



Review

G-protein coupled receptors as therapeutic targets for neurodegenerative and cerebrovascular diseases

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ABSTRACT

Neurodegenerative and cerebrovascular diseases are frequent in elderly populations and comprise primarily of dementia (mainly Alzheimer's disease) Parkinson's disease and stroke. These neurological disorders (NDs) occur as a result of neurodegenerative processes and represent one of the most frequent causes of death and disability worldwide with a significant clinical and socio-economic impact. Although NDs have been characterized for many years, the exact molecular mechanisms that govern these pathologies or why they target specific individuals and specific neuronal populations remain unclear. As research progresses, many similarities appear which relate these diseases to one another on a subcellular level. Discovering these similarities offers hope for therapeutic advances that could ameliorate the conditions of many diseases simultaneously. G-protein coupled receptors (GPCRs) are the most abundant receptor type in the central nervous system and are linked to complex downstream pathways, manipulation of which may have therapeutic application in many NDs. This review will highlight the potential use of neurotransmitter GPCRs as emerging therapeutic targets for neurodegenerative and cerebrovascular diseases.

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Abbreviations: NDs, neurological disorders; GPCRs, G-protein coupled receptors; AD, Alzheimer's disease; PD, Parkinson's disease; GABA, gamma-aminobutyric acid; SN, substantia nigra; A β , β -amyloid; MCI, mild cognitive impairment; AChRs, acetylcholine receptors; mAChRs, muscarinic acetylcholine receptors; CNS, central nervous system; 5-HT, serotonin; ARs, adrenergic receptors; nAChRs, nicotinic acetylcholine receptors; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; EAAs, excitatory amino acids; NMDA, N-methyl-D-aspartate; AMPA, α -amino-3-hydroxy-5-methyl-4-isoazolepropionic acid; 5,7-DHT, 5,7-dihydroxytryptamine; L-DOPA, L-dihydroxy phenylalanine; LID, L-DOPA-induced dyskinesia; 6-OHDA, 6-hydroxydopamine; AChEi, acetylcholinesterase inhibitors; mGlu, metabotropic glutamate; STN, subthalamic nucleus; SNc, substantia nigra pars compacta; MPEP, 2-methyl-6-(phenylethynyl)-pyridine; MTEP, 3-[(2-methyl-1,3-thiazol-4-yl) ethynyl] pyridine; SNr, substantia nigra pars reticulata; APPs, amyloid β precursor proteins.

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1. Introduction

Organisms, cells and even proteins are subject to time-dependent degenerative processes. As such, aging is characterized by the accumulation of adverse changes in cells over time, which augments the risk of diseases and causes the breakdown of homeostatic control and death (Harman, 2001). Neurological disorders (NDs) constitute highly disabling diseases, with appreciable impact on quality of life at the patient level, but also on society, both economically and socially (Chen et al., 2008; Martin et al., 2008; Yang et al., 2015). They are characterized by the loss of structure or function of neurons and are often associated with neuronal death. Alzheimer's disease (AD), Parkinson's disease (PD) and stroke are just some examples. Although the biochemistry and molecular mechanisms of these NDs are still not fully understood, several studies suggest that cellular metabolism alterations such as depressed mitochondrial oxidative phosphorylation (Mandemakers et al., 2007; Mounsey and Teismann, 2010; Pacelli et al., 2011), accumulation of aggregated and misfolded proteins and generation of free radicals (Baillet et al., 2010; Hsieh and Yang, 2013; Marlatt et al., 2008; Surendran and Rajasankar, 2010; Zhou et al., 2008) play a central role in their pathogenesis. Moreover, it was reported that progressive brain inflammation, autophagy impairment and metabolism disturbances observed in NDs lead to cognitive impairment and physical activity declines in patients (Duarte et al., 2014; Ghavami et al., 2014; Sankowski et al., 2015). These disorders are devastating to sufferers and their families, and perplexing to scientists and clinicians who have been unable to make significant headway towards their treatments.

Several studies presented compelling evidence implicating G protein coupled receptors (GPCRs) in the pathogenesis of NDs. With more than 800 members in the human genome, GPCRs constitute the largest and most diverse group of membrane receptors in vertebrates (Gloriam et al., 2007; Schulein et al., 2012). These receptors bind a tremendous variety of signaling molecules and mediate the action of messengers that are key modulators of different cell functions (Iacovelli et al., 1999). Common GPCR ligands in the nervous system are monoamines (adrenaline, noradrenaline, serotonin, dopamine and histamine) and other small neurotransmitters such as acetylcholine (muscarinic, mACh), gamma-aminobutyric acid (GABA-B), glutamate (metabotropic, mGluR), ATP (P2Y), adenosine and cannabinoids. GPCRs represent one of the most important targets in modern pharmacology because of the different functions they mediate, especially within the brain and the peripheral nervous system, and because of their functional and stereochemical properties (Belmonte and Blaxall, 2011; Du and Xie, 2012; Ghanemi, 2015; Lappano and Maggiolini, 2011). Here we review the involvement of these neurotransmitter receptors in the pathogenesis of NDs (mainly AD, PD and stroke) and discuss their potential use as emerging therapeutic targets for these debilitating diseases.

2. Clinical presentation and symptoms

Several NDs involve degeneration and death of specific neuronal populations in particular regions of the brain or spinal cord. In AD, pyramidal neurons in the entorhinal cortex, hippocampus and frontal and temporal lobes degenerate (Mattson, 2004). Neurons in the substantia nigra (SN) that employ the neurotransmitter dopamine degenerate in PD (Barzilai and Melamed, 2003), whereas in stroke, neurons in the brain region(s) that receive blood from the affected artery degenerate (Mergenthaler et al., 2004). Although the causes of each of these neurodegenerative conditions are different, they do share mechanisms that include oxidative stress, metabolic compromise, and disruption of cellular calcium homeostasis (Hashimoto et al., 2003; Mattson, 2003; Rao and Balachandran, 2002).

2.1. Alzheimer's disease (AD)

AD, the most common form of dementia, is an acquired disorder of cognitive and behavioral impairment that markedly interferes with social and occupational functioning. This ND is characterized by an accumulation of β -amyloid ($A\beta$) plaques and neurofibrillary tangles (Hardy, 2006; Kumar and Nisha, 2014; Thathiah and De Strooper, 2011) associated with synapse loss and neurodegeneration (Weiner, 2012), leading to memory impairment and other cognitive problems. There is currently no known treatment that slows the progression of this disease. According to the 2010 World Alzheimer Report, there is an estimated 35.6 million people worldwide living with this disorder and the incidence of AD is expected to double in the next 20 years (Weiner et al., 2013).

