Signaling Pathways Relevant to Cognition-Enhancing Drug Targets

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Abstract

Aging is generally associated with a certain cognitive decline. However, individual differences exist. While age-related memory deficits can be observed in humans and rodents in the absence of pathological conditions, some individuals maintain intact cognitive functions up to an advanced age. The mechanisms underlying learning and memory processes involve the recruitment of multiple signaling pathways and gene expression, leading to adaptative neuronal plasticity and long-lasting changes in brain circuitry. This chapter summarizes the current understanding of how these signaling cascades could be modulated by cognition-enhancing agents favoring memory formation and successful aging. It focuses on data obtained in rodents, particularly in the rat as it is the most common animal model studied in this field. First, we will discuss the role of the excitatory neurotransmitter glutamate and its receptors, downstream signaling effectors [e.g., calcium/calmodulin-dependent protein kinase II (CaMKII), protein kinase C (PKC), extracellular signal-regulated kinases (ERK), mammalian target of rapamycin (mTOR), cAMP response element-binding protein (CREB)], associated immediate early gene (e.g., Homer 1a, Arc and Zif268), and growth factors [insulin-like growth factors (IGFs) and brain-derived neurotrophic factor (BDNF)] in synaptic plasticity and memory formation. Second, the impact of the cholinergic system and related modulators on memory will be briefly reviewed. Finally, since dynorphin neuropeptides have recently been associated with memory impairments in aging, it is proposed as an attractive target to develop novel cognition-enhancing agents.

1   Introduction

Despite a general lengthening of life span in humans over the last decades, the quality of life still varies substantially among older adults. Some individuals are active and socially engaged, while others have physical or cognitive impairments and/or present depressive symptoms (Rowe and Kahn 1997; Frisardi et al. 2011). A better understanding of the processes leading to individual differences during aging might help identifying new pharmacological targets and develop innovative treatments to favor successful cognitive aging. This chapter summarizes the current knowledge on signaling pathways of particular importance in memory formation (especially spatial memory) in rodents and the changes occurring during normal (non-pathological) aging. Each section covers potential cognition-enhancing drug targets and includes an overview of related published studies, focusing on the data obtained in rats, and compounds already available (Fig. 1).

Normal aging is associated with increasing memory losses that can be detected in middle-aged rats (Deupree et al. 1993) similarly to humans (Davis et al. 2003). However, in aging rats of similar ages, important inter-individual differences in cognitive abilities have been reported (Gallagher et al. 1993, 2003; Aubert et al. 1995; Quirion et al. 1995; Rowe et al. 1998; Wilson et al. 2003; Menard and Quirion 2012b). Sex and strain differences have also been observed (Markowska 1999; Menard et al. 2014b) but will not be specifically addressed in this chapter. Variations of cognitive status in aged rats are not related to neuronal loss, as cell death in the hippocampus and neocortex does not characterize normal aging in rodents (Rapp and Gallagher 1996; Rasmussen et al. 1996; Merrill et al. 2001; Gallagher et al. 2003). Moreover, no regression of dendrites (Turner and Deupree 1991; Flood 1993; Pyapali and Turner 1996) or decrease of spine density (Curcio and Hinds 1983; Markham et al. 2005) has been reported in old rats. Most electrical properties of the neurons remain constant over the life span including resting membrane potential, threshold to reach an action potential, and the width and amplitude of Na^+ action potentials (Segal 1982; Landfield and Pitler 1984; Niesen et al. 1988; Kerr et al. 1989; Barnes et al. 1992; Potier et al. 1992, 1993; Burke and Barnes 2006). These observations suggest that in rodents, age-related memory impairments associated with normal aging might be linked to altered cell signaling and dysregulation of gene expression as reported by us and others (for a review, see Benoit et al. 2011).

2   Types of Memory

The hippocampus-dependent Morris Water Maze (MWM) task (Morris 1984) is one of the most widely used behavioral paradigms in neuroscience. It is particularly efficient to discriminate aged rat subgroups depending on their level of cognitive fitness. However, multiple tests and paradigms have been developed over the years to study different forms of learning and memory. The following sections will
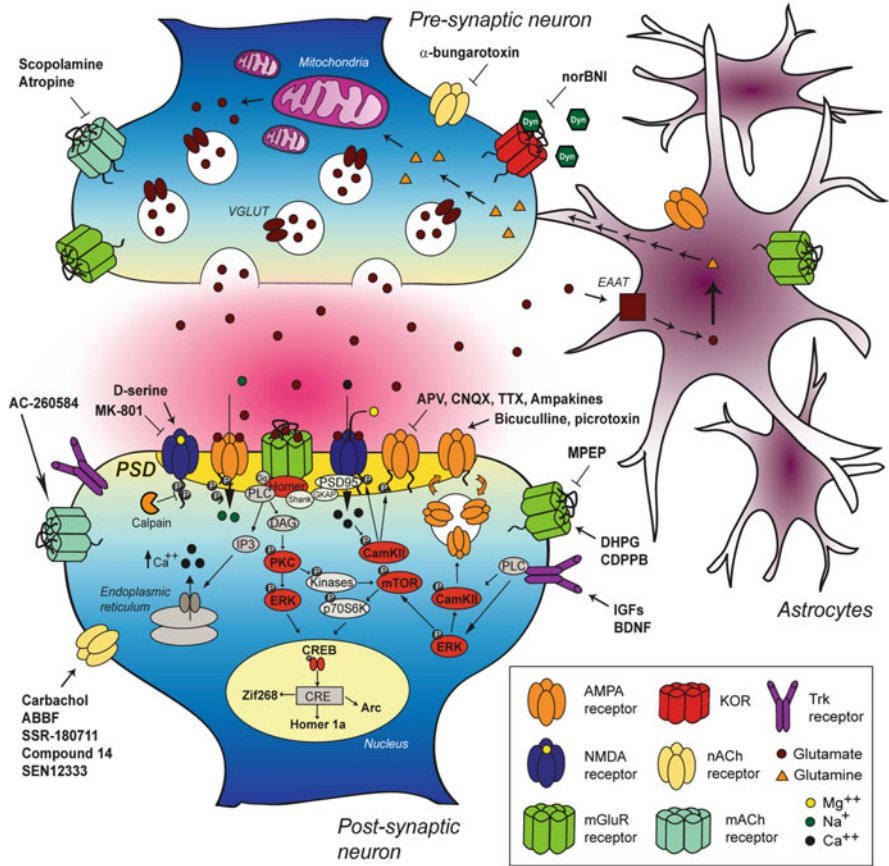
Fig. 1 Summary of the signaling pathways involved in memory formation. Following neurotransmitter glutamate release, postsynaptic ionotropic (AMPA, NMDA) and metabotropic (mGluR) receptors become activated leading to the phosphorylation of downstream signaling effectors, notably PKC, CaMKII, ERK, mTOR and CREB, and immediate early gene expression (Arc, Homer 1a, Zif268). Glutamatergic neurotransmission can be modulated by other neurotransmitters, such as acetylcholine and its nicotinic (nACh) and muscarinic (mACh) receptors, neurotrophins (BDNF) and growth factors (IGF) through the Trk receptors, or neuromodulators such as dynorphins (Dyn) that act on presynaptic κ-opioid receptors (KOR) to block glutamate release. Astrocytes play an active role in the glutamatergic system activity as they recapture glutamate through the excitatory amino-acid transporters (EAATs), where it is amidated and reconverted in glutamate in neuron mitochondria to finally be accumulated in synaptic vesicles through the vesicular glutamate transporters (VGLUTs)

summarize spatial, recognition, social, and fear memory neuronal processes and the behavioral paradigms to which they are associated.

