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Angiotensin II, a neuropeptide at the frontier between endocrinology and neuroscience: is there a link between the angiotensin II type 2 receptor and Alzheimer's disease?

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Amyloid-β peptide deposition, abnormal hyperphosphorylation of tau, as well as inflammation and vascular damage, are associated with the development of Alzheimer's disease (AD). Angiotensin II (Ang II) is a peripheral hormone, as well as a neuropeptide, which binds two major receptors, namely the Ang II type 1 receptor (AT1R) and the type 2 receptor (AT2R). Activation of the AT2R counteracts most of the AT1R-mediated actions, promoting vasodilation, decreasing the expression of pro-inflammatory cytokines, both in the brain and in the cardiovascular system. There is evidence that treatment with AT1R blockers (ARBs) attenuates learning and memory deficits. Studies suggest that the therapeutic effects of ARBs may reflect this unopposed activation of the AT2R in addition to the inhibition of the AT1R. Within the context of AD, modulation of AT2R signaling could improve cognitive performance not only through its action on blood flow/brain microcirculation but also through more specific effects on neurons. This review summarizes the current state of knowledge and potential therapeutic relevance of central actions of this enigmatic receptor. In particular, we highlight the possibility that selective AT2R activation by non-peptide and highly selective agonists, acting on neuronal plasticity, could represent new pharmacological tools that may help improve impaired cognitive performance in AD and other neurological cognitive disorders.

Keywords: angiotensin II, angiotensin type 2 receptor, neuron, cognition, brain damage, vasodilation, Alzheimer's disease

INTRODUCTION

Angiotensin II (Ang II) is the active end-product of the renin–angiotensin system (RAS). In the classical view, Ang II is produced from angiotensinogen through a series of proteolytic cleavage events, conducted successively by renin, followed by angiotensin-converting enzyme (for review see de Gasparo et al., 2000; de Kloet et al., 2010). However, in addition to this classical RAS, several alternative pathways have been identified, for which description is out of the scope of this review, but recently reviewed by de Kloet et al. (2010) and Abassi et al. (2009). Ang II is a peripheral hormone, as well as a neuropeptide, which plays a major role in the central regulation of blood pressure and in the stress response. Indeed, since the pioneer studies of Mendelsohn et al. (1988) and Unger et al. (1988), the existence of a RAS in the brain is now well established. The various components (angiotensinogen, renin, angiotensin-converting enzyme, Ang II, and Ang II receptors) are found in areas of the brain involved in the regulation of fluid and electrolyte balance, in the regulation of arterial pressure and in structures involved in cognition, behavior, and locomotion (for review see Phillips and de Oliveira, 2008; Horiuchi et al., 2010).

Angiotensin II binds two major receptors: the Ang II type 1 receptor (AT1R) and the type 2 receptor (AT2R). Since Ang II modulates blood pressure and the stress response by binding the AT1R, AT1R blockers (ARBs) have been widely used as antihypertensive drugs. There is also evidence that ARB treatment attenuates learning and memory deficits, increases cerebral blood flow, and helps protect against brain ischemia and inflammation (Li et al., 2005; Zhou et al., 2006; Phillips and de Oliveira, 2008; Mogi and Horiuchi, 2009; Sakata et al., 2009; Horiuchi et al., 2010). In the presence of ARBs, which selectively block the AT1R, Ang II binds to the less-abundant AT2R. Several studies suggest that the therapeutic effects of ARBs may reflect this unopposed activation of the AT2R as well as the inhibition of the AT1R (Li et al., 2007b; Tsukuda et al., 2007, 2009; Arganaraz et al., 2008; Gao et al., 2008; McCarthy et al., 2009).

Within the context of Alzheimer's disease (AD), modulation of AT2R signaling could improve cognitive performance not only through its action on blood flow/brain microcirculation but also through more specific effects on neurons. This review summarizes the current state of knowledge and potential therapeutic relevance of central actions of this enigmatic receptor.