The recognition that AD represents a continuous process that passes through a presymptomatic phase and a stage of "mild" cognitive impairment (MCI), with early cognitive but little or no evident functional impairment (Petersen et al., 2010), has led to a proposed revision of the research diagnostic criteria that incorporates both clinical and biomarker evidence of the disease, enabling its diagnosis at very early stages (Dubois et al., 2007). Typically, clinical AD appears to become evident first as a syndrome of amnesic MCI, in which cognitive impairment is largely confined to deficits in memory and complex activities of daily living (Morris et al., 2001; Petersen et al., 1999). Functional, behavioral, and social impairments inexorably emerge as the disorder segues into what is clinically recognized as dementia of the Alzheimer type (McKhann et al., 1984).

Patients with AD most commonly present with insidiously progressive memory loss, to which other spheres of cognitive impairment are added over several years. This loss may be associated with slowly progressive behavioral changes. After memory loss occurs, patients may also experience language disorders and impairment in their visuospatial skills and executive functions (Barnes et al., 2015). Patients with mild AD usually have less obvious executive, language, and/or visuospatial dysfunction. In

atypical presentations, dysfunction in cognitive domains other than memory may be most apparent. In later stages, many patients develop extrapyramidal dysfunction whose main clinical features are rigidity of limbs, bradykinesia of extremities, resting tremor and gait disturbance (Mitchell, 1999). Possible explanations for the existence of extrapyramidal symptoms in AD could be the presence of senile plaques in the putamen, caudate, and SN; the presence of neurofibrillary tangles in the SN; or a neuronal loss (Burns et al., 2005; Liu et al., 1997).

2.2. Parkinson's disease (PD)

PD is a slowly progressive ND that affects about 1–2% of the population over 65 years of age. It was first described by James Parkinson in 1817 in his monograph 'An Essay on the Shaking Palsy' (Alves et al., 2008). PD was, and still is, primarily considered as a movement disorder characterized by increasingly disabling motor symptoms that include bradykinesia, tremor at rest, and rigidity (Dauer and Przedborski, 2003). Postural instability, often considered as one of the cardinal signs of PD, is less specific and is generally a manifestation of the late stages of PD (Parkinson, 2002; Samii et al., 2004). PD patients do not suffer from motor deficits alone; several non-motor symptoms also contribute heavily to the deterioration of their quality of life. Among these, autonomic manifestations in PD are prominent, and most frequently comprise cardiovascular and gastrointestinal dysfunctions (Jain, 2011). Decreased olfactory function, including poor odor detection, identification and discrimination, is another common non-motor symptom observed in this disease (Doty, 2012). In addition to the autonomic and sensory abnormalities, sleep disorders, once largely attributed to the pharmacological treatment of PD, are now considered as an integral part of the disorder itself (Gjerstad et al., 2008).

2.3. Stroke

With 15 million new victims per year worldwide, stroke is the planet's second-largest cause of death and disability and remains the most serious and debilitating ND in the world (Ovbiagele et al., 2013). Strokes are heterogeneous multi-factorial diseases caused by the combination of different risk and genetic factors (Dichgans, 2007). Ischemic strokes are the most common, with an estimated incidence of approximately 80% (Rosamond et al., 2008) whereas hemorrhagic strokes, which occur due to subarachnoid and/or intracerebral hemorrhages, are less common. In addition to the impact on patients and families, strokes have major economic consequences with increasing rate of incidence and therefore represent a major challenge to health planners (Payne et al., 2002; Zweifler, 2003).

Stroke symptoms typically start suddenly, over seconds to minutes, and in most cases do not progress further. However in other instance, stroke symptoms may develop over hours or days. Depending upon the stroke type and the area of the brain affected, the person may lose the ability to speak, to move one side of the body, or a number of other functions (Goldstein and Simel, 2005; Nor et al., 2005). The more extensive the area of brain affected is, the more functions that are likely to be lost. The damage from a stroke may be temporary or permanent.

3. Alterations of neurotransmitter receptors in NDs

It has been well documented that, in addition to motor disorders, cognitive dysfunction characterizes the clinical presentation common to NDs. Although different mechanisms such as neuronal apoptosis and inflammatory responses (Pascual et al., 2011) are

involved in the pathogenesis of cognitive disorders observed in neurodegeneration, there is increasing evidence that alterations in various neurotransmitter receptors may account for the progression of cognitive decline. In eukaryotes, GPCRs are responsible for regulating a wide variety of physiological processes and represent the largest family of membrane receptors. This part highlights the current findings which report the effects of GPCRs alterations on cognitive dysfunction observed in NDs and provides a conceptual update on the multiple underlying mechanisms of neurodegenerative pathology.

3.1. AD and GPCRs

Although the neuropathological hallmarks of AD are the formation of A β peptide and neurofibrillary tangles (Barrantes et al., 2010; Medeiros et al., 2011), there is considerable evidence which implicates defects in acetylcholine receptors (AChRs) in the pathological mechanisms of this disease. The loss of basal forebrain cholinergic neurons has prompted extensive study of AChRs in AD brains and is thought to contribute significantly to the neuropsychiatric symptoms and the deterioration in cognitive function seen in patients with AD (Bartus et al., 1982; Francis et al., 1999; Lai et al., 2001; Minger et al., 2000; Mufson et al., 2008). There is compelling evidence that cholinergic dysfunction occurs early in the disease process (Ferrari-DiLeo and Flynn, 1993; Mufson et al., 2008). Muscarinic acetylcholine receptors (mAChRs), a family of five receptor subtypes (M1–M5) (Bonner et al., 1987; Levey et al., 1991; Wei et al., 1994), regulate a large number of central functions in the central nervous system (CNS) including cognitive, behavioral, motor and sensory processes (Hasselmo, 2006; Levey, 1993; Sarter et al., 2005). They have been implicated in the pathophysiology of major diseases of the CNS, including AD (Jiang et al., 2014; Koch et al., 2005). Evidence suggests that cortical and hippocampal M2 mAChRs levels, most of which are considered to be located on presynaptic cholinergic terminals, are reduced in AD brains (Araujo et al., 1988; Levey, 1996; Mash et al., 1985; Rinne et al., 1989). This is in contrast to a later study, using more specific ligands, which found that binding to M2 receptors is reduced in the striatum and increased in the insular cortex (Warren et al., 2007). Increased levels of M2/M4 mAChRs were found in the temporal cortex of patients with AD (Shiozaki et al., 1999). Another report showed that binding to M2/M4 receptors is increased in the basal ganglia (Piggott et al., 2003). Similarly, cortical M1 receptor mRNA was found to be increased in AD brains (Harrison et al., 1991). Another Study demonstrated a reduction in the number of M3 receptors in the frontal cortex (Shiozaki et al., 1999). Moreover, the ability of mAChR to form high affinity agonist-binding complexes with G proteins was found to be impaired in AD. Indeed, several lines of evidence indicate that the coupling between the M1 mAChRs, their G-proteins, and second messenger systems is disrupted (Alemany et al., 2007; Flynn et al., 1991; Warpman et al., 1993). The reduction in mAChR M1/G-protein coupling has been related to the severity of cognitive symptoms in the neocortex of AD patients (Tsang et al., 2006). Thus, impairment of mAChR M1-mediated signaling through uncoupling of its G protein may be a neurochemical cause of the cognitive decline observed in AD (Jiang et al., 2014; Tsang et al., 2006).