2.1 Spatial Memory

Spatial memory is probably the most studied form of cognition in rodents. It is required to navigate in an environment or to remember where objects have been placed and implies various representations and encoding (Bird and Burgess 2008). Initial information was obtained from epileptic patients showing the devastating effects of bilateral medial temporal lobe or hippocampal damage (Milner and Penfield 1955; Scoville and Milner 1957). In rodents, hippocampal lesions severely impair performances in the MWM task (Moser and Moser 1998) which consist in finding a hidden escape platform in a pool filled with opaque water (Morris 1984). The animals use spatial cues on the walls of the room to orient themselves in the environment and successfully navigate. Following several days of training (multiple trials per day), young rats or mice will reach the platform quickly. Old rat learning curves can then be compared to classify them in aged memory-impaired (AI) and -unimpaired subgroups (AU) (Gallagher et al. 1993, 2003; Aubert et al. 1995; Quirion et al. 1995; Rowe et al. 1998; Wilson et al. 2003; Menard and Quirion 2012b). A probe test for which the platform is removed can subsequently be conducted to confirm cognitive status. In this task, the number of platform crossings and time or distance spent in the target quadrant can be compared to assess memory accuracy. The classical paradigm can be modified to add a second week of training in which the platform is moved to another quadrant of the pool (Menard and Quirion 2012b). Inhibitory and reversal learning, which contributes to the extinction of previously acquired memories and learning of a novel similar task, is strongly altered in AI rats suggesting that adaptative synaptic plasticity is affected and less efficient than in young and AU animals (Menard and Quirion 2012b). This could be related to *place cells* which are an ensemble of cells that fired when an animal is moving in an environment, encoding a cognitive map with a specific spatial-firing pattern (O'Keefe and Dostrovsky 1971). Wrong encoding or recollection of the patterns could lead to cognitive deficits in old rodents (Wilson et al. 2003, 2006).

Other paradigms have been developed to study spatial memory in rodents including the Barnes maze, radial arm maze, and the hole-board task. In the Barnes maze, rodents have to find an escape box using visual cues on a circular surface with up to 20 holes around its circumference (Barnes 1979). The task is based on rodents' aversion of open bright spaces and is considered relatively unstressful and modestly demanding physically. Similarly to the MWM task, various parameters can be measured such as latency to escape, path length, velocity, etc. Some senescent rats exhibit poor performances in this test (Barnes 1979; Harrison et al. 2006; Barrett et al. 2009). Hippocampal lesions induced by traumatic brain injury also lead to memory deficits in this task (Fox et al. 1998). Another interesting behavioral paradigm to evaluate spatial memory is the radial arm maze (Walker and

Olton 1979; Hudon et al. 2002; Webster et al. 2014). In this task, the animals have to find food reward at the end of the baited arms and the design allowed to explore reference and working memory function separately (Roberge et al. 2008; Grayson et al. 2014). Indeed, reference memory errors are associated with visits in non-baited arms, while working memory errors are the results of reentry in a previously visited arm. Nevertheless, the MWM task is generally used to evaluate the impact of normal aging on spatial memory particularly in rats.

2.2   Recognition Memory

While spatial memory is necessary to explore and navigate in old or new environments, other skills such as the ability to discriminate novelty from stimuli that have been previously encountered are also necessary for survival. Interestingly, the ability to recognize a familiar versus novel stimulus (Rowe et al. 1998) or objects (Menard et al. 2013b, 2014b) declines with normal aging in rodents. Recognition memory tests compared time spent exploring familiar versus novel objects, smells, or tastes in distinct spatial locations (Fedulov et al. 2007; Dere et al. 2007; Tse et al. 2007; Menard et al. 2013b). In contrast, spatial memory which involves circuitry of the hippocampal formation, albeit recognition memory, is linked to the perirhinal cortex (Burke et al. 2012). AI rodents seem to falsely identify novel objects or stimulus as familiar leading to pattern separation deficits (Burke et al. 2010). As for spatial memory and hippocampal lesions, impairments of recognition memory have been reported in rats with lesions of the perirhinal cortex (McTighe et al. 2010). Again no significant loss of neurons has been observed in this brain structure over the life span (Rapp et al. 2002).

2.3   Social Memory

Another form of cognition essential for survivability is social memory. Rodents need to interact with each other, establish social networks, and learn how to respond to stimuli that define hierarchy and mate choice (Berry and Bronson 1992). Basic social interaction between rodents can be studied using video recording to analyze active interaction time between a test animal and a novel unfamiliar mouse or rat. Various behavioral paradigms were developed to study in detail memory formation processes by social recognition and learning (for a review, see van der Kooij and Sandi 2012). In rodents, androgens and estrogens control social information processing by regulating hormones and neuropeptides such as oxytocin and arginine–vasopressin (Winslow et al. 1993; Neumann 2008; Choleris et al. 2009). Interestingly, the memory of mice seems to be far superior to that of rats in social recognition paradigms and it could be related to differences in olfaction (Noack et al. 2010). Aging affects olfactory sensory function in rats, particularly in reversal learning (Schoenbaum et al. 2002; Brushfield et al. 2008), and thus impairs social memory recognition processes (Guan and Dluzen 1994). Social defeat stress can

induce behavioral adaptations relevant to depression such as anxiety-like behaviors, social avoidance, and anhedonia (Golden et al. 2011). In humans, depression-related cognitive deficits might be a risk factor for dementia while normal aging could involve memory impairments associated with enhanced anxious behaviors (Bunce et al. 2012).

2.4   Fear Memory

Stressful and emotionally arousing or challenging experiences are generally retained in memory (Schacter 1999; Smith et al. 2004; LaBar and Cabeza 2006; Joels et al. 2011). In fact, fear memory is essential not only to rodents but to all species to avoid dangerous situations and improve coping strategies. Fear learning is fast and efficient: single exposure to a stressful event can lead to the formation of long-lasting fear memories but also lead to detrimental behaviors (Najavits et al. 1998). Fortunately, adaptation and underlying brain plasticity allow for the damping of fear memories. However, these processes are slower than fear learning and often require multiple non-reinforcing expositions to the fear-associated cues of contexts (Myers and Davis 2002, 2007). While the hippocampus is still involved in the formation of fear learning and memory (Radulovic and Tronson 2010), the amygdala is central to these processes (Maren and Quirk 2004; McGaugh 2004; Hermans et al. 2014). Aversive learning can be evaluated with multiple behavioral paradigms including passive avoidance, contextual and cued fear conditioning, eyeblink conditioning, fear-conditioned startle, or taste aversion (for a review, see Crawley 2008). Anxiety-like behaviors and stress responses on the other hand can be measured with methods exploiting the approach-avoidance conflict between rodents' innate desire to explore new environments and fear of open bright space with apparatus such as the light dark box, elevated plus maze, or open field (Bouwknecht and Paylor 2002; Ducottet and Belzung 2005; Crawley 2008; Menard et al. 2013b). Old rodents are generally characterized by exacerbated anxious behaviors and stress responses (Menard et al. 2013b, 2014b) which affects brain synaptic plasticity and memory formation.

