercise are IGF1 independent. Some of these roles have been demonstrated by using genetic models of reduced circulating IGF1. Specifically, serum IGF1-deficient mice showed a greater susceptibility to brain injury and lack of neuroprotection by exercise (Trejo and others 2004) and a blockade of exercise-induced vessel remodeling (Lopez-Lopez and others 2004). Nevertheless, their brains display a wide array of disturbances, ranging from a lack of synaptic plasticity and unbalanced excitatory/inhibitory synaptic buttons (Trejo and others 2007), reduced neurogenesis (Trejo and others 2008), and amyloidosis (Carro and others 2002). Furthermore, these mice responded to neither physical exercise against amyloidosis, nor to the beneficial effects of exercise on neuronal plasticity and neurogenesis. Consequently, these mice were insensitive both to the memory-enhancing effects of exercise in hippocampus-dependent learning and memory tasks, and to the anxiolytic effects of exercise

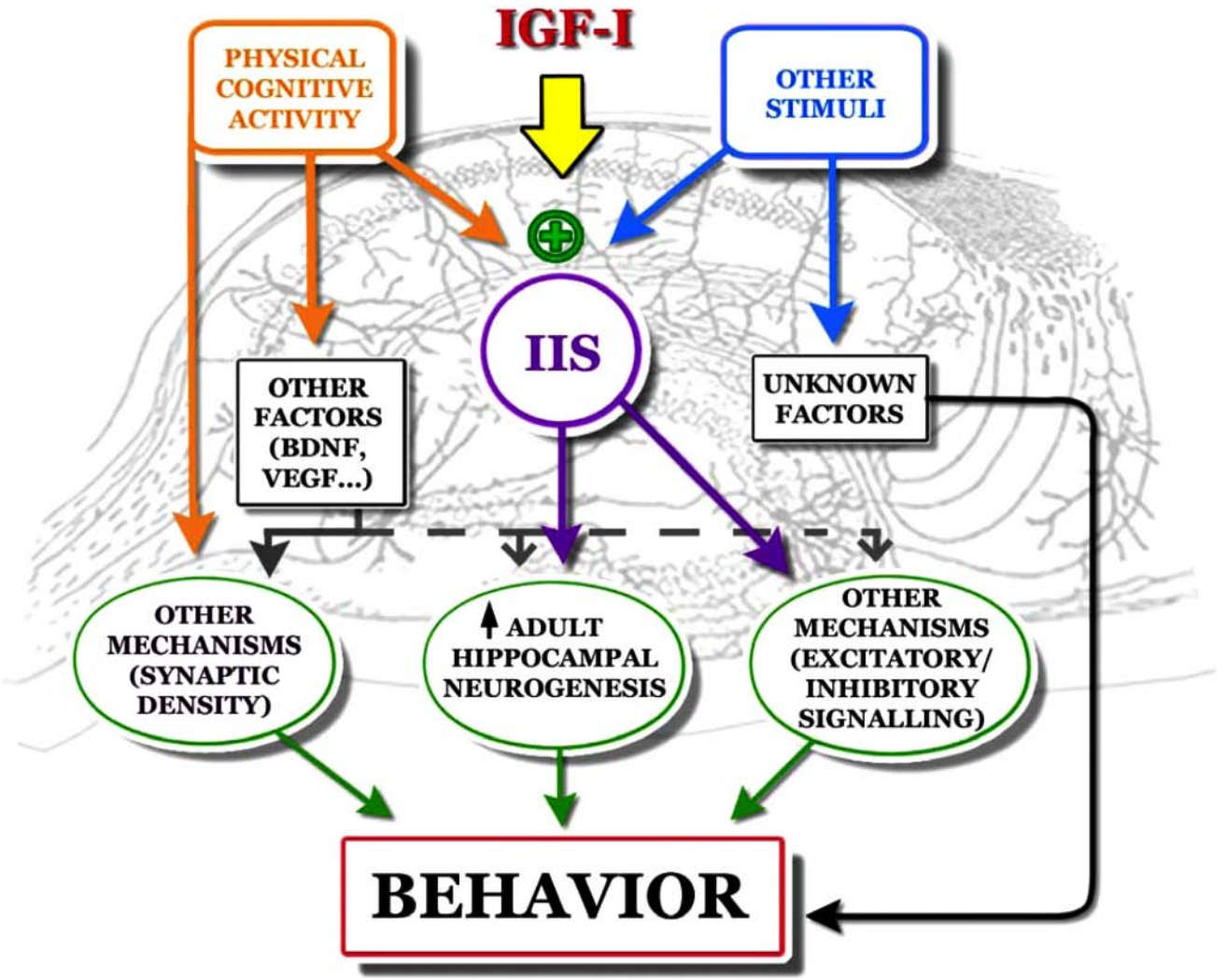

Figure 4. Many but not all the effects of exercise are mediated by serum insulin-like growth factor 1 (IGF1), although it plays some role not related to the organism's activity. As examples, physical exercise can influence behavior through the IGF1-independent modulation of a small number of morphological (and supposedly functional) changes in the hippocampus, whereas serum IGF1 influences some parameters of the immature subpopulation of newborn neurons (hippocampal neurogenesis) independently of the activity status of the individual.

(Llorens-Martin and others 2008; Trejo and others 2008). On the contrary, depressive-like behaviors appear IGF1 independent in response to exercise in serum IGF1-deficient mice. This evidence prompted us to go more deeply into the investigation of IGF1-dependent and independent mechanisms of the effects of physical activity in the brain. In this way, the exercise-induced increase in the dendritic spine density in hippocampus is IGF1 independent (Glasper and others, 2008, unpublished data) in both CA1 and dentate gyrus. Moreover, some effects of exercise on the neurogenic subpopulation appear to be IGF1 independent, because the exercise-induced increase in the survival of an intermediate stage of differentiating neurons is not mediated by IGF1, but survival of newborn neurons in different maturation stages is affected by exercise in an IGF1-dependent manner (LLorens-Martin M, and others, 2008, unpublished data; Fig. 4).