Dopaminergic receptors are a class of metabotropic GPCRs and are involved in many neurological processes, such as motivation, cognition and learning. There are two different classes of dopamine receptors, D1-like and D2-like, with five subtypes: D1, D2, D3, D4 and D5 (Contreras et al., 2002). Both D1 and D2 dopamine receptors are critical for learning and memory processes, which primarily function in the prefrontal cortex (Beaulieu and Gainetdinov, 2011). Although abundant studies have investigated the correlation

between dopamine receptors and PD as discussed below, few studies have investigated the association of dopamine receptors and AD. Postmortem studies on the brains of AD patients indicated lower dopamine levels in the striatum (Arai et al., 1984; Nazarali and Reynolds, 1992; Storga et al., 1996), cingulate gyrus, amygdala, SN, raphe nucleus (Storga et al., 1996) and the temporal cortex (Reinikainen et al., 1988) compared to those of controls. Dopamine levels in the synapse are regulated by the dopamine transporter, which is located on the presynaptic membrane of dopaminergic neurons. Joyce et al. showed that, in AD with parkinsonism, there is a significant reduction in the number of dopamine transporter sites located on dopamine terminals in the striatum (Joyce et al., 1997). It was also reported that the availability of dopamine receptors is reduced in the hippocampus and frontal and temporal lobes of AD patients and that alteration in D2 receptor binding potential in the right hippocampus is significantly and positively associated with verbal memory performance (Kemppainen et al., 2003; Kumar and Patel, 2007; Martorana et al., 2009; Tanaka et al., 2003). Furthermore, reduction in striatal D2 receptor density was found to be associated with severe behavioral abnormalities in AD (Tanaka et al., 2003). Thus, the reduction of dopamine receptors seems to be positively correlated with severity of cognitive dysfunction in AD patients.

There are at least 16 different types of serotonin receptors (5-HT), which can be broadly divided into seven subfamilies, 5-HT₁ to 5-HT₇, based on their primary physiological mechanisms (Kitson, 2007). Most of these receptors belong to the GPCR family of receptors, with the exception of the 5-HT₃ receptor which is classified as a ligand-gated ion channel. 5-HT_{1A} and 5-HT_{2A} remain the most pharmacologically and functionally characterized 5-HT receptor subtypes.

5-HT receptors function in either a stimulatory or inhibitory manner depending on brain localization and cell type and, thus, play an important role in the functioning of many neural circuits implicated in a large variety of cognitive and behavioral processes (Leiser et al., 2015; Lesch and Waider, 2012). Their activations stimulate intracellular responses through distinct signal transduction pathways which can subsequently influence cognitive impairment in NDs. Indeed, several lines of evidence from animal and clinical studies have indicated the role of 5-HT and its receptors in different aspects of cognitive dysfunction, such as cognitive deficits, learning and memory decline (Erkinjuntti et al., 1993; Marner et al., 2012; Sumiyoshi et al., 2007; Versijpt et al., 2003; Zola-Morgan et al., 1992). Some investigations demonstrated a negative correlation between verbal memory and the binding potential of 5-HT_{1A} receptors in hippocampus (Hirst et al., 2008; Meltzer et al., 1998; Yasuno et al., 2003). 5-HT_{1A} receptor density was found to be elevated in the brain of AD patients and this was correlated with the cognitive impairment observed in AD. Similarly, a study confirmed that 5-HT_{1B/1D} receptor density was significantly reduced in the frontal and temporal cortex of AD patients and was also associated with the cognitive dysfunction in this disease (Garcia-Alloza et al., 2004).

Similar to 5-HT_{1A} receptor, 5-HT₂ receptor is also widely distributed in the brain and is closely related to cognitive dysfunction. A significant reduction in the 5-HT₂ receptor binding in the cerebral cortex of AD patients compared to healthy controls was reported. 5-HT_{2A} receptor density was also found to be reduced in frontal and temporal cortical neurons in severely demented AD patients (Lai et al., 2005). This finding suggests that the amount of neocortical 5-HT_{2A} receptor loss could predict the rate of cognitive decline in AD (Lai et al., 2005).

Adrenergic receptors (ARs), a class of metabotropic GPCRs, are subdivided into two main groups, α and β , with several subtypes, including α 1, α 2, β 1, β 2 and β 3. Several lines of evidence

demonstrated that adrenergic receptors are closely associated with cognitive declines in AD (Laureys et al., 2010). A series of clinical studies by Kalaria et al. showed that β 2 receptors are significantly increased in the cerebral microvessels, prefrontal cortex, and hippocampus of AD patients (Kalaria et al., 1989a, 1989b; Kalaria and Harik, 1989). Another study conducted by Russo-Neustadt and Cotman examined the distribution and concentration of β 1, β 2, and α 2 ARs in the frontal cortex, hypothalamus, and cerebellum of AD brains. Results indicated that aggressive AD patients had markedly increased concentrations of α 2 receptors in the cerebellar cortex compared with nonaggressive AD patients with similar levels of cognitive deficit whereas β 1 and β 2 ARs showed smaller increased concentration in aggressive AD subjects versus both nonaggressive AD patients and controls (Russo-Neustadt and Cotman, 1997). No significant differences were found in AR concentrations within the frontal cortex or hypothalamus (Russo-Neustadt and Cotman, 1997). Moreover, it was reported that, compared to healthy old or young subjects, AD subjects manifest substantially greater agitation following α 2 ARs antagonist yohimbine (Peskind et al., 1995). Together, these data suggest that ARs may contribute to agitation, aggression, and disruptive behaviors associated with AD. Another genetic study demonstrated that Gly16Arg and Gln27Glu, two polymorphisms of the β 2-AR gene, interacted with the epsilon 4 allele and markedly increased AD susceptibility and risk (Yu et al., 2008). Furthermore, it was reported that β ARs may involve in the AD pathogenesis through effects on A β production or inflammation (Yu et al., 2011).

