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Review Article

Dopamine Receptors and Neurodegeneration

Claudia Rangel-Barajas[1,2], **Israel Coronel**[3], **Benjamín Florán**[4]

[1]Department of Psychological and Brain Sciences Program in Neurosciences, Indiana University Bloomington, Bloomington, IN 47405, USA
[2]Department of Pharmacology and Neuroscience, University of North Texas Health Science Center, Fort Worth, TX 76107, USA.
[3]Health Sciences Faculty, Anahuac University, Mexico Norte, State of Mexico, Mexico.
[4]Department of Physiology, Biophysics and Neurosciences CINVESTAV-IPN, Mexico.

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ABSTRACT: Dopamine (DA) is one of the major neurotransmitters and participates in a number of functions such as motor coordination, emotions, memory, reward mechanism, neuroendocrine regulation etc. DA exerts its effects through five DA receptors that are subdivided in 2 families: D1-like DA receptors (D_1 and D_5) and the D2-like (D_2, D_3 and D_4). All DA receptors are widely expressed in the central nervous system (CNS) and play an important role in not only in physiological conditions but also pathological scenarios. Abnormalities in the DAergic system and its receptors in the basal ganglia structures are the basis Parkinson's disease (PD), however DA also participates in other neurodegenerative disorders such as Huntington disease (HD) and multiple sclerosis (MS). Under pathological conditions reorganization of DAergic system has been observed and most of the times, those changes occur as a mechanism of compensation, but in some cases contributes to worsening the alterations. Here we review the changes that occur on DA transmission and DA receptors (DARs) at both levels expression and signals transduction pathways as a result of neurotoxicity, inflammation and in neurodegenerative processes. The better understanding of the role of DA receptors in neuropathological conditions is crucial for development of novel therapeutic approaches to treat alterations related to neurodegenerative diseases.

Key words: Dopamine receptors, neurotoxicity, neurodegeneration, Parkinson's disease

Dopamine (DA) is a catecholamine neurotransmitter widely distributed in the central nervous system (CNS) and some peripheral areas including cardiovascular and renal system. In the brain, DA is involved in control of the movements, cognition, emotions, memory, reward mechanism and the regulation of prolactin secretion by the pituitary. Several diseases have been related with disturbances of DA transmission like neuropsychiatric disorders, such as attention deficit hyperactivity disorder (ADHD), Tourette Syndrome (TS), schizophrenia, psychosis, depression, etc., and with neurodegenerative diseases like Parkinson's disease (PD), Huntington disease (HD), multiple sclerosis (MS). Here, we will focus on the role of dopamine receptors and changes in their signal transduction pathways in neurodegenerative diseases.

Historically, the importance of the DAergic system in the brain was pointed out due to the investigation of PD, which is the result of degeneration of the DAergic neurons of substantia nigra pars compacta (SNc). There are three main sources of DA in the CNS: the nigrostriatal pathway, the mesocorticolimbic pathway and the tuberoinfundibular pathway, all of them involved in different neurophysiological features.

***Correspondence should be addressed to:** Claudia Rangel-Barajas, Ph.D., Psychological and Brain Sciences Neurosciences Program, Bloomington Indiana University, Bloomington, IN, USA. Email: crangelb@indiana.edu

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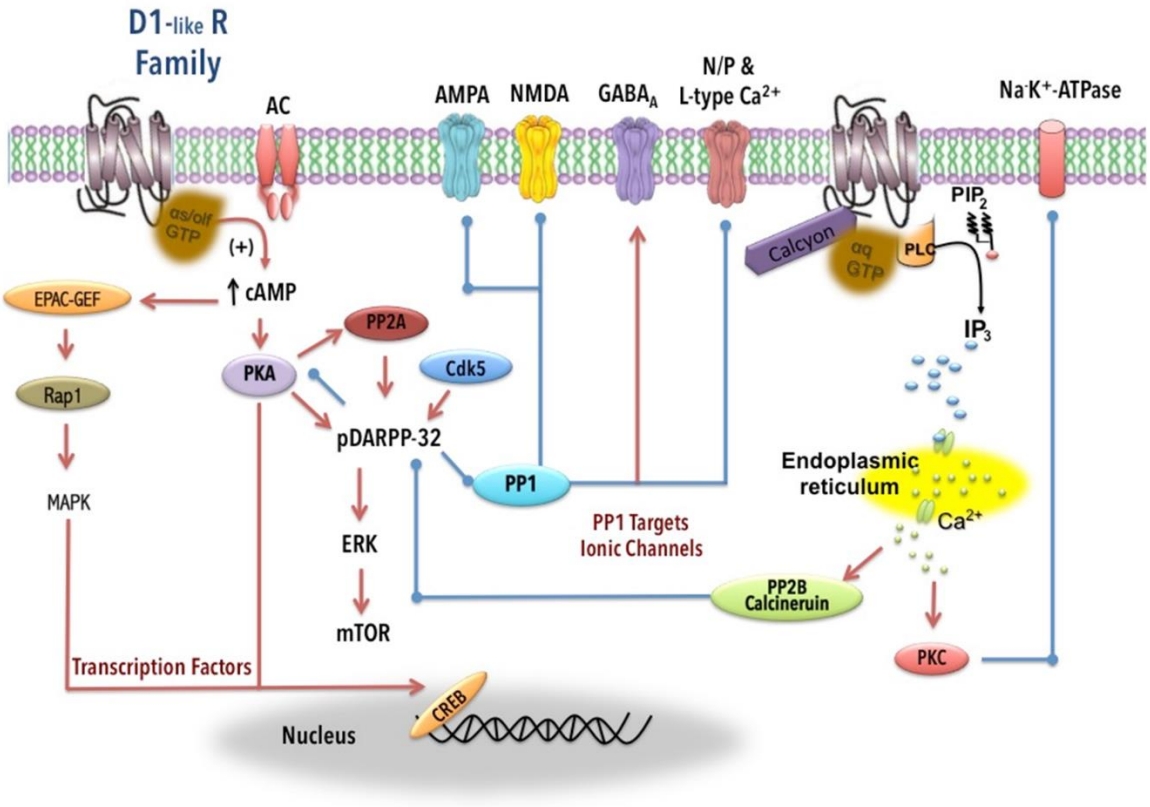

Figure 1. The D1-like DA Receptors Intracellular Signal Pathways. Shows the DA mediated effects through D1-like DA receptors that by the activation of intracellular signals. Stimulatory effects are indicated with red arrows and inhibitory effects in blue line ended with a circle. cAMP, 3'-5'-cyclic adenosine monophosphate; $\alpha_{s/olf}$ or α_q ATP, active Gα protein; PKA, protein kinase A; DARPP-32, dopamine and cyclic AMP-regulated phosphoprotein, 32 kDa; AC, adenylyl cyclase; PP1, PP2A or PP2B, protein-phosphatase 1, 2A or 2B; PKC, protein kinase C; PLC, phospholipase C; IP_3, inositol triphosphate; mTOR, mammalian target of rapamycin; PIP2, phosphatidylinositol 2; Ca^{2+}, calcium; MAPK, mitogen-activated protein kinase EPAC-GEF, guanine-nucleotide-exchange factor of Rap1; Rap1, Ras proximate 1. AMPA, α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors; NMDA, N-methyl-D-aspartate; $GABA_A$, γ-Aminobutyric acid A; CREB; cAMP response element-binding protein.