3   Synaptic Plasticity Associated with Learning and Memory Formation

Learning and memory processes benefit from brain plasticity and this induces reversible cellular and molecular changes in the central nervous system. These modifications can then be stabilized or consolidated to create long-lasting memories (Dudai 1996; McGaugh 2000; Lamprecht and LeDoux 2004; Frankland and Bontempi 2005; Baudry et al. 2011; Choquet and Triller 2013; Huganir and Nicoll 2013). In this section, the role of the neurotransmitter glutamate, its receptors, and related signaling pathways on cognitive function will be discussed.

3.1 Glutamate Receptors

3.1.1 NMDA Receptors

Glutamate is the main excitatory neurotransmitter in the brain and activation of its
N-methyl-D-aspartate receptors (NMDAR) play a critical role in synaptic plasticity
and memory formation (Morris et al. 1986; Sakimura et al. 1995; Tsien et al. 1996;
Kiyama et al. 1998; Nakazawa et al. 2002, 2003; McHugh et al. 2007; Lee and Silva
2009). NMDARs form a heterotetramer composed of two obligatory GluN1
subunits and two modulatory GluN2 (A, B, C and D subtypes) or GluN3 (A or B
subtypes) subunits. Receptor subunit composition changes during development
(Monyer et al. 1994; Sheng et al. 1994; Bellone and Nicoll 2007) and aging
(Kuehl-Kovarik et al. 2000; Zhao et al. 2009; Magnusson et al. 2010), influencing
the kinetics of the receptor channel opening. Greater ratios of GluN2B prolonged
NMDAR currents enhancing long-term potentiation (LTP) (Foster et al. 2010; Cui
et al. 2011; Muller et al. 2013). LTP is a form of synaptic plasticity closely related
to learning and memory formation (Bliss and Collingridge 1993) which is altered in
the aging brain and could contribute to cognitive decline (Landfield and Lynch
1977; Deupree et al. 1993; Rosenzweig et al. 1997; Shankar et al. 1998; Tombaugh
et al. 2002; Barnes 2003; Burke and Barnes 2006). Facilitation, saturation or
inhibition of LTP by pharmacological agents or genetic manipulation directly
affects behaviors in rodents (Morris et al. 1986; Sakimura et al. 1995; Tsien
et al. 1996; Kiyama et al. 1998; Tang et al. 1999). Trafficking of glutamate
receptors from the cytoplasm to the membrane and postsynaptic densities (PSD)
are crucial to facilitate LTP maintenance and synaptic plasticity (Malinow and
Malenka 2002; Rumpel et al. 2005). Accordingly, transgenic mice overexpressing
the kinesin-like protein KIF17, a protein involved in GluN2B transport along
microtubules, display better spatial learning and working memory performances
(Wong et al. 2002). In contrast, degradation of NMDAR by the protease calpain
decreases the number of functional receptors in the PSD (Simpkins et al. 2003;
Dong et al. 2006; Baudry et al. 2013). Cyclin-dependent kinase 5 (Cdk5) regulates
calpain-dependent GluN2B proteolysis (Su and Tsai 2011) and deletion of Cdk5
reduces GluN2B degradation favoring stronger LTP and memory processes
(Hawasli et al. 2007). Mice overexpressing GluN2B outperform age-matched
controls in hippocampus-dependent memory tasks up to 18 months of age (Cao
et al. 2007), suggesting that GluN2B and related downstream signaling pathways
could be promising targets for cognition-enhancing drugs (Mony et al. 2009).

Enhancement of NMDAR functioning has been a pharmacological target for
cognition for decades (for a review, see Collingridge et al. 2013). Briefly, NMDAR
activity can be modulated either directly with agonists or antagonists and regulation
of posttranslational modifications such as phosphorylation, palmitoylation,
ubiquitination, and proteolysis, or indirectly through its interactions with other
receptors and neuromodulators (Collingridge et al. 2013). NMDAR antagonists
generally impair NMDA-dependent LTP, learning, and memory (Morris 1989;
Manahan-Vaughan et al. 2008; Blot et al. 2013). However, exceptions exist,
notably memantine, a fast, voltage-dependent channel blocker (Bresink

et al. 1996; Frankiewicz et al. 1996), which is used to treat late-stage Alzheimer's disease as it delays cognitive decline (Danysz and Parsons 2003). NMDAR antagonists may enhance cognition by blocking aberrant activation of the receptors while preserving physiological functions (Frankiewicz and Parsons 1999; Fitzjohn et al. 2008).

Another attractive therapeutic avenue to rescue age-related memory deficits is the potentiation of NMDAR activity via the glycine-binding site (Baxter et al. 1994). Glycine or glycine-like substance such as D-serine acts as a co-agonist of glutamate to open the NMDAR channel (Johnson and Ascher 1987; Kleckner and Dingledine 1988; Mothet et al. 2000) and NMDAR full activation requires agonist binding at two glycine and two glutamate sites of the heterotetramer complex (Benveniste and Mayer 1991; Clements and Westbrook 1991). Age-associated changes in D-serine signaling could contribute to cognitive decline in aging (Billard and Rouaud 2007; Potier et al. 2010). Finally, other glutamatergic receptors such as α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) and group 1 metabotropic glutamate receptors (mGluR) interact physically with NMDAR regulating, to some extent, its activity.

3.1.2 AMPA Receptors

Like NMDAR, ionotropic AMPAR consists of four subunits (GluA1–4) that form heteromeric tetrameric complexes (Traynelis et al. 2010; Huganir and Nicoll 2013). GluA1–4 subunits can be phosphorylated on serine, threonine, and tyrosine residues by several protein kinases including Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and protein kinase C (PKC) on over 20 different phosphorylation sites (Shepherd and Huganir 2007; Lu and Roche 2012). Phosphorylation of AMPAR subunits regulates its function and intracellular trafficking, raising the hypothesis that posttranslational modifications could mediate synaptic plasticity (Isaac et al. 1995; Liao et al. 1995; Barria et al. 1997; Lee et al. 1998, 2000; Derkach et al. 1999). AMPAR trafficking between the plasma membrane and intracellular compartments is highly dynamic and can be modified by short-term and long-term changes in neuronal activity (for a review, see Bredt and Nicoll 2003; Huganir and Nicoll 2013). Synaptic scaling which is a homeostatic response to long-term changes in a network activity has been associated with AMPAR trafficking regulation by intrinsic activity (for a review, see Turrigiano 2008). Furthermore, AMPAR are mobile within the plasma membrane (Opazo and Choquet 2011), but their mobility decreases when entering the synapse (Borgdorff and Choquet 2002).