EXPRESSION AND ROLES OF THE AT2R IN THE BRAIN

One of the most striking features of the AT2R is its high level of expression in most fetal tissues, including the brain, and the dramatic increase in the AT1/AT2 receptor ratio after birth

(Millan et al., 1991; Tsutsumi and Saavedra, 1991). This pattern of expression strongly implicates the AT2R in fetal development. In the adult, the AT2R is predominantly expressed in the locus coeruleus, ventral and dorsal parts of lateral septum, superior colliculus and subthalamic nucleus, many nuclei of the thalamus, and nuclei of the inferior olive. The cingulate cortex, the molecular layer of the cerebellar cortex, the superior colliculus and paraventricular nuclei contain both AT1 and AT2 receptors (Millan et al., 1991; Tsutsumi and Saavedra, 1991; Lenkei et al., 1996, 1997). More recent studies have also identified AT2R RNA and protein in the substantia nigra pars compacta (Grammatopoulos et al., 2007) and in the hippocampus (Arganaraz et al., 2008; Abdalla et al., 2009). Thus, in the adult, the AT2R are concentrated in areas involved in control and learning of motor activity, sensory areas, and selected limbic system structures. At the cellular level, the AT2R is localized in neurons but not in astrocytes (Bottari et al., 1992; Lenkei et al., 1996; Gendron et al., 2003b). It is well-accepted that AT2R stimulation counteracts most AT1R-mediated actions, promoting vasodilation, inhibiting growth, decreasing the expression of pro-inflammatory cytokines, and increasing expression of anti-inflammatory cytokines, both in the brain and in the cardiovascular system (for reviews see Gendron et al., 2003b; Mogi et al., 2007a, 2008; Arganaraz et al., 2008; Mogi and Horiuchi, 2009; Porrello et al., 2009; Sakata et al., 2009; Tsukuda et al., 2009; **Figure 1**).

IS THERE A LINK BETWEEN AT2R ACTIVATION AND AD?

Amyloid-β (Aβ) peptide deposition in senile plaques and the presence of neurofibrillary tangles (NFTs) are the main pathological hallmarks of AD. However, other structural and functional alterations, including inflammation, increased oxidative stress, and vascular damage/ischemia, are also associated with AD; these alterations may contribute to neuronal and synaptic dysfunction and loss as well as the ensuing cognitive deficits and dementia of this disorder (Iadecola, 2004; Zlokovic, 2005; LaFerla et al., 2007; Boissonneault et al., 2009; Mucke, 2009; Nelson et al., 2009). In addition, since the development of the amyloid hypothesis of Hardy and Selkoe (2002), evidence strongly suggests that soluble oligomers of Aβ may cause early cognitive impairment, even in the absence of overt cell death (review in Mucke et al., 2000; Hardy and Selkoe, 2002; Lesne et al., 2006; Haass and Selkoe, 2007; Selkoe, 2008; Wray and Noble, 2009).

The abnormal hyperphosphorylation and altered conformation of the microtubule-associated protein (MAP) tau precedes its assembly into paired helical filaments and its accumulation in NFTs (Buee et al., 2000; Andorfer et al., 2003; Gallo et al., 2007; Hanger et al., 2009; Iqbal et al., 2009). Tau is a substrate for several protein kinases, such as glycogen synthase kinase-3 (GSK-3) and cyclin-dependent kinase (cdk5), and for phosphatases such as protein phosphatase-2A (PP2A); PP2A activity is down-regulated in the AD brain (Buee et al., 2000; Andorfer et al., 2003; Gallo et al., 2007; Hernandez and Avila, 2008; Hanger et al., 2009; Iqbal et al., 2009; Hernández et al., 2010).