The nigrostriatal pathway is related with motor function, the SNc send its projections to the dorsal striatum and regulates through DA release and its receptors the activity of the basal ganglia networks, the coordinated movements is the result of the balance of the basal ganglia circuitry. In the mesocorticolimbic pathway the ventral tegmental area (VTA) projects to the ventral striatum or nucleus accumbens (Nacc), amygdala, olfactory bulb, hippocampus, cingulate gyrus and orbital and medial prefrontal cortex, this pathway is related with the cognitive function, motivation and emotion. Finally the tuberoinfundibular pathway where, the arcuate nucleus of the hypothalamus projects to the anterior pituitary delivering dopamine and controlling neuroendocrine functions such as the secretion of prolactin [1, 2].

The physiological effects of DA are mediated by dopaminergic receptors, which have widespread expression throughout the brain. In fact DA receptors are the main target of several drugs such as psychostimulants and antipsychotics. Interestingly DA receptors expression and intracellular signal transduction pathways, change during degenerative process and neurotoxicity worsening the symptoms and/or progression.

Dopamine and Receptors Function

The DA receptors (DARs) belong to the G protein coupled receptors family (GPCRs). There are five subtypes of mammalian DARs that are divided in two families according their structure and biological response. The D1-like family includes D_1 and D_5 DA receptors (D_1R and

D_5R), while D2-like DARs family consist of D_2, D_3 and D_4 receptors (D_2R, D_3R and D_4R).

Typically the D1-like dopamine receptors family (D1Rs) are positively coupled to adenylyl cyclase (AC) inducing the intracellular cyclic 3,5 adenine-monophosphate (cAMP) accumulation and the activation of the protein kinase dependent of cAMP (PKA) (Fig. 1), in contrast the D2-like dopamine receptors family (D2Rs) are negatively coupled to AC, as a result their activation decreases the cAMP accumulation [3, 4] (Fig. 2), modulating the activity of PKA and its effectors [5]. However growing evidence has shown that activation of DARs is not only restricted to the AC modulation but also other signal pathways and might act differently depending of the brain area, physiological and/or pathological conditions that we will discuss further.

D1-like Dopamine Receptors Expression and Signal Transduction Pathways

The D_1Rs share 80% in the amino acid sequence homology with D_5Rs in the transmembrane domains [6, 7], this family of receptors is widely expressed in the brain, with higher densities in striatum or caudo-putamen, Nacc, substantia nigra pars reticulata (SNr) and olfactory bulb [8]. Moderated expression in the entopeduncular nucleus, cerebral aqueduct and ventricles [9] and lower densities has been reported in the dorsolateral prefrontal cortex, cingulate cortex and hippocampus [10, 11], D1Rs play an important role in locomotor activity, reward systems, learning and memory [12].

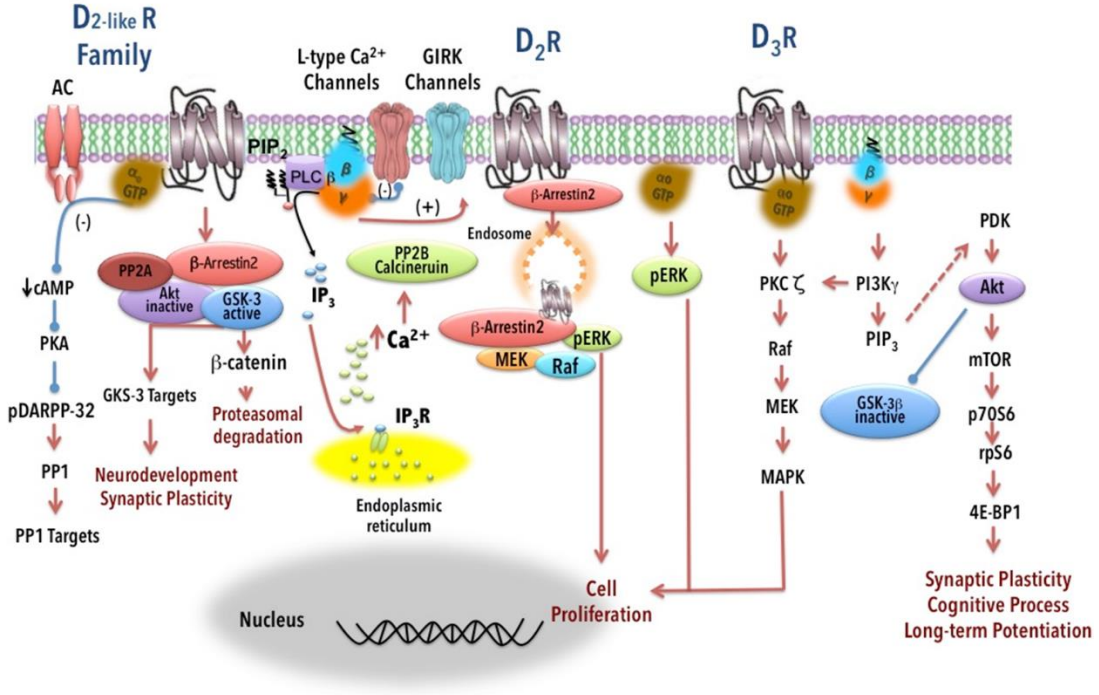

Figure 2. The D2-like DA Receptors Intracellular Signal Pathways. Shows the DA mediated effects through D2-like DA receptors that occur by a complex activation of intracellular signals that are related with events such as neurodevelopment, proteasomal degradation, cell proliferation and cognitive process. Stimulatory effects are indicated with red arrows, dashed red arrow indicates plausible activation and inhibitory effects in blue line ended with a circle. cAMP, 3'-5'-cyclic adenosine monophosphate; $\alpha_{i/o}$ ATP, active $G\alpha_{i/o}$ protein; PKA, protein kinase A; DARPP-32, dopamine and cyclic AMP-regulated phosphoprotein, 32 kDa; AC, adenylyl cyclase; PP1, PP2A or PP2B, protein-phosphatase 1, 2A or 2B; MAPK, mitogen-activated protein kinase; PKC, protein kinase C; Akt, thymoma viral proto-oncogene; GSK-3, Glycogen Synthase Kinase-3; PLCβ, phospholipase C isoform β; PI3K, phosphatidylinositol 3-kinase; PIP2, PIP3, phosphatidylinositol 2 and 3; IP_3, inositol triphosphate; Ca^{2+}, calcium ; GIRK, G protein coupled inward rectifier potassium; MEK; Raf,; ERK, extracellular signal-regulated kinase protein kinase; PDK, phosphoinositide-dependant kinase; mTOR, mammalian target of rapamycin; p70S6, p70S6 kinase; rpS6, ribosomal S6 protein; 4E-BP, eukaryotic initiation factor 4E-binding protein 1.