AMPAR synaptic levels and responsiveness can be modulated with various pharmacological agents including inhibitors [(2R)-amino-5-phosphonopentanoate, APV; 6-cyano-7-nitroquinoxaline-2,3-dione, CNQX; tetrodotoxin, TTX] and activators (bicuculline, picrotoxin) (Lissin et al. 1998; O'Brien et al. 1998; Turrigiano et al. 1998). Auxiliary subunits, known as transmembrane AMPAR regulatory proteins (TARPs), bind to the receptors and ensure proper maturation and delivery at the membrane and synapses (Tomita et al. 2003). TARPs can also affect biophysical and pharmacological properties of AMPAR (Priel et al. 2005; Menuz et al. 2007). For example, in the presence of TARPs, the antagonist CNQX

acts as a partial agonist (Menuz et al. 2007). Experiments conducted with ampakines, a class of compounds strongly interacting with AMPAR, suggest that region-specific expression of GluA1–4 and TARPs may explain the variations reported in experimental drug activity (Montgomery et al. 2009). Ampakines potentiate AMPAR-mediated synaptic currents by slowing the receptor deactivation and, consequently, enhance synaptic responses and LTP (Staubli et al. 1994; Arai and Kessler 2007). Early on, ampakines were targeted as cognition-enhancing drugs (Davis et al. 1997; Hampson et al. 1998a, b). Interestingly in pilot experiments, ampakines improved recall memory in aged humans (Lynch et al. 1997).

3.1.3   mGlu Receptors

Our group and others have recently highlighted the importance of group 1 mGluR-related synaptic plasticity in successful cognitive aging (Menard and Quirion 2012b; Menard et al. 2013b, 2014b; Yang et al. 2013a). Eight mGluR have been identified and divided into three groups: group 1 includes postsynaptic mGluR1 and mGluR5, while group 2 (mGluR2, mGluR3) and group 3 (mGluR4, mGluR6, mGluR7, mGluR8) are mainly presynaptic (for a review, see Nicoletti et al. 2011). Activation of presynaptic mGluR2/3 following an excess of glutamate release from neurons or astrocytes inhibits neurotransmitter release, regulating synaptic plasticity and excitatory synaptic transmission (Yokoi et al. 1996; Altinbilek and Manahan-Vaughan 2009). Group 3 mGluRs are localized at the active zone of neurotransmitter release negatively autoregulating glutamate release (Niswender and Conn 2010). Postsynaptic mGluR1s are concentrated in perisynaptic and extrasynaptic areas and coupled to Gq/G11 proteins. Their activation stimulates phospholipase C and intracellular second messenger release, such as inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) (Nicoletti et al. 2011). Finally, mGluR5s are also coupled to Gq/G11 protein, but their activation stimulates polyphosphoinositide (PI) hydrolysis. These receptors can functionally interact with NMDA receptor GluN2 subunits through a chain of interacting proteins including PSD-95, Shank, and Homer (Tu et al. 1999; Collett and Collingridge 2004).

Group 1 mGluRs are abundant in the hippocampus and cerebral cortex of the adult rat brain (Romano et al. 1996) and involved in hippocampus-dependent spatial learning and LTP (Balschun et al. 1999). Accordingly, mice lacking mGluR5 have reduced LTP and are characterized by cognitive deficits in the MWM task (Lu et al. 1997). Furthermore, spatial memory impairments are exacerbated in a reversal learning paradigm (Xu et al. 2009). This type of memory involves efficient pattern separation and inhibitory learning processes which can be affected by aging (Burke et al. 2010; Menard and Quirion 2012b; Menard et al. 2013b). Stimulation of group 1 mGluRs could act as a molecular switch to facilitate synaptic plasticity (Bortolotto et al. 2005; Manahan-Vaughan and Braunewell 2005; Bikbaev et al. 2008; Neyman and Manahan-Vaughan 2008) particularly in the aging brain (Menard and Quirion 2012a, b; Menard et al. 2013b, 2014b; Yang et al. 2013a).

Long-term depression (LTD), a form of synaptic plasticity involved in learning and memory processes (Ge et al. 2010; Dong et al. 2013; Menard et al. 2013b), can be induced by the group 1 mGluR-specific agonist 3,5-dihydroxyphenylglycine (DHPG) (Palmer et al. 1997). Age-related cognitive deficits have been associated with a reduction of DPHG-induced mGluR-LTD in old mice (Menard et al. 2013b). Over the years, multiple mGluR5 enhancers have been developed (for a review, see Cleva and Olive 2011; Nicoletti et al. 2011). Indeed, positive allosteric modulators can facilitate mGluR-related synaptic plasticity and improve spatial learning (Ayala et al. 2009; Menard et al. 2013b) possibly through NMDAR interaction (Rosenbrock et al. 2010) and/or AMPAR regulation (Uslaner et al. 2009). Conversely, mGluR5 antagonists impair learning and memory in adult (Christoffersen et al. 2008) and aged rodents (Menard et al. 2013b). Nevertheless, negative allosteric modulators are under clinical development because overactive mGluR functioning is thought to play a role in neurological disorders such as Alzheimer's disease and Fragile X syndrome (Luscher and Huber 2010).

3.2 Intracellular Glutamatergic Signaling

Learning and memory processes involve multiple signaling pathways triggered by glutamatergic receptor activation. Following Ca^{2+} entry in the neuron, cascades of kinases become phosphorylated leading to transcription factor activation and gene expression. The next section highlights several proteins essential for long-term synaptic plasticity establishment and maintenance.

3.2.1 CaMKII

The hypothesis that phosphorylation/dephosphorylation of AMPAR subunits regulates receptor function and modulates synaptic transmission was proposed in the early 1990s (Swope et al. 1992; Soderling 1993). Data from a number of studies have shown that protein kinase activity, particularly CaMKII, is required for LTP induction (Malenka et al. 1989; Malinow et al. 1989; Wyllie and Nicoll 1994). CaMKII is considered to be the primary downstream target following Ca^{2+} entry through NMDAR activation and associated with LTP, AMPAR trafficking, and memory formation (Anggono and Huganir 2012; Lisman et al. 2012). In fact, elevation of Ca^{2+} level in the cytoplasm induces recruitment of CaMKII to the PSD where it binds to NMDAR GluN2B subunits (Barria and Malinow 2005; Zhou et al. 2007; Halt et al. 2012) and phosphorylates multiple targets, notably GluN2B, AMPAR GluA1, and PSD-95 (Yoshimura et al. 2000, 2002; Dosemeci and Jaffe 2010). However, activation of CaMKII during LTP lasts only a few minutes (Lee et al. 2009), suggesting that downstream signaling cascades are required for LTP maintenance and memory consolidation.