3.2. PD and GPCRs

Many studies have explored the relationship between ARs and PD, but few have been successful in revealing the exact mechanism of cognitive impairment in PD patients. Cash et al. measured the amount of α 1, α 2, β 1 and β 2 ARs in the prefrontal cortex of parkinsonian patients postmortem. Data indicated an increase in the α 1 and β 1 ARs density particularly in demented parkinsonian patients and a decrease in the number of α 2 receptors (Cash et al., 1984). Studies of AR binding pattern showed a decrease in the binding sites of α 1 ARs in the cerebral microvessels of the prefrontal cortex and putamen regions of PD patients (Cash et al., 1985). In the following years, it has been found that α 1 ARs increased in the synaptosomal fraction, while β ARs increased in the synaptosomal and microsomal fractions in PD patients (Cash et al., 1986). A study conducted by Berlan and co-workers suggests that untreated PD is associated with a significant reduction in α 2 adrenergic sensitivity (Berlan et al., 1989). Thus, it is possible that patients with PD are more vulnerable to panic attacks because they have an alteration of α 2 ARs.

Many studies have investigated the relationship between AD and AChRs but only few reported a similar association between PD and AChRs. Members of the mAChR family (M1–M5) are known to be involved in a great number of important central and peripheral physiopathological processes. The cognitive dysfunction in PD may be related to impairment of the ascending cholinergic system which occurs in association with neuronal loss in certain brain regions. Indeed, mAChRs levels have been measured in the brain of PD patients and mAChR hypersensitivity was found in the frontal cortex, indicative of dysfunction of the ascending cholinergic system in this area (Ruberg et al., 1982). Moreover, neuroimaging (Asahina et al., 1998; Colloby et al., 2006) studies using nonselective ligands reported increased levels of cortical muscarinic receptors in the brains of PD patients with dementia. Postmortem studies with more selective ligands indicated that it is the M1 receptor which is increased in cortical, but not subcortical regions. However, some reports found unchanged levels of M1 receptors (Rodriguez-

Puertas et al., 1994) while Piggott et al. showed that M1 receptors are significantly reduced in the caudate from PD patients with dementia (Piggott et al., 2003). Similarly, there is conflicting evidence for changes in the M2/M4 receptors in PD, with reports of decreased (Quirion, 1993) and unchanged cortical (Piggott et al., 2003) levels.

Some investigations have focused on the relationship between dopamine receptors and dementia in PD and several lines of evidence have shown the association between the disturbance of dopaminergic receptors in some brain regions and cognitive deficits in PD (Fetsko et al., 2005; Reeves et al., 2005; Rieckmann et al., 2011). At early stages of PD, the dopamine D2 receptor binding was found to be elevated in some brain regions, while the progression of PD with dementia occurrence (over years rather than months) has been found to correlate with lower dopamine D2 receptor binding in these patients, strongly implying the association of dopaminergic receptors and cognitive impairment. With disease progression, dopamine receptor expression profoundly declines in the dorsolateral prefrontal cortex, temporal cortex, and medial thalami at a relatively faster annual rate compared to the rate in healthy individuals (Kaasinen et al., 2003). In advanced stages of PD, dopamine D2 and D3 receptor bindings were found to be significantly decreased in the dorsolateral prefrontal cortex, anterior cingulate cortex, and medial thalamus compared with healthy controls (Kaasinen et al., 2000).

Serotonin 5-HT_{1A} receptors modulate glutamatergic, serotonergic and dopaminergic neurotransmissions along the cortico-basal ganglia-thalamo-cortical loop. Numerous studies investigating 5-HT_{1A} receptors in PD and animal models of PD have been performed. In the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-lesioned macaque, 5-HT_{1A} receptor levels have been found to be altered in both the L-DOPA-naïve and the L-DOPA-chronic states, suggesting their involvement in the physiopathology of both parkinsonian and dyskinetic states. In idiopathic PD, 5-HT_{1A} receptor levels were found to be increased in the frontal and temporal cortices. High 5-HT_{1A} receptor levels in the temporal cortex were associated with depression in PD dementia (Sharp et al., 2008), whereas lower midbrain raphe 5-HT_{1A} receptor levels correlate with tremor (Doder et al., 2003). Serotonin 5-HT_{2A} receptors and their modulation have also been extensively studied in PD. 5-HT_{2A} receptor levels were found to be increased in the striatum and middle layers of the motor cortex of dyskinetic MPTP-lesioned macaques, as well as in the motor cortex of idiopathic PD patients. High 5-HT_{2A} receptor levels have also been found in the temporal cortex of PD patients experiencing visual hallucinations.

In Parkinsonian tissue, the level of cannabinoid receptors CB1 mRNA was found to be decreased in the caudate nucleus, anterior dorsal putamen and external segment of the globus pallidus (Hurley et al., 2003). In contrast, others have observed an increase in CB1 binding in the caudate nucleus and putamen (Lastres-Becker et al., 2001). These studies are complicated to interpret as all patients have undergone drug treatment whose effects on the cannabinoid system are not clear. Endocannabinoid levels have been investigated in some recent studies which showed dysregulation of the endocannabinoid system, highlighted its role in movement disorders in animal models of Parkinson's disease and indicated that targeting these key neuromodulators may have multiple therapeutic benefits (Concannon et al., 2015; Pisani et al., 2005; van der Stelt et al., 2005). These studies are supported by a comparatively smaller number of clinical studies that also indicate a role of the endocannabinoid system in the pathogenesis of PD and suggest that it represents a variable therapeutic target (Venderova et al., 2004; Zuardi et al., 2009). However, more clinical trials with larger samples sizes including untreated PD patients are required to further clarify the relationship between alterations of cannabinoid

receptors and the symptoms of this disease.

3.3. Stroke and GPCRs

Excitotoxicity has been a widely investigated area in stroke. Ischemic neuronal injury *in vitro* is dependent on synaptic release of excitatory amino acids (EAAs) and resultant elevation of intracellular free calcium. Even transient exposure to excess EAAs is toxic to cultured neurons, and alterations in neuronal energy balance increases the vulnerability of neurons to excitotoxic damage even in the presence of physiological concentrations of EAAs (Mehta et al., 2007; Muir and Lees, 1995). Evidence that this process progresses over several hours after the ischemic insult highlights a potential role for neuroprotective strategies administered during the critical window prior to irreversible loss, although the exact duration of this window in humans remains unknown (Tarawneh and Galvin, 2010). The action of glutamate on NMDA (N-methyl-D-aspartate) receptors seems to play an important role in glutamate-mediated toxicity (Arundine and Tymianski, 2004; Rothstein, 1996). Compounds that decrease glutamate levels or interfere with its binding to this receptor have been the focus of many studies in this area (Danton and Dietrich, 2004; Kawasaki-Yatsugi et al., 2000; Kermer et al., 1999; Legos and Barone, 2003; Nakanishi et al., 2009; Schurr, 2004; Yam et al., 2000).