Typically D1Rs induces the activation of the AC through the direct activation of guanosine nucleotide-binding proteins (G-proteins), the subunit $G\alpha_{s/olf}$ of G-proteins binds to the catalytic subunit C_2 of the enzyme inducing the interaction between the subunits C_1-C_2 of the AC which in turn, induces the conversion of adenosine triphosphate (ATP) into cAMP [13, 14]. The cAMP interacts with the regulatory subunits of PKA inducing the release of the catalytic subunits that phosphorylate different substrates [15, 16]. One of the most studied proteins involved in the regulation of signal transduction pathway mediated by DARs and PKA is the Dopamine and cAMP-regulated phosphor-protein, 32 kDa (DARPP-32). In fact dopamine receptors co-localize with DARPP-32 in several brain regions [17]. The phosphorylation of DARPP-32 by the PKA in the threonine-34 residue induces the inhibition of the protein phosphatase-1 (PP1) [18], while the phosphorylation of the residue threonine-75 of DARPP-32 by cyclin-dependent kinanse 5 (Cdk5) induces the inhibition of PKA [19, 20] causing a feedback loop in the activation of the PKA (Fig. 1). The activation of the PKA same as the inhibition of PP1 mediated by PKA, may cause directly changes in the phosphorylation state of several channels such as α-Amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptors (AMPA), Gamma Aminobutyric Acid channel A ($GABA_A$), N-methyl-D-aspartate (NMDA), $GABA_A$, L-, N-, P-type Ca^{2+} that play an important role in the electrical properties of the neurons [21, 22, 23, 5, 24], the PKA directly or through DARPP-32 can also regulates extracellular signal regulated kinases 1 and 2 (ERK 1/2) involved in the changes in the protein transcription, this pathways has been related with pathological conditions in PD [25].

D1Rs may elicit an alternate cAMP signaling pathway non-dependent of PKA [20]. The cAMP can activate through the Ras superfamily guanine nucleotide exchange factors (GEFs), which are activators of Ras and Ras-like small G-proteins, specifically has been shown activates Ras-proximate 1 (Rap1) [26] that has been involved in cell polarity and migration [27; 28], Rap1 can also activate MAPK signaling implicated in the phosphorylation of transcription factors such as cAMP response element binding protein (CREB) that is involved in the increased or decreased transcription of genes [29].

D1Rs family also activates a signal transduction pathway that has been related with various neuropsychiatric disorders, activating the phospholipase C (PLC), mediated by a single transmembrane protein calcyon, which promotes the D1Rs interaction with $G\alpha_q$ instead $G\alpha_{s/olf}$ [30], as a result PLC is activated and increases the accumulation of inositol triphosphate (IP_3) which in turn binds to the IP_3 receptors from the intracellular compartments inducing intracellular Ca^{2+} release (Fig.1). Ca^{2+} plays an important role not only in signaling pathways causing the activation of proteins such as protein kinase calcium-dependent (PKC) but also in the modulation of neurotransmitters release by exocytosis. It has been shown that this particular signaling pathways occurs primary in the prefrotal cortex and calcyon has been found co-localize with D1Rs in the dendritic spines on the pyramidal neurons [31]. The activation of this pathway in the medial prefrontal cortex is involved in impulsive choice in rats and neuropsychiatric disorders [32], in fact up-regulation of the interaction of calcyon and D1Rs has been found in schizophrenic patients [33].
The activation of D1Rs is also related with regulation of electrochemical gradient through Na^+K^+-ATPase, which pumps the sodium out and the potassium into del cells. It's been shown that the activation of D1Rs inhibit the Na^+K^+-ATPase through PKA and PKC signaling pathways in striatum [34, 35] (Fig. 1), it's also been shown that D1Rs are related with sodium homeostasis in the kidney [7, 36], where D1Rs might play an important role in nephropathy that we will briefly discuss later.

D2-like Dopamine Receptors Expression and Signal Transduction Pathways

The D2-like dopamine receptors family as we mentioned before, consists of D_2, D_3 and D_4 DARs. For D_2Rs subtype additionally there are 2 isoforms the $D_{2\text{-short}}$ and $D_{2\text{-long}}$. The D_2Rs share 75% homology in the transmembrane regions with D_3Rs, while 53% identity with D_4Rs [7]. The D2Rs are mainly expressed in striatum, external globus pallidus (GPe), core of Nacc, amygdala, cerebral cortex, hippocampus and pituitary. D2Rs mRNA also found in the temporal and enthorinal cortex and in the septal region as well in the VTA and SNc in the dopaminergic neurons [2, 7].

The activation of this family of receptors typically leads to the inhibition of AC activity [37, 1], as well inhibition of PKA and DARPP-32 [38], however slight but complex differences in the functional response and activation of signaling pathways have been observed in receptors from this family, specially for D_3Rs subtype (Fig. 2). For example it has been shown that D_2Rs induces a strong inhibition of forskolin-induced cAMP accumulation in HEK-293 cells, while stimulation of D_3Rs expressed in transfected HEK-293 cells showed either low or not inhibitory effect on AC activity [39, 40], however when D_3Rs were expressed in a human neuroblastoma cell line, the effects were consistent with HEK-293 cells [41]. Discrepancies could be due to a differential expression of the AC isoforms, because D_3Rs were able to inhibit the AC activity when were co-transfected with the AC isoform V (ACV) but not with isoform VI [42]. Furthermore the ACV is widely expressed in dopaminergic-innervated brain regions

especially in the striatum [43, 44] and it has been suggested that this particular isoform also plays an important role in anxiety, depression, abuse drug withdrawal and L-3,4-dihydroxyphenylalanine L-DOPA induced dyskinesia (LID) [45-47].

D2Rs also modulate G-protein-coupled inward rectifier potassium (GIRK) channels (Fig. 2), which mediate neuronal electrical response [48], through GPCRs coupled to $G\alpha_{i/o}$ protein and also varying the effects between the receptors of this family, the effect seems to be through the βγ subunits for D_2Rs and D_4Rs but not D_3Rs [49]. Furthermore it has been shown in D_2Rs knockout mice that D_2Rs but not D_3Rs couple to GIRK channel in the substantia nigra neurons [50].