3.2.2 PKC

Twelve PKC isoforms have been identified in mammals (Sun and Alkon 2010). These serine–threonine kinases are central to many signal transduction pathways

and densely expressed in the brain (Saito et al. 1988). PKC isoforms seem to play an essential role in multiple forms of learning and memory processes (Bank et al. 1988; Olds et al. 1989; Coalombo et al. 1997; Colombo and Gallagher 2002; Nelson et al. 2008; Nithianantharajah and Murphy 2009; Zhang et al. 2009; Menard and Quirion 2012b). Inhibition of kinases such as PKC can block LTP induction (Malinow et al. 1989). Phosphorylation of GluA1 by PKC controls synaptic incorporation of GluA1-containing AMPAR into the synapses during LTP (Boehm et al. 2006). Moreover, GluA2 phosphorylation by PKC modifies its binding to scaffolding proteins (Matsuda et al. 1999; Chung et al. 2000) and appears to be essential for LTD (Chung et al. 2000). Activation of both ionotropic and metabotropic glutamate receptors stimulate PKCγ activity (Codazzi et al. 2006). Moreover, mGluR activity can enhance NMDAR currents via a PKC-dependent mechanism (Tyszkiewicz et al. 2004). For example, following training in a spatial memory task PKC gamma (γ) expression increases (Nithianantharajah and Murphy 2009). This kinase was linked to the individual differences observed in the cognitive status of aging rats (Coalombo et al. 1997; Colombo and Gallagher 2002; Menard and Quirion 2012b), and its activation in small groups of hippocampal or cortical neurons improves old rat performances in the MWM task (Zhang et al. 2009). PKCγ activity may promote neuronal interconnections (Menard et al. 2013a) and synaptogenesis (Hongpaisan and Alkon 2007) and protects against neurodegeneration (for a review, see Sun and Alkon 2010). PKC enzymes can be activated by Ca^{2+}, DAG, arachidonic acid, phospholipids, and phorbol esters. The development of cognition-enhancing drugs based on PKC isoform pharmacology was proposed to treat dementias (for a review, see Sun and Alkon 2010).

3.2.3   ERK

The extracellular signal-regulated kinases (ERKs) signaling pathway plays a crucial role in neuronal processes including long-term synaptic plasticity and memory formation (English and Sweatt 1996; Blum et al. 1999; Thomas and Huganir 2004; Davis and Laroche 2006; Ciccarelli and Giustetto 2014). ERKs activities regulate AMPAR transmission, potentiation by CaMKII, and insertion into synapses (Zhu et al. 2002). When activated by phosphorylation, ERKs translocate to the nucleus where they activate downstream transcription factors and immediate early genes (IEG) expression (Thomas and Huganir 2004; Davis and Laroche 2006; Menard and Quirion 2012a; Yang et al. 2013b). Long-term synaptic plasticity can last for weeks and the late phase is dependent on gene transcription activation and synthesis of new proteins (Bliss and Collingridge 1993; Lynch 2004). Following NMDAR or voltage-gated calcium channel activation, Ca^{2+} level increases in the cytoplasm activating ERK through Ras signaling (Rosen et al. 1994). However, Ras GTPases signaling can be induced by other stimuli including activation of tyrosine receptor kinase (Trk receptor) or G-protein-coupled receptors (GPCR) (Ciccarelli and Giustetto 2014). Ca^{2+}-independent co-activation of NMDAR and mGluR5 can also lead to ERK phosphorylation and IEG expression (Yang et al. 2004). ERK signaling is necessary to establish mGluR-LTD in the hippocampus (Gallagher et al. 2004) and seems to be affected by aging (Williams et al. 2006), possibly

through age-related changes in Ca^{2+} homeostasis (Burke and Barnes 2010) leading to cognitive deficits (Menard and Quirion 2012b).

3.2.4 mTOR

The mammalian target of rapamycin (mTOR) serine/threonine kinase is another kinase regulating several translation regulatory factors and promoting protein synthesis (Page et al. 2006; Costa-Mattioli et al. 2009). Similarly to ERKs, mTOR inhibition blocks long-term synaptic plasticity and memory formation (Tang et al. 2002; Stoica et al. 2011). mTOR activation via phosphorylation can be triggered by various synaptic signals including glutamatergic agonists and neurotrophic factors such as insulin-like growth factor (IGF) or brain-derived neurotrophic factor (BDNF) (Costa-Mattioli et al. 2009; Costa-Mattioli and Monteggia 2013). mTOR complex 1 (mTORC1) has been associated with translational control, while mTORC2 seems to be involved in the cytoskeleton actin dynamics (for a review, see Costa-Mattioli and Monteggia 2013). Activation of NMDAR and mGluR modulates activity-dependent dendritic synthesis through mTOR activity in hippocampal neurons (Gong et al. 2006). Inhibition of mTOR prevents DHPG-induced mGluR-LTD (Hou and Klann 2004), while maintenance of good performances in the MWM spatial memory task was positively correlated with mTOR phosphorylation in aged rats (Menard and Quirion 2012b). Formation and stability of long-term fear memory is also compromised when mTOR activation is altered (Parsons et al. 2006). Altogether, mTOR function appears to be an attractive target in the cognition-enhancing target space. However, in addition to protein synthesis and actin polymerization, mTOR is involved in autophagy, lipid synthesis, ribosome biogenesis, nutrient support, and other growth-related processes (Costa-Mattioli and Monteggia 2013). Therefore, a better understanding of the various cell mechanisms associated with mTOR activity is necessary if one is to develop highly selective compounds that will improve cognition.

3.2.5 CREB

The transcription factor cAMP response element-binding protein (CREB) has probably been the most intensively studied kinase substrate with regard to cognition (for a review, see Alberini 2009). In fact, CREB-dependent transcription is essential for multiple forms of learning and memory such as fear conditioning and social recognition (Josselyn et al. 2001; Kida et al. 2002; Lonze and Ginty 2002; West et al. 2002; Han et al. 2007; Suzuki et al. 2011). Phosphorylation of CREB at the residue Ser133 regulates gene transcription (Shaywitz and Greenberg 1999) and this posttranslational modification is prevented by ERK inhibition (Wu et al. 2001; Hardingham et al. 2001). CaMKIV can also activate CREB-dependent transcription (Sun et al. 1996). Lower phosphorylation and total protein levels of CREB have been linked to age-related memory impairments in rats (Brightwell et al. 2004; Monti et al. 2005; Menard and Quirion 2012b). Compounds potentiating CREB activation have been identified as potential cognition-enhancing drugs (Tully et al. 2003; Xia et al. 2009). However, like mTOR, CREB is expressed ubiquitously and involved in several critical functions limiting its usefulness (Barco et al. 2003).

An alternative strategy might be to manipulate CREB primary gene targets and therefore, enhance treatment specificity.

3.3   Gene Expression

As mentioned previously, behavioral experience-induced activation of neuronal transmission and subsequent synaptic plasticity require the transcription of essential IEGs for long-term memory formation and consolidation (Marrone et al. 2008). These genes affect cell signaling, cytoskeletal dynamics, protein trafficking and degradation, and posttranslational modifications. In the following sections, the roles of five out of the growing list of genes involved in cognition (Benoit et al. 2011) are discussed.