The neurotoxicity of glutamate and other EAAs is the result of excessive activation of postsynaptic glutamate receptors. Activation of NMDA receptors leads to a massive inflow of calcium, and activation of AMPA (α -amino-3-hydroxy-5-methyl-4-isoazolepropionic acid) receptors facilitates the entry of sodium into the cell (Rothman and Olney, 1986). The accumulation of both ions leads to edema, and neuronal necrosis follows as a result of the activation of different cytoplasmic pathways, which include the formation of free radicals and nitric oxide, and induction of transcription factors that promote apoptosis (Farooqui and Horrocks, 1994). In animal models of stroke, elevated concentrations of glutamate, aspartate, taurine, and glycine were detectable in the extracellular space soon after focal cerebral ischemia (Davalos et al., 2000).

Initially the role of the serotonergic system in the pathophysiology of cerebrovascular diseases was not understood, but considerable progress has been made in recent years. The concentration of 5-HT in the cerebral cortex was found to be decreased in the ischemic brain (Kukley et al., 2001). However, neurotoxin that destroys 5-HT system (5,7-dihydroxytryptamine (5,7-DHT)), increases neuronal death after ischemia in gerbil hippocampus (Nakata et al., 1997). Moreover, rapid enhancement of serotonergic sprouting was demonstrated in response to excitotoxic stimuli in different brain areas (Harkany et al., 2001; Zhou et al., 1995) suggesting enhanced signaling.

The location of adenosine A_{2A} receptors in the brain may also influence ischemic injury. In a model of permanent focal ischemia, a decrease in A_{2A} receptor ligand affinity and an increase in receptor expression were seen in the striatum, but not in the cortex (Trincavelli et al., 2008). Moreover, brain adenosine A₁ receptors function and density were found to be reduced following ischemic insults (Lee et al., 1986; Nagasawa et al., 1994; Onodera et al., 1987).

4. Neurotransmitter receptors as targets for ND therapies

By virtue of their large number, specific distribution, selective functional roles and downstream effects, GPCRs play multiple important roles in clinical medicine and have been demonstrated as important new drug targets in many neurological conditions.

4.1. Adenosine receptors

Adenosine receptors modulate neuronal and synaptic function in a range of ways that may make them relevant to the occurrence, development and treatment of brain degenerative disorders. Adenosine A_{1A} receptors tend to suppress neural activity by a predominantly presynaptic action, while adenosine A_{2A} receptors are more likely to promote transmitter release and postsynaptic depolarization. A variety of interactions have also been described in which adenosine A_{1A} or A_{2A} receptors can modify cellular responses to conventional neurotransmitters or receptor agonists such as glutamate, NMDA and nitric oxide receptors. Part of the role of adenosine receptors seems to be in the regulation of inflammatory processes that often occur in the aftermath of a major insult or disease process.

Increasing evidence suggests that adenosine receptors change their pattern of localization and density in afflicted brain regions of AD (Cunha and Agostinho, 2010); however, the role of adenosine and its receptors in regulating the pathogenesis of this ND remained weakly known. Numerous studies find that the modulation of adenosine A_{2A} receptors could have neuroprotective effects in AD. *In vitro* studies showed that adenosine A_{2A} receptor antagonism prevents synaptic loss as well as neuronal death triggered by $A\beta$ synthetic peptides (Canas et al., 2009; Dall'Igna et al., 2003). The mechanisms of neuroprotection induced by adenosine A_{2A} receptor antagonism against $A\beta$ still remain to be fully characterized. This ability of adenosine A_{2A} receptors to control mechanisms involved in synaptic degeneration and subsequent neuronal death indicates the possibility that adenosine A_{2A} receptor antagonists might control this apparently reversible synaptic dysfunction, which might be an effective strategy to arrest NDs at their early stages before they evolve into overt irreversible neuronal loss (Coleman and Perry, 2002). Thus, benefits for cognitive deficits in AD patients and AD animal models might be achieved by antagonising adenosine A_{2A} receptor, since these receptors facilitate the synaptic mechanisms of memory and learning (Cunha and Agostinho, 2010; Takahashi et al., 2008).

Adenosine control of motor function is centered on the ability of adenosine A_{2A} receptor to tightly control dopamine D2 receptors functions (Schiffmann et al., 2007). Almost 20 years after the observation that adenosine receptor antagonists exert the same motor effects as dopamine receptor agonists (i.e. hyperlocomotion), it was found that adenosine A_{2A} receptors and D2 receptors colocalize (Fink et al., 1992; Hillion et al., 2002; Schiffmann and Vanderhaeghen, 1993), form heteromers (Ciruela et al., 2004) and alter each other's pharmacological properties (Hillion et al., 2002). Adenosine A_{2A} receptor and D2 receptors have antagonistic interactions not only at the membrane level but also at the intracellular signaling level. The net result of dopamine depletion in the striatum is an adenosine A_{2A} receptor over-signaling resulting in typical hypokinetic symptoms of PD and blockade of adenosine A_{2A} receptors became an attractive alternative (or adjunctive) to the dopamine-based therapeutic approaches. Adenosine A_{2A} receptor antagonists improved motor function in different rodent and primate models of PD, alone or co-administered with dopaminomimetic drugs, levodopa or dopamine agonists (Koga et al., 2000). Moreover, when administered after the onset of the most severe side-effect of levodopa (dyskinesia); adenosine A_{2A} receptor antagonists had an additive beneficial effect upon motor disability and do not worsen dyskinesia.

For some time, adenosine and its receptors have been viewed as potential therapeutic targets for the treatment of stroke. In practice, adenosine A_{1A} receptors activation has been shown to produce conflicting effects in both *in vivo* and *in vitro* models of cerebral ischemia. Acute stimulation via adenosine A_{1A} receptors provides

protection by decreasing synaptic transmission, but during recovery ischemia-induced downregulation of adenosine A_{1A} receptors may be beneficial. The advent of more selective adenosine A_{2A} receptor agonists and antagonists, and the generation of adenosine A_{2A} knockout mice have revealed an important role of adenosine A_{2A} receptors as mediators of neuroprotection in stroke. Stimulation of adenosine A_{2A} receptors would exacerbate ischemic damage as they are coupled to excitatory G proteins. Paradoxically when applied centrally, adenosine A_{2A} receptor antagonists afford protection in several *in vivo* models of ischemic injury (Melani et al., 2003). The effects of adenosine A_{2B} receptors during ischemia are not as well characterized as those of A_{2A} receptors. Adenosine A_{2B} receptors are perhaps the least studied member of adenosine receptors family. A_{2B} receptors might afford protection to the CNS when activated under ischemic conditions, either directly or by decreasing inflammation and reducing immune cell adhesion to vascular endothelium (Kobayashi et al., 2006; Melani et al., 2014; Yamagata et al., 2007; Yang et al., 2006). The effects of adenosine A_3 receptor signaling during ischemic injury may be beneficial or detrimental depending on the specific circumstances in which the stimulus occurs. Correctly timed, A_3 receptor modulation may be a potential target for therapeutic intervention. Early chronic stimulation of A_3 receptors leading to their downregulation, or acute A_3 receptor blockade, may be one strategy for inducing prophylactic neuroprotection in advance of predicted ischemic injury. In practice, however, adenosine-based therapies for the treatment of stroke have proven complex in their implementation (von Lubitz, 1999). Difficulties stem from the widespread distribution of adenosine receptors within the CNS and throughout the body. For this reason, even direct targeting of specific adenosine receptor leads to widespread off-target effects. Further complications in developing robust adenosine-based therapeutics include imperfect targeting of specific receptor subtypes by agonists and antagonists. Moreover, stroke is comprised of a complex set of pathophysiological processes that are influenced differentially by adenosine spatially and temporally.