It's been reported that D2Rs are also able to activate cell proliferation-related pathways such as Mitogen-activated protein kinase (MAPK) signaling. The activation of ERK1/2 has been also observed in a variety of cell lines, including in HEK-293 cells, COS-7 cells and C6 glioma cells, for this signaling pathway, D_2Rs and D_4Rs also display some differences in the intensity of ERK/MAPK activation compared to D_3Rs using highly selective compounds [51, 52]. On the other hand, the complex GPCRs-β-arrestin also activates ERK/MAPK once the receptor is internalized [53]. Recently it was demonstrated that the complex D_2Rs-β-arrestin can activate ERK but this effect was not observed in D_3Rs. However in the same conditions was found that ERK could be activated by D_3Rs in HEK-293 and COS-7 cell lines only when $G\alpha_o$ is co-expressed but not $G\alpha_i$, while D_2Rs can mediate the ERK activation by both isoforms $G\alpha_{i/o}$ proteins and by D_2R-β-arrestin complex (Fig. 2) [54]. MAPK signaling is activated by D_4Rs and we recently reported that the $D_{2\text{-short}}$-D_4Rs form functional heteromer inducing phosphorylation of ERK1/2, interestingly, this interaction was disrupted when the polymorphic variant $D_{4.7}$ was used, which has been associated ADHD [55].

Stimulation of D2-like receptors activates the Akt (thymoma viral proto-oncogene also knows as protein kinase B PKB) signaling [56, 57]. *In vivo* it has been shown activation of Akt in striatum and Nacc after the D2-like agonist administration [56]. The effect of D_3Rs has also been studied *in vivo* and *in vitro*. *In vivo* D_3Rs knock out mice showed that these receptors participates in Akt phosphorylation [58]. *In vitro* D_3Rs were able to increase PKC and PI3K activity [59]. Specific activation D_3Rs enhance the Akt activity, which has been associated to increased dendritic arborization in dopaminergic neurons from mouse embryos [60]. The activation of Akt regulates the activity of the mammalian target of rapamycin (mTOR) and consecutive targets related with synaptic plasticity and cognitive processing [61]. In contrast the inactivation of the Akt (by protein phosphatase 2A PP2A), turns in the activation of the two isoforms of Glycogen synthase kinase-3 (GKS-3α/β). The GSK-3 is a protein kinase abundantly expressed in brain and is involved in signal transduction cascades relevant to neurodevelopment [62] and also regulates proteasome degradation through β-catenin [63], which involved in neurodegenerative and psychiatric conditions such as HD, bipolar disorder and schizophrenia [64]. A recent study showed that D_3Rs activates Akt, which in parallel activates, mTOR/p70S6/4E-BP1 signaling, probably mediated by phosphoinositide dependent kinase (PKD) and also causes the inactivation of GSK-3 by Akt-dependent phosphorylation (Fig. 2), in medium-sized spiny neurons (MSNs) of striatum and Nacc [65], pathways that have been related with synaptic plasticity, cognitive process, long-term potentiation (LTP) and long-term depression (LDP) [61]. D_3Rs also induced the activation of phosphatidylinositol 3-kinase (PI3K) and the atypical protein kinase C (PKCζ) this effect is apparently mediated by βγ subunit of G-proteins and activates MAPK signaling [51]. Signaling pathways might occur differently in specific brain regions and more important in pathological conditions. We will further discuss the specific changes of signal transduction pathways in neurotoxicity and neurodegenerative diseases.

Dopamine and Dopamine Receptors in Neurotoxicity

At physiological concentrations DA do not exhibits toxicity, however malfunction on DA release and/or metabolism could lead neurotoxicity. Mechanisms still unclear, but several evidences have shown that is caused by oxidative stress, neuroinflamation and apoptosis. For example, it have been shown that cortical, striatal, mesencephalic cells displayed toxicity by DA treatment [66-68]. DA-induced toxicity was initiated by the interaction with mitochondrial oxidative phosphorylation system causing inhibition of Complex I and decreasing ATP (Fig. 3A) [69]. *In vitro* studies demonstrated that the application of DA induces death of striatal cells [70]. DA also activates apoptotic signaling through mechanisms of oxidation [71] and necrotic cell death [72]. The effects of DA in toxicity were for long time associated with quinones and reactive oxygen species (ROS) caused by the metabolism of DA [73, 74, 75]. However recent evidences have shown that angiotensin receptors and the renin-angiotensin system (RAS) are also involved in neurotoxicity (Fig. 3B) [76] and the DA receptors could be participating in this modulation. In renal tissue was described that AT_1Rs enhances D1Rs signaling [77]. In the brain, D1Rs antagonist partially blocked the neurotoxicity induced by DA [78]. Here we will briefly discuss the role of DA and DARs in RAS-induced neurotoxicity by oxidative stress and inflammatory

response but more detailed reviews have been published [74, 76, 79, 80].

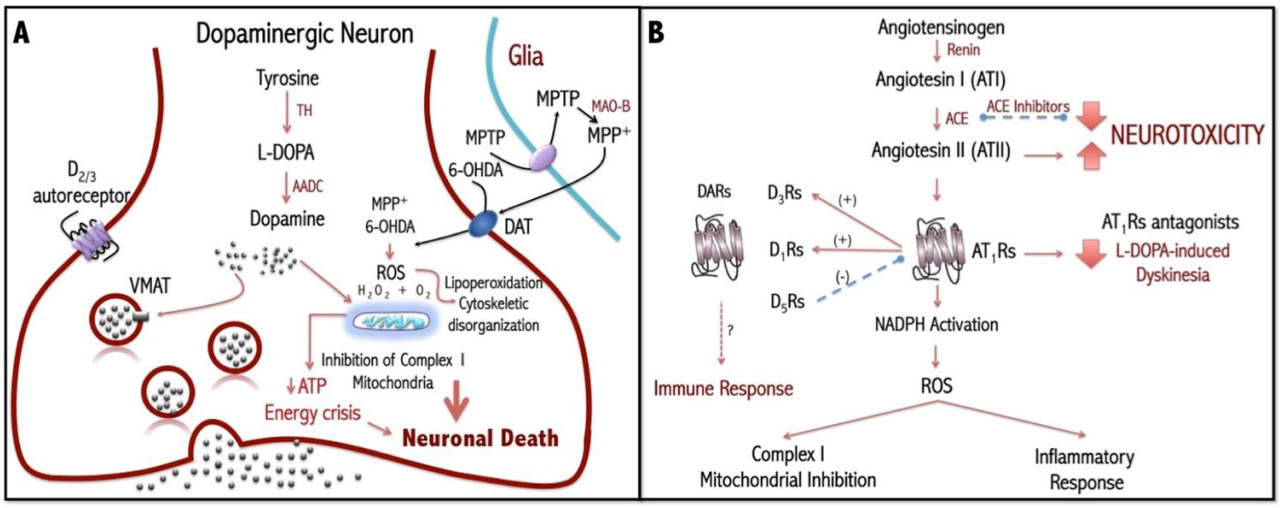

Figure 3. Oxidative stress and Neurotoxicity. A. Shows the neurotoxic mechanisms of DA and neurotoxins used to mimic PD in the dopaminergic neuron. DA and the neurotoxins 6-hydroxydopmine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), cause reactive species of oxygen (ROS) affecting the mitochondrial function and lipoperoxidation and cytoskeletal disorganization, which leads energy crisis and neuronal death. MPTP is first incorporated into the glial cells and metabolized to MPP^+, this metabolite can cross the membrane through the DA transporter (DAT) to reach intracellular compartments in DAergic neuron, while 6-OHDA can directly cross through DAT. **B.** Neurotoxicity by renin-angiotensin system (RAS) activation and DA receptors. In RAS, angiotensinogen is converted to Angiotensin I (AI) by renin, AI is converted into Angiotensin II (AII) thought angiotensin converting enzyme (ACE), AII mediate their actions by angiotensin receptors AT_1 and AT_2Rs. AT_1Rs activate the nicotidamine adenine dinucleotide phosphate oxidase complex (NADPH), which is the major source of ROS causing mitochondrial dysfunction and inflammatory response. The interaction AT_1Rs with of D_1 and D_3Rs increases the DA response while D_5Rs can regulate the AT_1Rs by proteasome mechanisms. DA receptors are also related with immune response in T cells.