3.3.1   Arc

The IEG activity-regulated cytoskeleton-associated protein (Arc) (Link et al. 1995; Lyford et al. 1995) is considered a master regulator of synaptic plasticity (Bramham et al. 2008; Shepherd and Bear 2011). In fact, cellular imaging of Arc mRNA and protein induction is currently used to detect the neuronal networks involved in behavioral encoding (Guzowski et al. 2005). Spatial exploration, for example, induces Arc transcription in ~40 % of hippocampal neurons of the hippocampus CA1 region after only 5 min (Guzowski et al. 2005). Several kinases and transcription factors are implicated in Arc expression including CaMKII, ERK, and CREB (Waltereit et al. 2001; Vazdarjanova et al. 2006; Shepherd and Bear 2011). Interestingly, Arc protein can be found in PSD and co-purified with NMDAR (Husi et al. 2000; Steward and Worley 2001). However NMDAR-independent synaptic transmission, notably through group 1 mGluR activity, can also regulate Arc transcription (Park et al. 2008). Our group reported higher Arc expression in memory-unimpaired old mice characterized by intact mGluR-LTD in comparison to aged mice for which mGluR-LTD and cognition were altered (Menard et al. 2013b). Arc mRNA is enriched in the dendrites of active synapses (Steward et al. 1998) possibly to facilitate protein expression, synaptic plasticity, and spine remodeling (Messaoudi et al. 2007). Downregulation of the Arc gene blocks consolidation of spatial memory (Guzowski et al. 2000) and fear conditioning (Ploski et al. 2008) while Arc knockout (KO) mice exhibit impaired long-term memory (Plath et al. 2006). Arc seems also crucial for the late phases and maintenance of LTP (Guzowski et al. 2000). Furthermore, mGluR-LTD requires Arc translation (Waung et al. 2008) which is impaired in Arc KO mice (Park et al. 2008). In fact, Arc affects AMPAR trafficking through interactions with the endocytic machinery (Chowdhury et al. 2006; Waung et al. 2008) and activity-dependent Arc induction is involved in AMPAR-mediated neuronal homeostasis (Shepherd et al. 2006; Beique et al. 2011). Development of cognition-enhancing drugs targeting Arc expression in specific area of the brain may therefore become a promising research avenue.

3.3.2 Homer 1a

Homer 1a is another interesting IEG dynamically regulated in response to synaptic activity and closely related to learning and memory formation (Vazdarjanova et al. 2002; Szumlinski et al. 2004; Celikel et al. 2007; Menard and Quirion 2012b; Menard et al. 2013b, 2014b). As mentioned previously, NMDARs directly interact with mGluRs through PSD-95, Shank, and Homer scaffolding proteins (Tu et al. 1999; Collett and Collingridge 2004). In fact, Homer proteins act as both scaffolding and transduction molecules (Brakeman et al. 1997; Ciruela et al. 2000; Ango et al. 2002; Fagni et al. 2002). Long Homer isoforms are constitutively expressed, enriched in PSD where they form synaptic clusters (Xiao et al. 1998) and facilitate signal transduction (Duncan et al. 2005; Shiraishi-Yamaguchi and Furuichi 2007). In contrast, the Homer 1a short isoform is an IEG produced following neuronal activity (Brakeman et al. 1997; Vazdarjanova et al. 2002) and when bound to mGluRs disrupts the protein clusters by dominant negative competitive binding (Kammermeier and Worley 2007). Homer 1a can also inhibit NMDAR currents by altering Homer–Shank complexes (Bertaso et al. 2010). Overexpression of Homer 1a in the hippocampus impairs LTP maintenance and spatial memory in adult mice (Celikel et al. 2007). Furthermore, elevated Homer 1a protein level has been correlated with cognitive deficits in aged rodents (Menard and Quirion 2012b; Menard et al. 2013b), which may be related to persistent uncoupling of mGluRs with its downstream signaling effectors (Menard and Quirion 2012b). To our knowledge, no drug has been proposed so far to directly modulate Homer protein expression or function.

3.3.3 Zif268

Induction of LTP is associated with a rapid and robust transcription of the IEG Zif268 in the hippocampus (Cole et al. 1989; Wisden et al. 1990; Jones et al. 2001; Alberini 2009). Learning-related increases in Zif268 expression have been reported for spatial (Guzowski et al. 2001) and fear memory (Hall et al. 2001). In mice lacking the Zif268 gene, LTP early phases are intact but late LTP is absent, and long-term memory is impaired in multiple tasks after a 24-h delay (Jones et al. 2001). Thus, expression of Zif268 may be critical for LTP persistence and memory consolidation (Abraham et al. 1993; Jones et al. 2001; Alberini 2009). Interestingly, learning task repetitions seem to reduce Zif268 expression (Guzowski et al. 2001). This observation is in line with similar Zif268 protein levels in aged rats trained for several consecutive weeks in the MWM task despite individual difference in cognitive status (Menard and Quirion 2012b). In a recent study, we reported a negative correlation between NMDAR, mGluR5, Arc, and Zif268 protein levels in old rats, suggesting that persistent transcription of this IEG may be involved in age-related cognitive deficits (Menard et al. 2014b). Such as for Homer 1a, no drug is currently available to modulate Zif268 expression or function.

3.3.4 IGF

As mentioned earlier, mTOR activity can be triggered by the binding of the neurotrophic factor IGF to Trk receptors, initiating intracellular signaling (Costa-

Mattioli et al. 2009; Costa-Mattioli and Monteggia 2013). PKC activity modulates IGF-1-induced activation of the serine–threonine protein kinase Akt (Zheng et al. 2000), a major actor of neuronal survival regulation (Dudek et al. 1997). IGFs play an important role in development, tissue repair, apoptosis, and regeneration (Dore et al. 1997; Werther et al. 1998; Russo et al. 2005) as well as in memory formation, consolidation, enhancement and extinction (Svensson et al. 2006; Agis-Balboa et al. 2011; Chen et al. 2011; Stern et al. 2014). IGF-I and IGF-II are growth-promoting peptides acting on plasma membrane Trk receptors on the cell surface, the type I IGF receptors (IGF-IR) (Russo et al. 2005). IGF binding to the IGF-IR promotes the activation of downstream signaling cascades including ERK (Russo et al. 2005). IGF-II is the most abundantly expressed IGF in the adult brain and is particularly concentrated in the hippocampus (Kar et al. 1993). Interestingly, an IGF-II polymorphism has been associated with cognitive functions in humans (Alfimova et al. 2012) and IGF-II expression declines with aging (Kitraki et al. 1993). Intra-hippocampal injection of recombinant IGF-II enhances memory retention and prevents forgetting via an increase of AMPAR GluA1 subunits and generation of persistent LTP (Chen et al. 2011). Moreover, systemic treatment with IGF-II increases Arc and Zif268 expression in the hippocampus (Stern et al. 2014). These recent studies suggest that IGF-II may represent an attractive target to develop cognition-enhancing drugs.