4.2. Dopamine receptors

The multiplicity of dopamine receptors in the brain offers a range of potential targets. Currently, first line pharmacotherapeutic strategy in PD aims at restoring dopamine levels and/or effects, by the use of a dopamine precursor, dopamine agonists and inhibitors of enzymatic degradation of dopamine. The discovery of dopamine deficiency in PD and the therapeutic introduction of levodopa (L-dihydroxy phenylalanine, L-DOPA), the precursor of dopamine, in the mid-1960s revolutionized the treatment of this neurological disease. However, motor fluctuations and dyskinesia complicate levodopa treatment in most patients (>90%) within 5–10 years of treatment initiation (Jenner, 2008). Finding alternative symptomatic pharmacological treatments that bypass the dopamine system and avoid L-DOPA-induced dyskinesia (LID) by reducing the overactive glutamate transmission still represents a major challenge.

Dopamine D1 and D2 receptor agonists displayed positive effects on cognitive dysfunction (Rektorova, 2010; Rektorova et al., 2005). Treatment with the dopamine D2/3 receptor agonist, pramipexole significantly ameliorated the decline in cognition observed in Nigrostriatal 6-hydroxydopamine (6-OHDA)-lesioned PD rats (Turle-Lorenzo et al., 2006). Treatment of advanced PD patients with the dopamine receptor agonists pergolide and pramipexole resulted in a significant improvement in the visual-spatial, visual-object, and verbal working memory tasks in these patients (Costa et al., 2009). Several other dopamine receptor agonists, including apomorphine, bromocriptine, ropinirole, rotigotine, and other

compounds have been developed in recent years (Bonuccelli and Pavese, 2007; Millan, 2010). However, it should be noted that none of these dopamine agonists can be compared in efficacy to the first choice in PD treatment, L-DOPA.

A role for the dopaminergic system in AD brains has long been sought and it is still debated. Based on evidence for the involvement of the dopaminergic system in cognitive dysfunction observed in AD as outlined previously, the use of targeted dopamine agents for AD has been proposed. Using animal models of AD, Himeno et al. revealed that dopamine agonists may improve memory function of transgenic-AD mice (Himeno et al., 2011). A recent experience showed that the use of dopaminergic drugs, in particular of the dopamine D2 agonist rotigotine, has beneficial effects on some cognitive domains in AD patients (Koch et al., 2014). The use of these drugs was well tolerated with no relevant behavioral side effects. Moreover, CNS stimulants that target dopamine, most notably methylphenidate, have been found to safely ameliorate symptoms of apathy in patients with AD (Galynker et al., 1997; Herrmann et al., 2008; Padala et al., 2010). Future clinical trials are needed to verify the potential therapeutic effectiveness of dopaminergic drugs in AD patients.

A growing body of evidence indicates an important role of dopaminergic brain pathways in learning and motor skill acquisition (Wise, 2004; Ziemann et al., 2006). Gorgoraptis et al. showed that the dopamine agonist rotigotine may have a beneficial effect on hemispatial neglect in stroke patients (Gorgoraptis et al., 2012). A recently released study indicates that combining carbidopa/levodopa (co-careldopa) with physical and occupational therapy may improve the recovery of arm and leg movements and lead to improved function in patients with stroke (Bhakta et al., 2014).

4.3. Acetylcholine receptors

Both nicotinic and muscarinic AChRs seem to be associated with memory disturbance, and stimulation of these receptors may be efficacious for the treatment of AD (Potter et al., 1999). Stimulation of central nicotinic receptors was found to have an acute cognitive benefit in AD patients. However, many problems still need to be solved before an effective stimulant can be developed. Meanwhile, all of the prescription medications currently approved for the symptomatic treatment of AD are in a class of drugs called acetylcholinesterase inhibitors (AChEI) (Clark and Karlawish, 2003; Kapaki et al., 2003).

Naturally occurring or synthetic compounds with anticholinergic activity (antagonists of mAChRs) were the primary mode of treatment for PD in the years prior to the discovery of L-DOPA and directly acting dopamine receptor agonists. As reviewed by Duvoisin (1967), although the use of these compounds was originally “based on empirical observations”, there is now a large body of evidence that attributes their antidyskinetic mechanism of action to blockade of central cholinergic mechanisms. The anticholinesterase physostigmine was found to worsen parkinsonian symptoms and this effect was ameliorated by the mAChR antagonist benztropine. Conversely, benztropine improved pre-existing parkinsonian symptoms and this benefit was antagonised by physostigmine (Duvoisin, 1967). Thus, co-treatment using a combination of anticholinergics and anticholinesterases would correct acetylcholine deficits while counteracting the hypersensitivity of cortical muscarinic receptors. Although L-DOPA has largely superseded the use of anticholinergic drugs for the treatment of PD, these compounds are still used in a clinical setting (Katzenschlager et al., 2003). However, this class of drug is beset with liability for peripheral and central side effects (Lees, 2005). Therefore, the discovery of selective antagonists of single receptors of the mAChR family which will provide better symptomatic treatment of

parkinsonian tremor and rigidity without the attendant side effects remains to be seen.

It has been shown that impaired cholinergic dilation of cerebral vasculature is implicated in focal cerebral ischemia (Scarr, 2012). Yamada et al. have proposed that M5 mAChRs play a role in the cerebrovascular vasodilatation induced by acetylcholine by mediating the diameter of cerebral arterioles and arteries (Yamada et al., 2003). As a result, the authors suggest that selective M5 mAChR agonists may have a potential clinical utility for increasing cerebral blood flow in certain diseases, including cerebral ischemia.