Oxidative Stress

The oxidative stress is the result of the imbalance between ROS such as peroxides and free radicals and the ability of the biological system to detoxify them. ROS causes lipid peroxidation, cytoskeleton disorganization and DNA defects phenomena that convey in cell death and in this particular scenario on DAergic neurons; the DA auto-oxidation might increase ROS levels (Fig. 3A). In fact basal ROS levels are high in dopaminergic neurons. Indeed, normal enzymatic metabolism of DA induces the formation of hydrogen peroxide via monoamine oxidase activity [74]. It has been shown that DA oxidized metabolites inhibit the mitochondrial respiratory system by the inhibition of complex I and reduction of ATP causing energy crisis [69]. In fact neurotoxins used to experimentally model nigral degeneration *in vitro* as well as *in vivo* such as 6-hydroxydopamine (6-OHDA) and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) cause neurodegeneration mediated by both ROS and mitochondrial inhibition (Fig. 3A) [74]. However ROS is involved in a complex process of neurotoxic pathways where RAS and the nicotidamine adenine dinucleotide phosphate oxidase complex (NADPH) are also participating.

Renin-Angiotensin System

RAS influence and modulate the sodium balance, extracellular fluid volume in the kidney and systemic vascular resistance, which was initially considered only as a circulating humoral system that regulates blood pressure, sodium and water homeostasis [76]. The precursor in this system is the glycoprotein angiotensinogen, which is converted by renin and Angiotensin-Converting Enzyme (ACE) into Angiotensin II (AII) (Fig. 3B). The AII mediates its actions via two GPCRs, the Angiotensin II type 1 Receptor (AT_1Rs) and Angiotensin II type 2 Receptor (AT_2Rs) [81, 82]. The AT_1Rs receptors mediate most of the classical peripheral actions of AII such as the induction systemic vasoconstriction, which leads to elevated peripheral

resistance and ultimately increases blood pressure, while the function of the AT_2Rs receptors remains more elusive and controversial. Although, it's generally considered that the AII by AT_2Rs mediated responses exerts effects directly opposed to those mediated by AT_1Rs [83], thereby antagonize many of their effects. Interestingly in the last years, all components of the classical RAS have been identified in different brain areas and inside the blood-brain barrier, this system has been involved in vulnerability to neurodegenerative diseases like Alzheimer's disease [84], MS [85] and PD [86] and it's also been reported to participate in alterations of memory process [87]. Furthermore, it has been described that brain levels of AII are higher than circulating levels [88], and that the precursor protein angiotensinogen is mainly produced by astrocytes [89] with lower levels in neurons [90]. The components involved in the effects of AII in peripheral tissues such as NADPH-oxidase have also been found in neurons [91] and glial cells [92, 93]. It has been demonstrated the presence of different cytoplasmic and membrane subunits of the NADPH complex in mesencephalic DAergic neurons, astrocytes and microglia [94, 95, 96]. NADPH-oxidase complex is the most significant source of ROS other that mitochondria [97]. As a matter of fact, the neuronal loss is reduced by inhibitors of NADPH-oxidase, which suggests that NADPH activation and NADPH-derived ROS are involved in the AII-enhanced DAergic neuronal death [98, 95, 96]. Impaired RAS has been reported especially in aging diseases [99]. For example, several studies have reported the presence of RAS components in the basal ganglia, particularly in the nigro-striatal system [100, 101, 102, 103]. The AT_1Rs and AT_2Rs were found to be expressed in primary mesencephalic cell cultures [104, 95, 96], in nigral DAergic neurons and glial cells in both rodents and primates [105] and it was shown that AII induces DA release, which is blocked by AT_1Rs antagonists [106]. The interaction between the RAS and the DAergic system is particularly interesting, previous evidences suggested that DA and angiotensin systems directly counter-regulate each other in renal cells [107] and that abnormal counter-regulatory interactions between dopamine and AII play an important role in renal degeneration and hypertension [108]. In renal proximal tubule cells, evidences suggest functional interaction between several types of DA receptors and AT_1Rs receptors, as well as dimerization of AT_1Rs-D_1Rs inducing potentiation of D_1Rs signaling [77]. For example AT_1Rs-D_3Rs aberrant interaction has been related with hypertension [109], the AT_1Rs-D_5Rs interaction was also showed, where DA induces activation ubiquitin-proteasome pathway for AT_1Rs through D_5Rs [108] (Fig 3B). In neurotoxin-induced parkinsonism with 6-OHDA and MPTP the role of RAS has been studied and evidences indicate that in these models up-regulated levels of AII, exacerbates the DAergic neuronal death mediated by AT_1Rs [86]. Experimental data also support the involvement of brain RAS in dopaminergic degeneration [110, 111, 112]. It was demonstrated that AII increased the neurotoxic effect induced by low doses of 6-OHDA, and the treatment with inhibitors of ACE [113, 114, 112] or blockage of AT_1Rs [98, 95, 96] resulted in a significant reduction of both the loss of dopaminergic neurons and the levels of protein oxidation and lipid peroxidation induced by the neurotoxins [115]. Furthermore antagonist of AT_1Rs has been shown to be neuroprotective [116].

Interaction between AII and DA was suggested by early microdialysis studies, which showed that acute AII perfusion induces DA release and the effect was blocked by AT_1Rs antagonists [106, 117]. The mechanism responsible for the AII induced DA release has not been completely clarified, although it's been thought that involvement of D_2 auto-receptors could be participating [106]. AT_1Rs antagonists were capable to inhibit the LID (Fig. 3B), which is the major complication of L-DOPA treatment in PD [118]. An important number of studies in peripheral tissues, a direct counter-regulatory interaction between AT_1Rs and D_2Rs has been also demonstrated [119, 120]. Furthermore pro-renin receptors were found expressed in the nigral DAergic neurons and microglial cells in humans, monkeys and rats [121, 105]. Moreover, the pro-renin, AT_1Rs and AT_2Rs have been located intracellular compartments in DAergic neurons and glial cells [105]. These observations suggest the existence of an intracellular and intracrine RAS in dopaminergic neurons and functional interaction between DA receptors and AII receptors.