3.3.5   BDNF

Age-related cognitive deficits might be related to impaired LTP stability (Deupree et al. 1993; Burke and Barnes 2010). Synaptic transmission stimulates the release of BDNF (Balkowiec and Katz 2002; Aicardi et al. 2004), which is associated with rapid modifications of spine actin networks and LTP consolidation (Rex et al. 2007). LTP expression is impaired in BDNF KO mice (Korte et al. 1995), but this deficit can be completely rescued by recombinant BDNF (Patterson et al. 1996). Neurotrophins such as BDNF stimulate process outgrowth during development but also modified the axonal and dendritic cytoskeletons in the mature nervous system directly controlling synaptic plasticity (for reviews, see Huang and Reichardt 2001; Miller and Kaplan 2003). Through Trk receptors activation, neurotrophins regulate CaMKII activity (He et al. 2000) and ERK signaling pathway (Kaplan and Miller 2000). Exogenous BDNF can directly potentiate synaptic transmission (Kang and Schuman 1995) and this effect was proposed to be Arc dependent (Messaoudi et al. 2007). Contextual learning induces a rapid and selective increase of BDNF expression in the hippocampus (Hall et al. 2000) and BDNF-mediated signaling is involved in spatial learning (Mizuno et al. 2003) and fear memory (Andero and Ressler 2012). Physical exercise benefits cognitive processes and neuronal plasticity and this phenomenon seems to be mediated by IGF-1 and signaling cascades triggered by BDNF expression (Ding et al. 2006). Clinical trials have been conducted with BDNF as a therapeutic target for psychiatric diseases with undesirable side effects (Lynch et al. 2008). An alternative strategy would be to increase the production of endogenous BDNF. Ampakines, for example, increase

BDNF production in vitro and in vivo in rodents up to an advanced age (Lauterborn et al. 2000).

4   Cholinergic System and Cognition

The neurotransmitter acetylcholine (ACh) and its receptors play an active role in cognitive processes (Sarter and Parikh 2005). ACh action might be mediated through the regulation of NMDA. Indeed, stimulation of muscarinic ACh receptors (mAChR) potentiates NMDAR responses in the hippocampus (Markram and Segal 1990) and can facilitate NMDAR-LTP induction (Shinoe et al. 2005). In addition, mAChR activation can also promote NMDAR-LTD (Kirkwood et al. 1999; Jo et al. 2010) and induce a NMDAR-independent form of LTD (Dickinson et al. 2009). This last form of plasticity does not appear to involve the same mechanisms as mGluR-LTD (Dickinson et al. 2009). ACh can bind and activate two main classes of receptors: metabotropic mAChRs and nicotinic AChRs (nAChRs) which are ionotropic and permeable to Na^+, K^+, and Ca^{2+} (for a review, see Deiana et al. 2011). An age-related downregulation of the cholinergic system has been proposed to explain the progressive impairments of cognitive abilities associated with normal and pathological aging (Bartus et al. 1982; Bartus 2000; Auld et al. 2002). In fact, increased activation of the cholinergic system generally facilitates learning and memory processes (Scali et al. 1997a, b; Bradley et al. 2010). However, an increased expression of the negative autoreceptor mACh2 was reported in aged rats exhibiting memory deficits (Aubert et al. 1995) and inhibition of these receptors may facilitate spatial memory function (Quirion et al. 1995).

4.1   Impact of AChR Agonists and Antagonists on Memory Function

Early on, studies showed that muscarinic antagonists such as scopolamine or atropine impair cognitive abilities in animals and humans (Deutsch 1971; Drachman 1977). Systemic administration of scopolamine impairs learning acquisition and memory formation in multiple tasks (Aigner and Mishkin 1986; Aigner et al. 1991; Miller and Desimone 1993; Brouillette et al. 2007). Interestingly, IEG Homer 1a expression is enhanced in the hippocampus of amnesic scopolamine-treated rats (Brouillette et al. 2007). Conversely, treatment with a mACh1R allosteric agonist improves cognitive performances (Bradley et al. 2010). Neurotrophins enhance ACh release through TrkA receptor signaling (Auld et al. 2001) and activation of the TrkA receptor with a selective partial agonist can rescue age-related memory deficits in rats through modulation of the cholinergic system (Bruno et al. 2004). IGFs differentially regulate ACh release: IGF-I acts as an inhibitor, while IGF-II potentiated ACh-related currents in rat hippocampal slices (Kar et al. 1997). TTX alters the effect of IGF-I (Kar et al. 1997) suggesting an

interaction with AMPAR. Treatment of rat cultured olfactory bulb neuronal cells with carbachol, a cholinergic agonist, increases neuritic outgrowth and this effect is mediated by nAChR since it can be mimicked with nicotinic agonists (Coronas et al. 2000). Furthermore, low concentrations of carbachol can potentiate NMDA responses in the hippocampus (Harvey et al. 1993). These results suggest that nAChR may be actively involved in neuronal plasticity and could represent an attractive target to develop cognition-enhancing drugs.

4.2   α-7 Nicotinic ACh Receptor Agonists and Cognitive Deficits

Multiple nAChR agonists have been examined as possible treatments for memory impairment associated with aging or in psychiatric disorders. In this regard, modulation of the ionotropic α7 nAChR is of particular interest, considering its high density in the hippocampus and cerebral cortex and its implication in cognitive processes (Paterson and Nordberg 2000; Levin and Rezvani 2002; Leiser et al. 2009; Floresco and Jentsch 2011). Treatment with of α7 nAChR agonists such as N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-7-[2-(methoxy)phenyl]-1-benzofuran-2-carboxamide (ABBF), 5-morpholin-4-yl-pentanoic acid (4-pyridin-3-yl-phenyl)-amide (SEN12333), or 4-bromophenyl 1,4diazabicyclo (3.2.2) nonane-4-carboxylate, monohydrochloride (SSR180711) rescue cognitive deficits in spatial (Boess et al. 2007; Pichat et al. 2007), recognition (Wishka et al. 2006; Boess et al. 2007; Pichat et al. 2007; Hashimoto et al. 2008; Roncarati et al. 2009), social (Boess et al. 2007), and fear (Roncarati et al. 2009) memory tasks. Multiple studies have tested the efficacy of α7 nAChR agonists and demonstrated positive cognitive effects following activation of these receptors (for a review, see Leiser et al. 2009). Several clinical trials are currently ongoing notably to treat negative symptoms of schizophrenia (Davis et al. 2014) and Alzheimer's disease (Geerts 2012).