4.4. Metabotropic glutamate receptors

Recent evidence indicates that mGlu receptors are potential drug targets for the therapy of PD, AD and stroke. The imbalanced situation in favor of excitation in these NDs may accelerate excitotoxic processes, thereby representing a potential target for neuroprotective therapies. In PD, the loss of nigrostriatal dopamine neurons results in an excessive activity of glutamatergic neurons at different levels of the basal ganglia in the corticostriatal pathway (Gubellini et al., 2002, 2004) and the subthalamic nucleus (STN) (Chase et al., 2003; Greenamyre, 2001). This overactive glutamate transmission plays a key role in the expression of PD symptoms and in the development of dopamine cell death. Based on this, it is possible that reducing glutamate transmission at this level could lead to symptomatic improvement for PD patients and may promote the survival of dopamine neurons. Moreover, recent studies highlight the use of selective mGlu4 receptor agonists for the treatment of PD (Agari et al., 2008; Amalric et al., 2013; Beurrier et al., 2009; Lopez et al., 2007; Sibille et al., 2007). Activation of pre-synaptic mGlu receptors might at one time delay the degeneration of substantia nigra pars compacta (SNc) neurons and improve motor activity.

Several negative allosteric modulators of mGluR5 have been shown to possess antiparkinsonian effects in animal models. The mGluR5 antagonists 2-methyl-6-(phenylethynyl)-pyridine (MPEP) and 3-[(2-methyl-1,3-thiazol-4-yl) ethynyl] pyridine (MTEP) reverse parkinsonism in 6-OHDA lesion and haloperidol rat models of PD following systemic administration (Ossowska et al., 2005; Turle-Lorenzo et al., 2005). Antagonists of group I mGluRs may also exert antiparkinsonian effects by reducing the hyperactivity of STN and/or SNr (substantia nigra pars reticulata) neurons (Marino et al., 2001, 2002). Evidence from electrophysiological studies demonstrates that activation of presynaptic group II mGluRs at the STN-SNr synapse reduces excitatory synaptic transmission, suggesting that agonists of these receptors may be beneficial for treating PD. Targeting glutamate receptors may also be a valuable strategy for treating neurological and psychiatric comorbidities associated with PD, which include depression, anxiety, and cognitive impairment (Schneider et al., 2008). Antagonists of mGluR5, as well as agonists of group II mGluRs, have shown anxiolytic-like effects in preclinical models of anxiety and have been validated in proof-of-concept studies in humans (Palucha and Pilc, 2007), suggesting that these types of drugs have the potential to treat both motor and psychiatric symptoms of this disease. Furthermore, antagonists of mGluR5 and group II mGluRs, as well as agonists of group III mGluRs, are efficacious in preclinical models of depression (Lavreysen and Dautzenberg, 2008), indicating that several subtypes of mGluRs may be targets for the treatment of comorbid depression in PD patients.

Activation of mGlu receptors might also interfere with the pathophysiological events underlying AD. Apoptosis induced by A β was found to be substantially attenuated by agonists of group II and group III mGlu receptors, as well as by voltage operated Ca²⁺ channels inhibitors (Copani et al., 1995). The protective activity of

mGlu-receptor agonists against apoptosis induced by A β might be related to their ability to reduce the influx of extracellular Ca²⁺, although whether or not A β peptide destabilizes the homeostasis of intracellular free Ca²⁺ is still a matter of controversy. Therefore, activation of group I mGlu receptors might increase the production of amyloid β precursor proteins (APPs), thus reducing A β formation, whereas activation of group II mGlu receptors might protect neurons against the toxic effect of A β peptide.

One of the most clear potential beneficial effects of mGluR agonists and antagonists is reduction of excitotoxic neuronal damage that occurs after stroke or traumatic brain injury. For instance, selective antagonists of mGluR subtypes involved in potentiating responses to activation of ionotropic glutamate receptors could be effective in reducing excitotoxicity, as could agonists at mGluR autoreceptors. Further, the tremendous heterogeneity of mGluR subtypes that serve as autoreceptors at different synapses provides an opportunity for development of drugs that are highly selective for mGluRs in specific brain regions that may be affected in different cerebrovascular diseases. Consistent with a potential neuroprotective effect of mGluR ligands, several studies suggest that agonists of group II and group III mGluRs may be beneficial in the prevention of stroke, whereas agonists of group I mGluRs are usually without effect or may potentiate excitotoxicity (Conn and Pin, 1997). More recent investigation suggests that YM-202074, a mGluR1 antagonist, exhibits great potential as a novel neuroprotective agent for the treatment of stroke (Kohara et al., 2008). But whereas targeting of glutamate receptors showed dramatic neuroprotective effects in the lab, clinical trials aimed at reducing ischemic brain injury by targeting NMDA and AMPA glutamate receptors were disappointing (Wahlgren and Ahmed, 2004).

4.5. Cannabinoid receptors

Highly distributed throughout the central and peripheral nervous system, the cannabinoid system plays a neuromodulatory role, with influence over the release and activity of a range of other neurotransmitters. The cannabinoid CB1 receptors are found in high density in the nervous system (Herkenham et al., 1990) where they mediate cannabinoid psychoactivity. CB1 receptors have gained much attention as potential pharmacotherapeutic targets in various NDs including AD. However, the relation of CB1 receptors to cognitive function in AD is at present unclear. Deletion of the CB1 gene in rodents resulted in improved learning, putatively through enhancing cholinergic neurotransmission (Degroot et al., 2005). This supports the proposal of utilizing CB1 receptor antagonists as potential therapeutics for AD which might be useful in the late phases of the disorder to reduce the cognitive deficits (Basavarajappa et al., 2009; Bisogno and Di Marzo, 2008). On the other hand, several findings indicate that the activation of both CB1 and CB2 receptors by natural or synthetic agonists, at non-psychoactive doses, have beneficial effects in Alzheimer experimental models by reducing the harmful A β peptide action (Aso et al., 2012, 2013; Chen et al., 2011; Janefjord et al., 2014; Ruiz-Valdepenas et al., 2010; Tolon et al., 2009; Wu et al., 2013) and tau phosphorylation (Aso et al., 2013; Esposito et al., 2006a, 2006b), as well as by promoting the brain's intrinsic repair mechanisms (Campbell and Gowran, 2007). Moreover, the use of these compounds has been demonstrated to modulate numerous concomitant pathological processes, including neuroinflammation (Esposito et al., 2006a; Fakhfoury et al., 2012; Martin-Moreno et al., 2011; Wu et al., 2013), mitochondrial dysfunction and oxidative stress (Aso et al., 2013; Ehrhart et al., 2005; Esposito et al., 2011; Martin-Moreno et al., 2011).

