Chapter 12
What Is the Role of Adenosine Tone and Adenosine Receptors in Huntington's Disease?

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Abstract Huntington's disease (HD) is a devastating hereditary neurodegenerative disorder caused by a CAG mutation within the IT15 gene encoding huntingtin protein. Even though mutant and normal huntingtin are ubiquitously expressed, the degenerative processes primarily occur within the striatum and particularly hit the striatopallidal neurons, particularly enriched with adenosine A_{2A} receptors ($A_{2A}R$), suggesting that the latter might play a role in HD. In agreement, variants in the *ADORA2A* gene influence the age at onset in HD, and $A_{2A}R$ dynamics is largely altered by mutated huntingtin. More generally, adenosine tone and adenosine receptors are involved in a number of processes critical for neuronal function and homeostasis, such as the modulation of synaptic activity and excitotoxicity, the control of neurotrophin levels and functions, and the regulation of protein degradation mechanisms. In the present review, we critically reviewed the current knowledge involving alterations of adenosine tone and adenosine receptors in HD and discussed whether they represent suitable therapeutic targets.

Keywords Adenosine receptors · Huntington's disease · Neurotransmission · A_{2A} heteromers

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12.1 Pathogenetic Mechanisms of Huntington's Disease

12.1.1 Overview

Huntington's disease (HD) is a monogenic autosomal dominantly inherited neurodegenerative disorder generally affecting young adults and characterized by involuntary abnormal movements and postures (chorea, dyskinesia, dystonia), psychiatric disturbances, and cognitive alterations (for review, see Ross and Tabrizi 2011; McColgana and Tabrizi 2018). Prevalence is 4–10/100.000. This disorder is fatal within 15–20 years after onset of symptoms. Although several cerebral regions (cerebral cortex, layers III, V, and VI; pallidum, subthalamic nucleus, cerebellum) show signs of neurodegeneration, primary and prominent neuronal loss is found in the caudate and putamen (Vonsattel and DiFiglia 1998). Within the striatum, the striatopallidal neurons, a subpopulation of medium spiny neurons (MSNs, see 2.1.) that express enkephalin, dopamine D_2 receptors (D2Rs), and adenosine A_{2A} receptors (A_{2A}Rs) (Canals et al. 2003), appear more vulnerable (see Reiner et al. 1998; Schiffmann and Vanderhaeghen 1993).

HD is caused by a mutation in the gene IT15 encoding the protein huntingtin (Htt; The Huntington's Disease Collaborative Research Group 1993). The mutation consists in a CAG triplet repeat expansion translated into an abnormal polyglutamine (polyQ) tract within the N-terminal region of the protein. Penetrance is full, with a CAG length above 40 repeats and longer CAG repeats associated with earlier onset. It is important to stress that although the number of CAG repetitions is the primary determinant of disease onset, it accounts for only ~60% of the variation in age of onset (see Walker 2007 for review). This supports that other genetic and environmental factors are to take into account as disease modifier components.

Htt is a ubiquitous and large protein of about 350 kD involved in an important number of cellular functions (for reviews, see Bantubungi and Blum 2007a, b; Popoli et al. 2008; Ross and Tabrizi 2011; Zuccato et al. 2010). In the central nervous system, Htt has a large distribution, being prominent in neurons, particularly cortical pyramidal neurons, Purkinje cells, and striatal interneurons (Gourfinkel-An et al. 1997; Trottier et al. 1995), as well as glial cells (Shin et al. 2005). The cellular functions of Htt remain incompletely understood (see Ross and Tabrizi 2011; Saudou and Humbert 2016). Among others, physiological Htt function is involved in early embryonic development (Dragatsis et al. 1998), fate of cortical progenitors (Godin et al. 2010; Barnat et al. 2017), axonal transport (Colin et al. 2008; Gauthier et al. 2004), and brain-derived neurotrophic factor (BDNF) expression/transport (Zuccato and Cattaneo 2009). Mutated Htt (mHtt) is thus prone to impair several mechanisms important for neuronal activity and survival by promoting a toxic-gain-of-function but also impairing the normal Htt function through loss-of-function mechanisms (Zuccato et al. 2010). It is not clear yet to which extent HD can be considered as a prion-like disorder, like Alzheimer's or Parkinson's diseases, but transcellular propagation of protein aggregation could underlie the pathological progression in HD (Stopschinski and Diamond 2017). Experimental evidence