Moreover, experimental evidence suggests that cerebral perfusion is decreased in AD (Farkas and Luiten, 2001; de la Torre, 2004; Zlokovic, 2008; Liu et al., 2009). Indeed, the structural and functional integrity of the brain depends on the delicate balance between substrate delivery through blood flow and energy demands imposed by neural activity. Neurons, astrocytes and vascular cells seemingly constitute a functional unit, the primary purpose of which is to maintain the homeostasis of the brain's microenvironment. Alterations of these vascular regulatory mechanisms lead to brain dysfunction and disease. The emerging view is that cerebrovascular dysregulation is a feature not only of

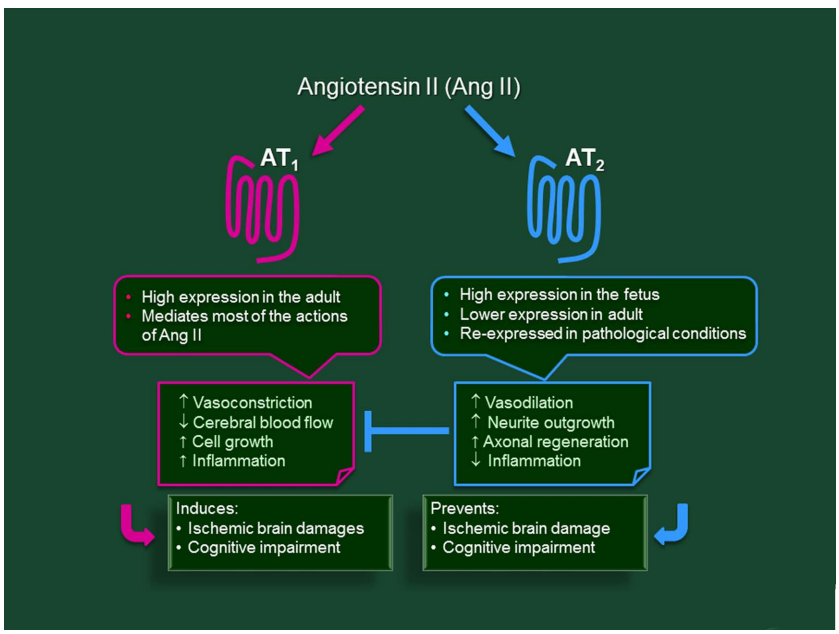

FIGURE 1 | Summary of the properties and main effects targeted by AT1 and AT2 receptors of angiotensin II in the brain.

cerebrovascular pathologies such as stroke, but also of neurodegenerative conditions such as AD (Iadecola et al., 2009). Since studies suggest that Aβ has deleterious actions both on neurons and cerebral blood vessels, the neuronal and vascular actions of this peptide may act synergistically to induce brain dysfunction in AD (Iadecola, 2004; Zlokovic, 2005).

Recent studies have revealed that aging, hypertension, and AD trigger common signaling pathways that lead to deleterious effects on the regulation of the cerebral circulation. These findings reinforce the notion that cerebrovascular dysfunction plays a key role in the cognitive impairment associated with these conditions (Iadecola et al., 2009). In the entire trademark dysfunctions associated with AD mentioned above, there is several indirect lines of evidence suggesting that AT2 receptor activation may have a beneficial effect (de la Torre, 2004).

All of the components of the RAS are found in the brain, where they actively modulate functions such as stress (Saavedra et al., 2005; Saavedra and Benicky, 2007), exploratory behavior, anxiety, learning, and memory acquisition (Wright et al., 2002; Phillips and de Oliveira, 2008). Both the AT1R and the AT2R have been detected in brain areas responsible for these functions, including the amygdala, hippocampus, lateral septum, and frontal cortex (Song et al., 1991, 1992; Lenkei et al., 1996; Phillips and Sumners, 1998; Arganaraz et al., 2008; Abdalla et al., 2009). The initial studies indicating a role of AT2R in cognitive improvement arise from observations in AT2R-deficient mice. The targeted disruption of the *Agtr2* gene (which codes for the AT2R) resulted not only in a significant increase in blood pressure, but also in attenuated exploratory behavior and impaired performance in a spatial memory task (Hein et al., 1995; Ichiki et al., 1995; Okuyama et al., 1999; Maul et al., 2008). Several recent studies have indicated a beneficial role for ARBs in the cognitive impairment associated with vascular diseases, AD, and other neurodegenerative diseases (Phillips and de Oliveira, 2008; Fujita et al., 2009; Mogi and Horiuchi, 2009). For instance, treatment with the ARB valsartan attenuates oligomerization of Aβ peptides into high molecular weight oligomeric peptides and reduces cognitive deterioration in Tg2576 mice, a model of AD-type neuropathology that expresses a pathogenic mutant of the amyloid precursor protein (APP; Wang et al., 2007). On the other hand, other studies with the same model (Tg2576 mice) have shown that Aβ induces the formation of cross-linked AT2R oligomers in the hippocampus that disrupt Ang II signaling. This Aβ-induced AT2R oligomerization was associated with enhanced neurodegeneration. Conversely, stereotactic inhibition of AT2R oligomers by RNA interference delayed tau phosphorylation in Tg2576 (Abdalla et al., 2009).