In recent years, an increased understanding of the physiological role of transmission at CB1 receptors throughout the basal ganglia

circuitry has led to the identification of novel therapeutic approaches to both the symptoms of PD and the side effects of current anti-parkinsonian therapies, especially LID. Recent studies in animal models and in clinic suggest that CB1 receptor antagonists could be useful in the treatment of parkinsonian symptoms and LID, whereas CB1 receptor agonists could have value in reducing LID (Brotchie, 2003; Fernandez-Espejo et al., 2005; Ferrer et al., 2003; Gonzalez et al., 2006; Kelsey et al., 2009; van der Stelt et al., 2005).

Cannabinoids reduce neuronal death from a variety of insults, including excitotoxicity, oxidative stress, hypoxia, ischemic stroke, and trauma, but the mechanism that underlies their neuroprotective action is uncertain. The cannabinoid agonist R(+)-2,3-dihydro-5-methyl-3-[(morpholinyl) methyl] pyrrolo[1,2,3-de]-1,4-benzoxazin-yl-1-naphthalenylmethanone mesylate [R(+)-WIN55212-2] was found to decrease hippocampal neuronal loss after transient global cerebral ischemia and reduce infarct volume after permanent focal cerebral ischemia induced by middle cerebral artery occlusion in rats, and thus may have therapeutic potential in disorders resulting from cerebral ischemia, including stroke (Nagayama et al., 1999). Furthermore, a number of investigations have shown that CB2 receptor activation has anti-inflammatory therapeutic potential in stroke (Jackson et al., 2005; Zhang et al., 2007, 2009).

4.6. Serotonin receptors

Mounting evidence accumulated over the past few years indicates that the neurotransmitter 5-HT plays a significant role in cognition. As a drug target, 5-HT receptors have received notable attention due in particular to the role of several 5-HT receptor subclasses in cognition and memory. Compounds are currently being investigated for activity against serotonin 5-HT₁, 5-HT₄ and 5-HT₆ receptors (Geldenhuis and Van der Schyf, 2011).

5-HT receptors are crucial to motor control in health and disease (De Deurwaerdere et al., 2004). In PD, 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A} and 5-HT_{2C} deserve special attention, particularly with respect to involvement in LID. One motor feature of PD that may be mediated in part by 5-HT is tremor. In a proposed model of PD, 5-HT_{2A} antagonists reduced tremor via a selective action in the SNr. Mirtazapine, an antidepressant with multiple mechanisms of actions, including 5-HT_{1A} agonist and 5-HT₂ and 5-HT₃ antagonist actions, was found to reduce parkinsonian tremors (Gordon et al., 2002). Moreover, the atypical antipsychotic clozapine, which binds to 5-HT_{2A/2C} receptors, also suppresses tremor (Bonuccelli et al., 1997). In clinical trials, sarizotan and buspirone (5-HT_{1A} agonists) reduced LID (Bara-Jimenez et al., 2005; Olanow et al., 2004) and extended the duration of L-DOPA action (Bara-Jimenez et al., 2005).

Several studies have examined the effects of 5-HT drugs on cognitive function in AD. Clinical trials using selective serotonin reuptake inhibitors demonstrated consistent improvement of behavioral symptoms associated with this disease, including depression, agitation, irritability, anxiety, affective symptoms and aggressive behavior. A recent study also reported improvements of behavioral symptoms associated with AD following treatment with milnacipram, a selective 5-HT and noradrenalin reuptake blocker (Mizukami et al., 2009). Agonists of 5-HT₄ receptors have been proposed as valuable drugs for treating the cognitive deficits observed in AD. 5-HT₆, the most recently identified member of the 5-HT receptor superfamily, is a subtype localized almost exclusively in the CNS, predominating in brain regions associated with cognition and behavior. Recent investigations showed that 5-HT₆ receptors antagonists lead to an improvement of cognitive performance in patients with AD, either as stand-alone therapy or in combination with established agents (Benhamu et al., 2014;

Maher-Edwards et al., 2010, 2011; Maher-Edwards et al., 2015; Upton et al., 2008). Receptor blockade by a 5-HT_{1A} receptor antagonist appears to enhance activation and signaling through heterosynaptic neuronal circuits known to be involved in cognitive processes and, as such, represents a therapeutic approach for the treatment of cognitive deficits associated with AD (Schechter et al., 2002). Another approach to improve cognitive deficits involves the simultaneous stimulation of cholinergic and 5-HT neurotransmitter systems (Smith et al., 2009).

There is compelling evidence from animal stroke models that drugs-induced hypothermia reduce brain damage. Therefore, they constitute a promising neuroprotective approach against brain injury induced by hemorrhagic or ischemic strokes (Abdullah and Husin, 2011; Fingas et al., 2009; Kollmar et al., 2010; van der Worp et al., 2010; van der Worp et al., 2007). Johansen et al. showed that 5-HT_{1A} agonists significantly reduce infarct volumes in middle cerebral artery occlusion rats primarily by mediating hypothermic effect (Johansen et al., 2014). Authors proposed that 5-HT_{1A} agonists may be introduced to reduce body temperatures rapidly and prepare stroke patients for further therapeutic hypothermia (Johansen et al., 2014). Moreover, serotonin agonists have been shown to hyperpolarize glutamatergic neurons and thus can reduce glutamate-induced excitotoxicity in cerebral ischemia. Bielenberg and Burkhardt demonstrated neuroprotective properties of the 5-HT_{1A} agonists buspirone, gepirone, isapirone, 8-OH-DPAT, and Bay R 1531. These drugs decreased cortical size in mice and rats models of permanent focal cerebral ischemia after pre-ischemic application (Bielenberg and Burkhardt, 1990). Ipsapirone and Bay R 1531 showed the most pronounced effect with greater than 60% reduction in infarct size (Bielenberg and Burkhardt, 1990). In global ischemic models, ipsapirone was protective of 53% of neurons and Bay R 1531 100% of neurons (Bode-Greuel et al., 1990). BAY x 3702, or repinotan, is a highly potent 5-HT_{1A} receptor agonist with strong neuroprotective efficacy that has shown therapeutic benefit in several animal and preclinical models of stroke and traumatic brain injury (Lutsep, 2005; Mauler and Horvath, 2005; Teal et al., 2009).

5. Conclusion

GPCRs represent the largest therapeutic target in the pharmaceutical industry and provide ample opportunities for neurodegenerative and cerebrovascular diseases-related drug development. Therapeutics acting on GPCRs have traditionally been classified as agonists, partial agonists or antagonists. While these compounds hold some promise in the therapy of NDs, new highly promising avenues of GPCRs research have recently emerged suggesting that a more functional approach towards the classification of GPCRs might enhance their therapeutic potential and assist in the development of selective GPCR candidate drugs for AD, PD, stroke and many other diseases. However, the design of such drugs may present a multitude of challenges due to the complex nature of brain function, the lack of good disease models and the wide ranging and often prohibitive adverse effects.

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Conflicts of interest

All authors declare no conflicts of interest.

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