Most of the evidence about an activity-dependent role IGF1 plays inside the brain points to long-term, hippocampus-associated, and learning- and anxiety-related actions. It is not a coincidence that these actions have been significantly correlated with adult hippocampal neurogenesis. These findings define more clearly the role of serum IGF1 as a mediator of exercise, revealing a very complex regulatory system of the effects of activity on brain.

Conclusion

The capacity of the brain for reorganization during adult life is an amazing feature. Mainly because the higher the

activity of the organism, the more drastic are the changes in the structure, connectivity, and the neuronal operation. The mechanisms by which this is achieved are beginning to be unveiled. What is especially relevant is the ability of a circulating growth factor like IGF1 to respond to physical activity, by recruiting serum IGF1 to play both energy- and cognition-related roles. The higher the activity, the higher the energy consumption and the demands for information/memory processing. But also the higher the cell exhaustion. IGF1 appears to serve both roles through a common signaling pathway. Probably for that reason, IGF1 has also been adapted to gain neuroprotective roles.

IGF1 modulates the adult hippocampal neurogenesis by controlling crucial aspects of proliferation and survival of the precursor cells and the immature differentiating neurons. Consequently, IGF1 participates in the modulation of hippocampus-dependent behaviors like the spatial learning and memory, and anxiety. Together with its actions on synaptic plasticity, this makes IGF1 a mediator of the activity-induced neural plasticity. This way IGF1 contributes to control a relevant part of the hippocampal circuit and also to promote a flexible capacity to respond to different degrees of activity, what is called metaplasticity. Moreover, by adjusting the survival of the newborn neurons to the demands of information processing linked to the activity of the organism, IGF1 is a mediator factor of the cognitive reserve.

The investigation of the mediator factors of the effects of physical/cognitive activity in the brain are beginning to make sense both because modern life favors sedentary nature and because normal and pathological aging is associated with decreased activity. The activity-induced signaling inside the brain can be closely related with neuroprotection, as well as can be associated with lifespan. A detailed analysis should be made to determine the neuroprotective versus aging effects of insulin-like signaling. In this paradigm, the investigation of the IGF1-dependent and independent effects of physical activity, as well as the activity-dependent and independent signals triggering the IGF1 actions in the brain, merit further attention.

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