Numerous studies suggest that the beneficial cellular effects of the AT2R result in improved physiological parameters relevant to AD patients:

- Ang II type 2 receptor activation promotes vasodilation and the anti-inflammatory process – Considerable evidence suggests that AT1R blockade and increased AT2R stimulation improve cerebral blood flow, thereby helping to protect against brain ischemia and inflammation (Iwai et al., 2004; Li et al., 2005; Zhou et al., 2006; Sakata et al., 2009), and, moreover, that AT2R activation improves the microcirculation (for reviews, see Phillips and de Oliveira, 2008; Horiuchi et al., 2010).
- Ang II type 2 receptor activation protects against brain damage – Numerous recent studies conducted in rodents treated with ARBs suggest that AT2R protects against cerebral ischemia-induced neuronal injury (Grammatopoulos et al., 2004; Li et al., 2005; Tsukuda et al., 2007, 2009; McCarthy et al., 2009), and altered dendritic and neuronal spine morphology (Maul et al., 2008; for review see Mogi and Horiuchi, 2009). Confirming these observations, it has been reported that AT2R stimulation supports neuronal survival and neurite outgrowth in response to ischemia-induced neuronal injury (Li et al., 2005; Sakata et al., 2009). Further supporting a role of AT2R in neurite outgrowth are observations from models of nerve injury which have elegantly shown that the AT2R has regenerative capabilities associated with restored behavioral function and anatomic innervation after sciatic nerve crush and optical axotomy (Gallinat et al., 1998; Lucius et al., 1998; Reinecke et al., 2003; Li et al., 2005).
- Alzheimer's disease and the neurotrophic hypothesis: a role for AT2R? –As recently summarized by Schindowski et al. (2008), neurotrophic factors [such as nerve growth factor (NGF) and brain-derived neurotrophic factor] are key regulators not only for development, maintenance and survival but also for cognition and storage of memory. They activate various cell signaling pathways acting through the tropomyosin-related kinase or tyrosine receptor kinase family (Trk). Most neurodegenerative dementias are linked to failures in axonal transport of neurotrophic factors from the cell body (where they are synthesized) to their sites of action. For example, in the absence of NGF, morphology and functions of cholinergic neurons are impaired, resulting in a decrease in cholinergic transmission. In this context, we have shown that AT2R-mediated effects *in vitro* are modulated by the presence of growth factors in the culture medium, and are mediated by growth factor-related signaling pathways. In particular, the signaling mechanisms leading to neurite outgrowth in NG108-15 cells involves the TrkA-mediated activation of Rap1/B-Raf, which in turn, activates MEK to induce a delayed but sustained activation of $p42/p44^{mapk}$ (Gendron et al., 2003a; Plouffe et al., 2006).
- Alzheimer's disease as a consequence of hypertension and metabolic syndrome: a role for AT2R? – Several recent studies indicate that ARBs may protect against the cognitive impairments associated with vascular disease, AD, and other neurodegenerative diseases (Mogi and Horiuchi, 2009). For example, pretreatment with a non-hypotensive dose of telmisartan significantly inhibits the cognitive decline induced by intracerebroventricular (i.c.v.) injection of Aβ1–40, an experimental model of AD (Tsukuda et al., 2007, 2009; Mogi et al., 2008), and also prevents Aβ deposition in AD models (Mogi et al., 2006, 2007b, 2008; Tsukuda et al., 2007, 2009). However, the link between AT2R and cognitive defects is not yet clearly established. **Figure 2** provides a general overview of the functional changes of AD and how AT2R could help recover some of these changes.
- Type 2 diabetes mellitus (T2DM), hypertension and metabolic syndrome (which is defined as a cluster of obesity, high blood pressure, hyperglycemia, and insulin resistance) are associated