suggests that mHtt triggers misconformation of wild-type Htt. Neuropathological observation in patients who received intracerebral allografts supports the transfer of HD pathology from cell to cell (Stopschinski and Diamond 2017). In the next two paragraphs, we will specifically address pathways impaired by mHtt and prone to be modulated by adenosine receptors, namely, excitotoxicity as well as glial and BDNF functions.

12.1.2 Excitotoxicity and Mitochondrial Dysfunctions

Excitotoxicity is primarily defined as cell death ensuing from the toxic action of glutamate through excessive activation of glutamate receptors. Despite it remains unclear whether glutamate is over-released or not by cortical afferents in HD, there is clear evidence indicating that dysfunctions of the glutamatergic system in the striatum account for the toxic effect of mHtt (Fan and Raymond 2007; Stack et al. 2007). Several neuronal impairments contribute to excitotoxicity, such as deficient glial reuptake of glutamate and/or NMDA receptor hypersensitivity, the latter being itself dependent on mitochondrial function (Brouillet et al. 2005; Fan and Raymond 2007; Jacquard et al. 2006). Interestingly, several previous studies involved abnormal NMDA receptor arrangement/activity in HD. R6/2 transgenic HD mice exhibit a reduced NR2A/NR2B ratio, which is an index of vulnerability to excitotoxic cell death (Ferrante et al. 2010; Martire et al. 2010), and an enhanced response to NMDA (Cepeda et al. 2001). Intraneuronally, mHtt increases the activity of the NR2B subunit of the NMDA receptor – preferentially expressed by the medium spiny neurons within the striatum – possibly through a dysfunction of PSD95, a docking protein whose interaction with NR2B is reduced in the presence of the mutated protein (Chen et al. 1999; Sun et al. 2001; Zeron et al. 2002). These abnormal interactions lead to increased NMDA currents itself accompanied by an altered NMDA receptor trafficking (Fan and Raymond 2007) and neuronal vulnerability to NMDA (Shehadeh et al. 2006; Zeron et al. 2002). Recent data particularly support that the latter is related to an increased expression of extrasynaptic NR2B-contaning NMDA receptors (Milnerwood et al. 2010).

In HD, increased NMDA response is probably favored by environmental modulation of NMDA receptor. Indeed, it has been demonstrated there is an early endogenous increase of quinolinic acid (QA) in the striatum from HD patients and animal models (Guidetti et al. 2006, 2004). QA is an NMDA agonist, derived from the kynurenine pathway, a major route of tryptophan degradation, able to produce lesions reminiscent of HD in animals (Beal et al. 1986) and favoring glutamate release from corticostriatal endings (Blum et al. 2003a; Popoli et al. 2002). In addition, mHtt has been shown to impair expression of glutamate transporters and glutamate handling by astrocytes (Bradford et al. 2009; Faideau et al. 2010; Lievens et al. 2001; Shin et al. 2005), favoring its increase in the synaptic cleft.

Excitotoxicity is favored by mitochondrial alterations underlying HD. Several imaging studies have revealed an early metabolic dysfunction in the striatum of HD