Interestingly, chronic inhibition of RAS by the use of ACE inhibitors resulted in increased dopamine levels, probably as a compensatory effect [122,123], as a matter of fact, the ACE inhibitor peridonpril was beneficial in PD patients [123]. In addition chronic treatment with AT_1Rs blockers such as candesartan do not change DA receptors expression, nor cause motor side effects and more importantly do not interfere with the beneficial effects of L-DOPA treatment [116], which is the most used therapy in PD. All these recent evidences together suggest that regulation of RAS and oxidative stress is a potential therapy in PD and LID.

Neuroinflammation

Neuroinflammation constitutes a fundamental process involved in the progression of several neurodegenerative disorders, such as PD, Alzheimer's disease, and MS. The neuroinflammation process includes activation of microglia, astrocytes and immune cells by inducing the

release of inflammatory mediators such as cytokines, chemokines, neurotransmitters and oxidative stress, leading to neural cell death [124, 125, 126]. As mentioned before, the oxidative stress mediated by AII is also inducing inflammation. It has been shown that up-regulation of local AII, induces oxidative stress and exacerbates inflammation [127, 128, 80].

In addition to that, inflammation mediated by the activation of the immune system is also related to neurodegenerative diseases. Lately DA has been related with regulation of immune system. DA is present in immune cells and it's been shown that immune system cells can be regulated by DA receptors, which are expressed in the surface of T cells, B cells, neutrophils, eosinophils and monocytes [129]. Since immune cells have all the machinery molecules for DA synthesis, they are able to produce DA, which may act as autocrine/paracrine mediator on immune cells but also on neighboring cells [130, 131].

The DA receptors expression was found in leukocyte subpopulations where in T lymphocytes and monocytes showed low expression, neutrophils and eosinophils, moderate expression and B lymphocytes and natural killer (NK) cells had higher and more consistent expression for example, D_3Rs and D_5Rs were consistently in most of immune cells, while D_2Rs and D_4Rs had more variable expression, and D_1Rs was not found [132]. DA exhibits different affinity for their receptors and it's been shown that depending of the concentration of DA is which receptor could be activated. For example activation of D_2Rs and D_3Rs induces polarization of the cluster of differentiation-4 ($CD4^+$T) cells and D_1Rs antagonist caused the same effect [133]. The activation of D_5Rs increases the production of interleukins (IL) IL-23, cytokine that induces polarization of $CD4^+$T cells, which has been related with inflammatory response [134]. On the other hand activation of D_2Rs and D_3Rs in normal resting T cells induces production of IL-10 and tumor necrosis factor-α (TNF-α) [135], while stimulation of D_3Rs activates $CD4^+$T cells inhibiting IL-4 and IL-10 synthesis [136].

Under pathological condition such as neurodegeneration or imbalance of homeostasis, inflammatory systems are active. Specialized patterns of adhesion of the cell surface during inflammation allow active T cells adhere to vessels and infiltrate to the brain, which contribute to neurodegenerative process [137, 138]. In fact it has been shown that D_3Rs expression in $CD4^+$T cells is crucial for the destruction of DA neurons of the SNc in PD models and the D_3Rs knock out mice were resistant to MPTP [139], several evidences have shown that DA receptors expressed in immune cells play an important role in the autoimmune disorder MS.

Alterations of Dopamine Receptors in Neurodegenerative Diseases

Parkinson's disease and DA receptors.

PD is a neurodegenerative disorder characterized by the progressive loss of DAergic neurons of the SNc. The loss of dopamine has serious consequences in the balance of the pathways of the basal ganglia. According to the classic anatomical and functional basal ganglia models [140, 141], the lost of dopamine cause imbalance in the motor networks that stimulate and/or inhibit the initiation of movements. There are two main pathways in the basal ganglia, the direct pathway, primary associated with D1-like dopamine receptors [142], where activation of D1Rs increases the GABA release in striato-nigral terminals [143] whereas, the indirect pathway mainly express D2-like dopamine receptors [142] and their activation inhibit GABA release in striato-pallidal terminals [144, 145]. The adequate balance between the direct (stimulatory) and indirect (inhibitory) networks facilitates the execution of movements [141]. In PD, the lost of DAergic control leads to a hyperactivity of the inhibitory pathway, which induces bradykinesia, the main symptom of this disorder [146]. In addition pathological conditions occur when long lasting cellular modifications, especially if those have important influence in the response to dopaminergic receptors activation. For example, it has been shown that PD causes also reorganization in the level of expression of DA receptors, phenomena that has been called supersensitivity of DA receptors. Early evidence showed that DA receptors changes during PD using the hemiparkinsonian rat model induced by 6-OHDA, where the GABAergic medium-sized spiny neurons, which are most prominent neuronal phenotype in the striatum (95%), showed increased mRNA coding for D2Rs in encephalin positive neurons which form the indirect pathway, while decreased mRNA coding for D1Rs were found in dynorphin/substance-P positive neurons that are related with the direct pathway of the basal ganglia [142], but not only the expression of the DA receptors is compromised in PD, it has been shown that also proteins and signaling transduction molecules are altered in this pathological condition probably as a compensatory effect to the supersensitivity [147]. The supersensitivity of DARs and signal molecules was further described in several structures of the basal ganglia such as in caudo-putamen, striato-pallidal terminals and striato-nigral terminals [148-151].

The decreased expression of D1Rs in hemiparkinsonian animal models [152,151] could explain in part one of the most important symptoms of this disease, the bradykinesia [153]. The most widely used pharmacological treatment for PD is L-DOPA,

unfortunately chronic L-DOPA treatment causes several side effects, the most debilitating is the LID, which is characterized by the development of abnormal and involuntary movements. Alterations in D1Rs have been also related with this pathological condition. Despite the decreased expression of D1Rs, a increased signaling transduction pathway of D1Rs has been related with LID, no only in the striatum the input nuclei [25] but also in the SNr, the output nuclei of the basal ganglia, where the expression of the ACV is increased as well the cAMP in the striato-nigral terminals and these changes were directly related with the development of dyskinesia and increased GABA release [47]. As described before, D1Rs activates the AC, inducing cAMP accumulation and activation of PKA, which has several effectors and activation transcription factors, interestingly, it has been shown that effectors of PKA such as DARPP-32, ERK1/2 and mTOR are altered during LID in hemiparkinsonian mouse model [25, 154, 155], Cdk5 also is increased in LID using MPTP primate parkinsonian models (Fig. 1) [148]. However, in agreement to our findings, recent evidence showed that ACV might be critical for the development of dyskinesia since the silencing specific ACV silencing in the striatum attenuates LID [156].