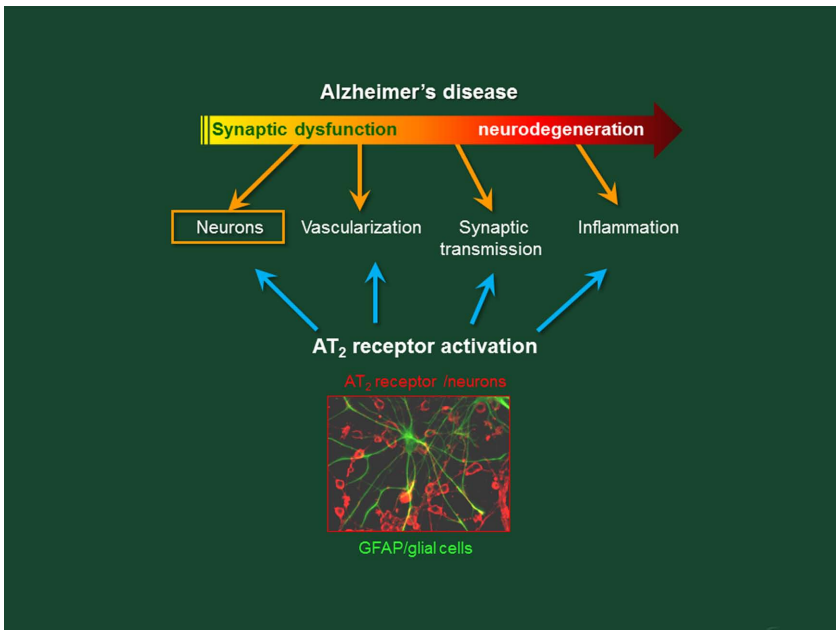

FIGURE 2 | Alzheimer's disease: targets of functional disruptions and proposed protective functions associated with the activation of the AT2 receptor of angiotensin II.

with an increased risk of dementia (both AD and vascular dementia) (Yaffe et al., 2004a,b; Biessels and Kappelle, 2005; Qiu et al., 2005; Whitmer et al., 2005; Craft, 2006, 2009; Mogi et al., 2006; de la Monte, 2009; Mogi and Horiuchi, 2009). In T2DM patients, a major clinical study (Study on Cognition and Prognosis in the Elderly, SCOPE; Lithell et al., 2003) and a clinical double-blind study (Tedesco et al., 1999) have indicated that ARBs have a further therapeutic effect on impaired cognitive function beyond their antihypertensive effects compared with other antihypertensive drugs. In this context, Tsukuda et al. have demonstrated that candesartan improves the impaired cognitive function induced by T2DM, with multiple beneficial effects (Tsukuda et al., 2007; Mogi et al., 2008).

LINKING SIGNALING AND FUNCTION: ALWAYS A DIFFICULT CHALLENGE!

During the past 5 years, significant progress has been achieved in elucidating some of the puzzling elements of the AT2R-signaling pathway proteins (Gendron et al., 2003a; Mogi and Horiuchi, 2009; Porrello et al., 2009; Steckelings et al., 2010a; **Figure 3**). Some of these elements may be linked to improvement of impaired signaling functions as observed in AD:

- Ang II type 2 receptor may improve synaptic plasticity through effects on ionic channel activity, since AT2R activation decreases T-type calcium channel activity, increases K^+ channel activity (Kang et al., 1992, 1993; Buisson et al., 1995), and alters actin cytoskeleton dynamics (Kilian et al., 2008).
- Ang II type 2 receptor activation may support microtubule organization and dynamics. Indeed, several studies have reported that AT2R activates PP2A phosphatase (Huang et al., 1995, 1996a,2008; Kilian et al., 2008). PP2A is markedly deficient in AD, and responsible for a sustained increase in ERK1/ERK2, one of the kinases involved in glycogen synthase kinase-3 (GSK-3) inactivation. We have also shown that activity of Fyn, a src-family kinase member, is required for AT2R-induced neurite outgrowth (Guimond et al., 2010a). Since tau is a substrate for both PP2A phosphatases, GSK-3 and Fyn, AT2R activation may control the equilibrium between tau phosphorylation and dephosphorylation (Hernandez and Avila, 2008; Hanger et al., 2009; Hernández et al., 2010).
- Ang II type 2 receptor may also improve neurite architecture, through effects on MAPs, as shown in neuronal cell lines (Laflamme et al., 1996; Meffert et al., 1996; Côté et al., 1999; Li et al., 2007a).
- Through methyl methanesulfonate sensitive 2 (MMS2; Mogi et al., 2007a) and peroxisome proliferator-activated receptor (PPARγ; Mogi et al., 2008), the AT2R improves cognitive function and the decrease in hippocampal neurogenesis observed in amyloid-β-injection-induced cognitive decline (Mogi et al., 2008) or in AT2R-deficient mice (Mogi et al., 2007a; for review, see Mogi and Horiuchi, 2009; Horiuchi et al., 2010).
- Ang II type 2 receptor activation may counteract vasoconstriction, and favor vasodilation/vasorelaxation, through an increase in nitric oxide (NO)–cGMP production and a decrease in superoxide production, NADPH oxidase superoxide production, and NADPH oxidase (reviewed in Volpe et al., 2003; Widdop et al., 2003; Steckelings et al., 2005).
- Ang II type 2 receptor activation by CGP42112 increases neuronal survival and minimizes experimental post-stroke injury (McCarthy et al., 2009), indicating that centrally administered CGP42112 exhibits a neuroprotective effect. Such protective

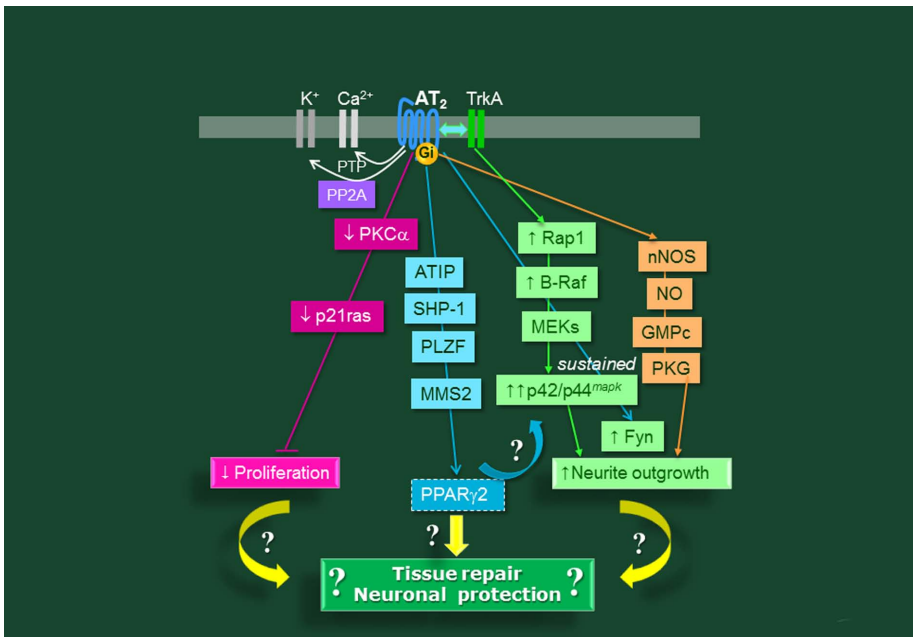

FIGURE 3 | Main signaling pathways for the AT2 receptor of angiotensin II in the brain.