5   Dynorphinergic System and Memory Function

Dynorphins, a class of endogenous opioids peptides expressed in the brain (for a review, see Schwarzer 2009), have been linked to learning and memory processes since the 1990s (McDaniel et al. 1990; Wagner et al. 1993; Sandin et al. 1998). Intra-hippocampal administration of dynorphin in rats impairs spatial learning (McDaniel et al. 1990; Sandin et al. 1998). Encoded by the prodynorphin gene (Pdyn), dynorphin peptides are also involved in emotional control and stress responses (Schwarzer 2009). In humans, Pdyn gene polymorphisms have been associated with episodic memory deficits in the elderly (Kolsch et al. 2009). Furthermore, enhanced dynorphins expression might be related to Alzheimer's disease pathogenesis (Yakovleva et al. 2007). Surprisingly, dynorphin A-(1–13) injection can improve scopolamine-induced cognitive deficits in mice by activating kappa-opioid receptors (KOR) (Itoh et al. 1993) and possibly regulating ACh release (Hiramatsu et al. 1998; Hiramatsu and Watanabe 2006). Pdyn-derived peptides

preferentially bind to the postsynaptic GPCR, KOR (Chavkin et al. 1982), modulating PKC (Barg et al. 1993), and ERK signaling pathway activation (Belcheva et al. 1998). Presynaptic KOR can act as an autoreceptor and inhibits the release of dynorphin peptides (Nikolarakis et al. 1989). These peptides can also interact with other opioid receptors (Quirion and Pert 1981; Schwarzer 2009) and NMDAR (Shukla and Lemaire 1994; Schwarzer 2009). Release of endogenous dynorphins inhibits excitatory transmission and blocks LTP induction in the hippocampus (Wagner et al. 1993). Furthermore, dynorphins and activation of presynaptic KORs suppress glutamate release (Drake et al. 1994; Simmons et al. 1994). These findings suggest that dampening of the dynorphinergic system may be a relevant strategy to modulate glutamatergic function and cognition.

5.1 Dynorphins and Age-Related Cognitive Decline

Expression of dynorphins increases with age in the hippocampus of rats (Jiang et al. 1989; Zhang et al. 1991; Kotz et al. 2004) and mice (Menard et al. 2013b) and this upregulation may be associated with cognitive deficits generally observed in old rodents (Jiang et al. 1989; Zhang et al. 1991; Menard et al. 2013b). In line with this idea, knocking down the Pdyn gene improves spatial learning in middle-aged mice (Nguyen et al. 2005). Our group has recently shown that elevated Pdyn expression correlates with age-related body weight gain, memory deficits, and reduced glutamatergic signaling in rats (Menard et al. 2014b). Furthermore, we rescued loss of group 1 mGluR function, related signaling, and cognitive decline in old mice by knocking down the Pdyn gene (Menard et al. 2013b). Whereas aged wild-type (WT) mice developed spatial and recognition memory deficits, aged Pdyn KO mice performances were similar to those of young mice in both tasks (Menard et al. 2013b). Old WT mice performed poorly in an inhibitory learning acquisition task, which has been related to mGluR5 function (Xu et al. 2009). Accordingly, group 1 mGluR protein level was increased and mGluR-LTD unaltered in old KO mice (Menard et al. 2013b). Intact synaptic plasticity and cognition were associated with increased expression of IEG Homer 1a and Arc in aged Pdyn KO mice (Menard et al. 2013b). Pharmacological treatments with 3-cyano-N-(1,3-diphenyl-1H-pyrazol-5-yl) benzamide (CDPPB, positive modulator of mGluR5) or norbinaltorphimine (norBNI), a KOR antagonist, rescued memory function in old WT mice. These results are in line with previous studies in which positive modulation of mGluR5 (Uslaner et al. 2009; Reichel et al. 2011; Fowler et al. 2013) as well as norBNI treatment (Bilkei-Gorzo et al. 2014) promoted memory formation. Conversely, mGluR5 antagonism impaired spatial memory of old Pdyn KO mice (Menard et al. 2013b), suggesting that dynorphinergic and glutamatergic systems closely interact to establish memories in the aging brain (Menard et al. 2013b, 2014a, b). Gene expression profiling reveals increased Pdyn expression in the hippocampus of amnesic scopolamine-treated rats (Brouillette et al. 2007), raising the possibility of complex interactions between these systems in cognitive functions.

5.2   Dynorphins and Social Memory

Considering its role in emotional behaviors and stress responses (Schwarzer 2009), the dynorphinergic system might also regulate the strength of social memories. In young mice, genetic deletion of the Pdyn gene enhanced partner recognition ability without affecting recognition memory for objects (Bilkei-Gorzo et al. 2014). Pharmacological blockade of KOR with norBNI enhanced social memory in control animals, whereas KOR activation impaired the abilities of transgenic mice (Bilkei-Gorzo et al. 2014). Emotionally arousing situation such as partner recognition induces higher expression of dynorphins than novel object recognition (Bilkei-Gorzo et al. 2014), raising the possibility that stress-related release of these peptides may affect the formation of social memories.

5.3   Dynorphins, KOR and Stress-Related Memory Deficits

Aging is generally characterized not only by reduced cognitive abilities but also by increased anxiety-related behaviors (Lenze et al. 2001; Lupien et al. 2009; Bedrosian et al. 2011; Menard et al. 2013b, 2014b). Stress exposure over a life span may accelerate cellular aging and promote cognitive dysfunction (Lupien et al. 2009). Furthermore, exacerbated neurobiological sensitivity to threat may even increase the risk of developing age-related diseases (for a review, see O'Donovan et al. 2013). The first association between the dynorphinergic system and anxious behaviors was observed with naloxone, an opioid partial agonist, reversing the effect of benzodiazepines (Billingsley and Kubena 1978). Similar to Pdyn gene deletion, pharmacological treatment with norBNI reduces anxious behaviors and increases exploratory activity in young (Knoll et al. 2007; Wittmann et al. 2009) and aged rodents (Menard et al. 2013b). Conversely, treatment with dynorphin peptides and KOR agonists is anxiogenic (Tsuda et al. 1996; Wittmann et al. 2009; Smith et al. 2012). Endogenous KOR activation has been linked to stress-induced learning and memory deficits (Carey et al. 2009). KOR signaling could also play a role in fear memory extinction (Bilkei-Gorzo et al. 2012). Indeed, mice lacking Pdyn gene are characterized by enhanced cue-dependent fear conditioning, an effect that can be reproduced by blocking KOR before the extinction trials (Bilkei-Gorzo et al. 2012). Interestingly, functional imaging has revealed reduced fear extinction in human volunteers bearing Pdyn polymorphisms (Bilkei-Gorzo et al. 2012), suggesting that dynorphins might be essential to efficient fear memory consolidation. All these results identify the dynorphinergic system as a promising target to develop novel cognition-enhancing drugs that could be efficient in not only in normal but also pathological aging.

6 Conclusions

In summary, despite memory function involving multiple types and processes at synaptic, cellular, and molecular levels, promising targets have been identified that could lead to novel cognition-enhancing drugs. Up to now, glutamatergic and cholinergic receptor modulators have been extensively studied and, in some cases, tested in clinical studies with equivocal results. Here we propose novel targets involved in crucial signaling pathways. Nonetheless, to create efficient tissue-specific and even cell type-specific compounds, modulating these effectors remains a challenge at the chemistry, pharmacokinetic, and formulation levels. However, considering the increase in life span generally observed in various populations, reduction of age-related cognitive deficits represents a biomedical issue deserving a multidisciplinary global approach.

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