With very good agreement is known that D2Rs in the indirect pathway of the basal ganglia also changes during dopaminergic denervation in opposite way. D2Rs are up-regulated in pallido-nigral neurons [142]. Increased levels of mRNA coding for D2Rs were early showed [142, 148] and increased binding for D2Rs has been associated with PD, however no differences where found in LID of primate parkinsonian model induced by MPTP [148]. Furthermore the LID develops gradually over time and D2Rs, despite dopamine denervation increases the mRNA levels and protein, D2Rs are not further elevated in LID neither in animal models nor postmortem studies, as a matter of fact in PD patients L-DOPA normalizes the up-regulation [157, 158]. By then it was unclear whether or not the D_3Rs subtype was participating in the supersentitivity by dopamine denervation, however their low expression in striatum made focus the attention in D_2Rs [159, 160]. In the last decade, D_3Rs attracted the attention, it's important to mention that the helical transmembrane spanning region (TMS) of D_2Rs and D_3R receptors share 75-80% homology in amino-acid sequence and the TMS is directly involved in the orthosteric-binding site, main reason why targeting D_3R has been challenging, however D_3Rs-preferring compounds have been developed making possible the study of the role of D_3Rs in PD.

Despite the low abundance of D_3Rs are expressed in the direct pathway [21], we previously reported functional response in the GABAergic striato-nigral terminals [161], where presynaptic D_3Rs are modulated by the calcium calmodulin kinase IIα (CAMKIIα) [162]. The mRNA codifying to D_3Rs remains unchanged during dopamine denervation [163]. However L-DOPA treatment induces a remarkable increase in dynorphin positive striatal neurons, which project to the SNr where D_3Rs normally has moderate expression. Probably pathological conditions enhance their expression, according with that; recently it has been shown that D_3Rs are up-regulated in caudo-putamen and SNc in Lewy Body disease and Parkinson disease Dementia [164]. Recently the LID has been related to interactions between D1-D_3Rs where CAMKIIα might play an important role [165].

The role of D_3Rs has been also studied in neurodegenerative process because it's been shown their importance in neuroprotection. For example, the stimulation of D_3Rs-preferring DA receptors agonist 7-OH-DPAT promotes proliferation and possibly differentiation of dopaminergic neurons of the SNc in rats [166]. Chronic administration of 7-OH-DPAT was reported to restore the dopaminergic neurons in the nigrostriatal pathway in unilaterally lesioned rats treated with the neurotoxin 6-OHDA [167]. In addition to cell proliferation, the SNc neurons were reported to adopt a mature neuronal dopaminergic phenotype with projections arising from newly generated cells. These effects might be related to a mitogenic response elicited via D_3Rs activation of receptors expressed on mesencephalic dopaminergic neurons, which then may release neurotrophic factors.

DA receptors still been the main target in PD through L-DOPA, however growing evidences have shown that DA receptors act differently in pathological conditions and some changes in the expression level and DA receptors interaction could lead a potential novel therapeutic targets. Interestingly several reports have shown that targeting D_3Rs reduces LID, in addition to that D_3Rs interact with D1Rs [168, 169] and enhances D1Rs stimulated GABA release in SNr [161], the functional effects and dynamic of this interaction seems to be mediated by CAMKIIα [162] and could be involved in LID and other pathological conditions. All these recent evidences about the modulation of D_3Rs over the D_1Rs might lead to novel approaches to treat PD and LID, however further studies are needed to examine potential side effects when targeting D_3Rs in this pathological conditions since D_3Rs exhibit a higher expression in other brain regions.

Huntington disease and DA receptors.

Huntington's disease is a dominant inherited neurodegenerative disease that is characterized by chorea (involuntary jerk movements), cognitive deficits and psychiatric disturbances such as agitation irritability and

psychosis, symptoms progressively worsen until dead occurs. The cause is a mutation in the gene coding for hutingtin (*htt*) where it has been shown increased CAG repeats (glutamine), more than 35 repeats predispose to HD [170] and increased number of repeats is correlated with the HD onset [171]. The main histopathological feature is a profound lost of MSNs [172] in the striatum the input nuclei of the basal ganglia, however other structures are also affected such as, cerebral cortex, thalamus, hypothalamus and hippocampus but with less degree [173]. It has been suggested that the lost of MSNs neurons might be related to increased glutamatergic release from cortical and thalamic regions, which could be increasing the sensitivity of glutamate receptors [174, 175], but also glutamate transporter 1 (GLT1) might play an important role because it has been shown that the expression of GLT1 is reduced in HD [176], since GLT1 plays a critical role in glutamate removal by the astrocytes, excitotoxicity might occur. Alterations in DA transmission may also play a role, because it has been also shown that DA regulates the expression of GLT1 in striatal astrocytes [177], maybe the loss of the balance dopamine-glutamate contributes to the toxicity.

DA plays an important role in the motor and cognitive functions and is also known that DA can regulate glutamatergic cortical neurons [178]. Early studies reported extensive atrophy of the SNc [179], postmortem studies showed also decreased expression of tyrosine hydroxylase (TH) the limiting enzyme in the synthesis of DA [180] suggesting impairments of DA transmission in HD. In addition the DA transporters also showed alterations in the striatum, a decreased binding for the membrane DA transporter (DAT) and for the vesicular monoamine transporter 2 (VMAT2) probably due to the decrease in the dopaminergic striatal innervation [181, 182]. However other studies showed increased levels of DA in the nigro-striatal pathway in HD, according to that, the therapeutic agent to treat HD is tetrabenazine (TBZ). TBZ is a VMAT blocker and it's been shown to be beneficial to treat HD, unfortunately TBZ is only helpful in the early stages of the disease and then becoming ineffective, interesting neurochemical studies have shown that increased DA occurs only in early stages of HD as well [183], where a significant decrease of striatal dopaminergic terminals was also reported [184].

The DA receptors also changes in HD, it has been shown that the binding for DARs is decreased in HD patients [185]. Similar results were showed in transgenic mice used as animal model of HD [186]. Positron emission tomography (PET) studies showed that DARs are decreased in striatal regions in both symptomatic and asymptomatic HD patients suggesting that DA alterations disrupts the expression level of the DARs in early stages [187]. Furthermore the DA loss in pre-symptomatic HD patients was correlated with cognitive impairs [188].

In R6/2 HD model which is a HD transgenic mouse that has an aggressive disease onset and progression that shows motor abnormalities [189] and learning impairments [190], important loss of striatal neurons met-enkephalin positive were reported but not in substance-P positive [186], under the basal ganglia network, the met-enkephalin positive neurons express preferentially the D2Rs and projects to GPe, while the substance-P positive neurons primary express D1Rs and projects to SNr [142, 191]. Consistent with other neurodegenerative situations related to dopamine, the DA receptors expression change. All the D2Rs family showed significant loss in striatum, while in the D1Rs family D_1Rs showed a decreased expression in but not D_5Rs. However in similarity with PD, despite the decrease in D_1Rs increased cAMP was found [186]. Changes of dopamine receptors expression and signaling molecules have also been reported in HD patients [192]. Interestingly robust elevations in the cAMP accumulation and transduction pathways occurs when a decreased expression of D1Rs in neurodegenerative process [193, 194, 151, 47]. As a matter of fact, D_1Rs can also regulate the excitatory postsynaptic potentials (EPSCs) in layer V pyramidal neurons of the prefrontal cortex [178]. D1Rs has been also related with motor alterations by the abnormal regulation of GABA release in the SNr during LID [47], and abnormal burst patterns in the SNr were found in 140 CAG knock in HD mouse model too, where increased bursting rates where found in the SNr compared with wild type littermates [195], suggesting that changes in the output nuclei could be involved in the motor alterations symptoms of HD.