effects may be consecutive to an increase in nitric oxide (NO)–cGMP production and a decrease in superoxide production and NADPH oxidase superoxide production and NADPH oxidase (de la Torre, 2004; Iadecola et al., 2009) or to decreased inflammation. Indeed, AT2R attenuates chemical hypoxia-induced caspase-3 activation in primary cortical neuronal cultures (Grammatopoulos et al., 2004). As recently reviewed (Rompe et al., 2010; Stegbauer and Coffman, 2011), AT2R activation, as in other inflammatory models, may decrease tumor necrosis factor-alpha (TNF-α) and NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) activity, resulting in decreased production of interleukin 6 (IL-6). This effect is initiated through increased activation of protein phosphatases and increased synthesis of epoxyeicosatrienoic acid (Rompe et al., 2010).

Nevertheless, certain contradictory studies suggest that AT2R expression and conformation may change with age and may be associated with some of the deleterious changes in AD (Kerr et al., 2005; Abdalla et al., 2009). These conflicting hypotheses have been difficult to reconcile because of experimental limitations, particularly the lack of an orally active, selective ligand for the AT2R, as discussed in the next section. Moreover, the earliest events associated with activation of AT2R and the contribution of AT2R signaling to cognitive decline remains unclear.

Other advances in the field of AT2R signaling include the identification of direct intracellular partners, including the phosphatase SHP-1 (Cui et al., 2001; Feng et al., 2002; Nouet et al., 2004; Mogi et al., 2006; Li et al., 2007b), the transcription factor promyelocytic zinc finger protein, PLZF (Senbonmatsu et al., 2003) and the AT2 receptor-interacting protein (ATIP), also called AT2R binding protein of 50 kDa (ATBP50; Nouet et al., 2004; Wruck et al., 2005; reviewed in Mogi et al., 2007a; Funke-Kaiser et al., 2010; Rodrigues-Ferreira and Nahmias, 2010; see **Figure 3** for a synopsis). Moreover, recent studies have identified intracellular crosstalk pathways between the AT1R and the AT2R at the gene expression level. Indeed, AT1R activation enhances AT2R mRNA degradation, but AT2R activation increases AT2R mRNA transcription (Shibata et al., 1997).

THE AT2R: PREVIOUS LIMITATIONS AND NEW PERSPECTIVES

As previously mentioned, the identification of AT2R-specific actions has been hampered by the absence of appropriate selective ligands. Until recently, CGP42112A was the only AT2R agonist available, but it also acted as an antagonist at high concentrations (Dubey et al., 1998; Martineau et al., 1999; Ruiz-Ortega et al., 2000; Fabiani et al., 2001). Furthermore, due to its peptidic nature, CGP42112A could not be used readily in *in vivo* studies. Anders Hallberg and colleagues, as recently summarized by Steckelings et al. (2010a,b) and Unger and Dahlof (2010), have characterized the properties of several non-peptidic compounds derived from the prototype non-selective AT1/AT2 receptor agonist L-162,313 (Wan et al., 2004; Georgsson et al., 2005, 2006; Rosenstrom et al., 2005; Wu et al., 2006; Murugaiah et al., 2007). One of these ligands, the M24 compound (originally called C21; Wan et al., 2004; Georgsson et al., 2007), exhibits high affinity for the AT2R (0.4 nM), but very low affinity for the AT1R (>10,000 nM) and acts as an AT2R agonist (Wan et al., 2004). Using a neuronal/glioma cell line (a variant of NG108-15 cells expressing only the AT2R), we found that C21/M24 stimulates neurite outgrowth through sustained activation of p42/p44^{mapk}, as observed with Ang II or CGP42112A (Wan et al., 2004). In addition, C21/M24 also decreases cell proliferation in NG108-15 cells, as does CGP42112A. In addition to our results,

others have found that C21/M24 lowered mean arterial blood pressure in hypertensive rats (Wan et al., 2004; Gelosa et al., 2009; Bosnyak et al., 2010), improved ventricular function in a model of rat myocardial infarction (Kaschina et al., 2009), and corrected several intracellular perturbations and pro-inflammatory conditions (Kaschina et al., 2009; Rompe et al., 2010). Thus, C21/M24 is the most selective AT2R agonist available to date and represents a unique tool to delineate the specific roles of AT2R in different cellular and animal models (Steckelings et al., 2010a; Unger and Dahlof, 2010; recently reviewed in Steckelings et al., 2010b).