D1Rs could also play a role in progression of the disease. For example the activation of D1Rs receptors using agonists showed to accelerates the formation of *htt* nuclear aggregates, and it was found that the direct activation of AC using forskolin, mimic the effect and the response seems to be related with transcription factors, suggesting that the signal transduction pathway is involved in the aggregation of *htt* [42].

On the other hand GSK-3β also might participate in the neurodegenerative process of HD. As mentioned GSK-3β is a very promiscuous kinase that phosphorylate several substrates and is involved in many aspects of cell biology **(**Fig. 2**)**, such as energy metabolism, microtubule stability and inflammation [196]. It's been known that an important factor in HD is changes in energy metabolism, *htt*-expressing cells showed important reduction of adenosine triphosphate (ATP) [197]. Recent studies showed a 50% reduction of GSK-3β in the frontal cortex in brain from HD patients and this also occurred in R6/1 mice model, suggesting this could be related with the

cognitive alterations [197]. It's been shown that the GSK-3β is increased in lipid rafts of knock-in HD mice brains and inhibitors of GSK-3β significantly reduced the neuronal dead in *htt* expressing neuronal culture cells [198], however since GSK-3 has an important number of substrates, the inhibition as a therapeutic approach has to be considered with caution, but a possibility could be pharmacological modulation mediated by receptors. Interestingly D_2Rs and D_3Rs knock-out mice display enhanced striatal Akt activation [199], and in HD transgenic model a profound loss of these receptors was found [186]. In addition, atypical antipsychotics used to manage psychiatric alterations in HD, have been shown to antagonize D_2R/β-arrestin2 interactions more efficaciously than G-protein-dependent signaling (Fig. 2), whereas typical antipsychotics inhibit both pathways with similar efficacy [200]. GSK-3 also regulates the proteasomal degradation through β-catenin (Fig. 2) and it has been shown that both typical and atypical antipsychotics induce alterations in the expression of β-catenin and GSK-3 in the striatum and prefrontal cortex [201]. Recently D_3Rs have been involved in the inactivation of GSK-3β through Akt (Fig. 2), however in the best of our knowledge there is no studies linking D_3Rs in HD related with this signaling pathway.

Abnormalities in DA system might underlie some of the behavioral symptoms in HD, as a matter of fact HD patients treated with D2Rs agonist prevented the chorea but not the cognition impairments [202], as mentioned before hyperdopaminergic tone has been shown in early stages of HD, and TZB alleviates motor deficits as well as antagonist of D1Rs were able to prevent MSNs dead in a HD mouse model [203].

The development of novel and selective DA receptors compounds open a new field of study in HD, probably other potential therapies to treat motor alterations and psychiatric conditions in HD, as well modulate the aggregates of *htt* as previously showed. Further studies are needed to fully understand the role of the specific DA receptors subtypes in HD, which might lead to novel therapeutic approaches.

Multiple Sclerosis and DA receptors.

MS is a complex disease that affects the brain and spinal cord, resulting in loss of muscle control, vision, balance, and sensation of numbness. In MS, the brain and spinal cord are damaged by the immune system, reason why this condition is called an autoimmune disease. MS is characterized by inflammation, demyelination and neurodegeneration, causes disability in both young and older populations.

Several autoimmune processes are mediated by myelin-specific $CD4^+$ T helper (Th), which are cells capable to cross the blood-brain barrier and cause damage [204]. It's been known that Th contributes to MS secreting pro-inflammatory cytokines, such as TNFα and IFN-γ [205]. In addition, disruption of the blood-brain barrier allows the entry of B cells and T-cell dependent B cell activation results in neural damage [206].

DA and generally all catecholamines has been involved with MS. However recently, growing evidences shown that DA receptors are closely related with immune system and abnormalities of DA receptors and their function may participate in MS. In fact DA levels are increased in striatum [207].

The role of DARs has been also studied, decreased D_5Rs could be related with the onset of MS, in peripheral blood mononuclear cells D_5Rs was found to be decreased in non-treated MS patients [208], while in treated patients with (IFN)-γ, D_5Rs were found increased. Interestingly the treatment with (IFN)-γ induced enhanced tyrosine hydroxylase (TH) expression too and DA synthesis [209]. Furthermore dendritic cells, which are antigen-presenting cells, also synthesize DA that is released in autocrine manner and can stimulate D_5Rs inducing production of IL-23, which causes polarization of $CD4^+$ T cells toward the inflammatory phenotype [134]. DA increases production of TNFα via D_1, D_5 and D_3Rs and the production of IL-10 through D_2, D_1 and D_5Rs [135]. The role of DA and their receptors still unclear but several studies has shown that the changes in DA function and DA release are co-related with inflammation in autoimmune diseases. DA exhibits different affinities for the five DA receptors, showing higher affinity for D_3, D_4 and D_5Rs and lower D_2 and D_1Rs [210]. When lower levels of DA are released likely the main activation is D_3Rs in T cells, which could lead to T cell migration, while higher levels of DA could activate D_5Rs instead and as a consequence inhibition of the T cell function [129].

Despite the potential role of DA in MS, a pilot study in MS patients treated with D2Rs agonist after a year of treatment no changes were observed in the progression of this disease [211]. It's important to mention that other catecholamines are also participating such as β-adrenergic receptors (AR) and balance between DA and β-AR inhibitory and stimulatory effects play an important role in the lymphocytes activation. As the matter of fact in MS patients the dysregulation of β-AR and DA receptors might alter the balance of these catecholamines inducing dysfunctional events in the lymphocytes [206].

Although in the clinical experience the DA compounds showed very limited therapeutic benefits the recent research points DA as a potential target due to the ample expression of DA receptors in the immune system [208]. The understanding of the role of DA receptors in immune system could lead to novel pharmacological

strategies to modulate the immune response by dopamine in MS.

Conclusion

The DA neurotransmission system and DA receptors play an important role in neurotoxicity and neurodegeneration. DA receptors are susceptible to change under pathological conditions and rearrangements of intracellular signal pathways might occur that worsen the symptoms in aging diseases or neurodegenerative process. The better understanding of the changes that occur in the DA receptors and their functional responses during pathological conditions is crucial for the development of novel and efficacious therapeutic approaches in neurodegeneration, neurotoxicity and neuroinflammation.

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