The next challenge is now to verify whether AT2R activation by C21/M24 could rescue or improve cognitive performance. To answer this question, we have induced learning deficiency by a 2-week treatment with intracerebral injection of amyloid-β (Aβ). Key findings from our preliminary experiments are that selective AT2R activation by C21/M24 attenuates the learning disturbance in the Y-maze and water-maze tasks more efficiently than AT1R blockade by losartan (Guimond et al., 2010b and unpublished results). It is indeed well documented that Aβ treatment significantly induces a significant learning disturbance in the Y-maze and water-maze tasks, in addition to resulting in moderate neuronal loss and promoting amyloid deposition in the cortex and hippocampus (Yamaguchi and Kawashima, 2001; Tajima et al., 2005; Mogi et al., 2006, 2008; Liu et al., 2009; Klyubin et al., 2011; Srivareerat et al., 2011).

From the previous results demonstrating that AT2R stimulation modulates phosphorylation of MAPs, including MAP2 and MAP1B or tau, as well as modulates interactions between MAPs and microtubules (Laflamme et al., 1996; Meffert et al., 1996; Côté et al., 1999; Li et al., 2007b), it appears therefore that elucidating the signaling mechanisms linking AT2R activation and cytoskeletal remodeling is key to understanding the cognitive roles of the AT2R in hippocampal neurons.

Based on the current paradigms of AT1R/AT2R function, one aspect of AT1R/AT2R regulation is particularly intriguing. Could the age-related shift in the relative expression of the AT1R and AT2R, in which AT1R expression increases and AT2R expression decreases, explain some cellular aspects of aging, especially those relating to altered cell number (von Bohlen und Halbach et al., 2001)?

CONCLUSION – RELEVANCE TO ALZHEIMER'S DISEASE AND RELATED DEMENTIAS

Poor cognitive performance in AD significantly impairs social interaction and the quality of life of patients. Therefore any treatment aimed at improving cognitive functions is likely to slow down symptoms and improve quality of life. An estimated 33 million elderly persons worldwide suffer from dementia, and this number is expected to reach 81.1 million by 2040 (Ferri et al., 2005; Source: *Rising Tide: the Impact of Dementia on Canadian Society*, a report of the Alzheimer's Society of Canada). Life style-related disorders, such as hypertension, diabetes mellitus, and obesity have moreover been implicated as risk factors for dementia (Yaffe et al., 2004a,b; Biessels and Kappelle, 2005; Qiu et al., 2005; Whitmer et al., 2005; Craft, 2006, 2009; Mogi et al., 2006; de la Monte, 2009; Mogi and Horiuchi, 2009).

As described in the previous sections, AT2R activation may act at several locations in the cascade of alterations leading to cognitive impairment and neuronal dysfunction observed in AD. In particular, AT2R may act not only at the neuronal level, but also on vasculature and on inflammation associated with Alzheimer's. As outlined in this review, an increasing number of studies suggest that the protective effects of angiotensin II (AT1) receptor blockers on brain damage and cognition may result not only from the inhibition of AT1R effects, but also from the beneficial effect due to unopposed activation of AT2R. In addition, the relationship between impaired energy metabolism/obesity/insulin resistance and the increased risk of dementia (both AD and vascular dementia; Yaffe et al., 2004a,b; Qiu et al., 2005; Whitmer et al., 2005; Mogi and Horiuchi, 2009) emphasizes that all the mechanisms by which AT2R acts may have a beneficial protective effect. If further research confirms the promising early results, the neuroprotective effect of central AT2R stimulation with the recently developed C21/M24, a non-peptide, selective AT2R agonist, may thus represent a new pharmacological tool in AD and others neurological cognitive disorders. In addition, unraveling the underlying effects of the AT2R on neuronal plasticity may lead to the development of even more selective therapies.

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