patients (Brouillet et al. 1999, 2005; Liot et al. 2017). Importantly, the severity of metabolic alterations correlates with the size of the CAG expansion (Jenkins et al. 1998). Several postmortem studies point to a significant reduction in the activity of complexes II–III (which includes succinate dehydrogenase) in the caudate nucleus of HD patients (Browne et al. 1997; Gu et al. 1996; Tabrizi et al. 1999). Such alterations could be related to an altered expression of the complex II subunits induced by mHtt (Benchoua et al. 2006) and be favored by dopamine (Benchoua et al. 2008). The instrumental role of complex II inhibition in the striatal degeneration in HD is also suggested by the specific profile of degeneration in animals treated by the irreversible complex II inhibitor 3-nitropropionic acid (3NP) (Brouillet et al. 2005). Accordingly, several other works have reported strong mitochondrial alterations promoted by mHtt. Indeed, the latter, found localized in the neuronal mitochondrial membrane (Panov et al. 2002), has been shown to impair mitochondrial biogenesis, fission (Kim et al. 2010; Weydt et al. 2006), axonal transport (Shirendeb et al. 2011), calcium handling, and membrane potential (Panov et al. 2002) as well as ATP production (Milakovic and Johnson 2005; Seong et al. 2005) and calcium handling (Choo et al. 2004; Panov et al. 2002). With regard to mitochondria impairments, mitophagy has been involved in HD (Liot et al. 2017). In line with the above hypothesis, prevention of mitochondrial fission and cristae remodeling has been shown to delay HD progression (Costa et al. 2010; Guo et al. 2013). Such mitochondrial defects represent one of the events contributing to the emergence of neuronal excitotoxicity in HD (Brouillet et al. 2005; Jacquard et al. 2006). Therefore, rescue of impaired mitochondria (Lee and Chern 2014) and poor energy homeostasis might represent a valuable therapeutic approach to HD (Guo et al. 2013; Ju et al. 2011; Lin et al. 2013).

12.1.3 BDNF

BDNF is an abundant neurotrophin in the mammalian brain involved in a variety of brain processes as development, differentiation, neuronal plasticity, or synaptic activity (Chao 2003). In the striatum, BDNF essentially comes from the cerebral cortex, anterogradely transported to cortical nerve endings to be released in the striatum (Zuccato and Cattaneo 2007). In HD, mHtt alters BDNF transcription (Zuccato et al. 2001), trafficking, and axonal transport (Gauthier et al. 2004). It has been established that mHtt perturbates the negative modulation exerted by wild-type Htt on the silencing activity of the RE1/NRSE silencer, favoring the downregulation of a set of genes, including the one coding BDNF (Zuccato et al. 2003). The mHtt also alters the axonal transport of BDNF vesicles (Dompierre et al. 2007) as well as the post-Golgi trafficking of this factor (del Toro et al. 2006). More recently, alteration of BDNF transport in HD has been suggested to involve abnormal interaction between pro-BDNF and Htt-associated protein 1 (Wu et al. 2010). Importantly, loss of striatal BDNF may preferentially affect the function of the striatopallidal neurons, known to be early impaired in HD. These latter observations support that

BDNF impairment is crucially involved in the early vulnerability of striatopallidal neurons. In accordance with such important role of BDNF in HD, its increase, by gene overexpression and pharmacological or environmental modulation, has been shown to be beneficial in several experimental models of HD (Borrell-Pages et al. 2006; Gharami et al. 2008; Giralt et al. 2010; Lynch et al. 2007; Peng et al. 2008; Simmons et al. 2009; Xie et al. 2010).

12.1.4 Two Major Protein Degradation Systems: Proteasome and Autophagy

In HD, the expansion of polyglutamine (polyQ) in the N-terminal region of Htt results in protein misfolding and aggregation (Goldberg 2003; Gusella and MacDonald 2006; Kopito 2000). The ubiquitin-proteasome system (UPS) plays an important role in the degradation of damaged or misfolded proteins via polyubiquitination targeted by E3 ligases (Demartino and Gillette 2007; Hershko and Ciechanover 1998). Global changes in the ubiquitin system, an indicator of the UPS function, were found in HD patients and in HD animal models (Bennett et al. 2007; Finkbeiner and Mitra 2008; Ortega and Lucas 2014). Suppression of the UPS function by mHtt has been demonstrated in the cells and brains of mice and humans with HD (Seo et al. 2004; Wang et al. 2008; Zheng et al. 2016). Enhancement of UPS activity, which facilitates the degradation of soluble mHtt at its pathological stage, has been shown to improve proteasome function and motor coordination in HD (Jeon et al. 2016; Jia et al. 2012; Kim and Seo 2014; Lin et al. 2013; Liu et al. 2014; Seo et al. 2007; Wong et al. 2008). Macroautophagy, hereafter referred to as autophagy, is also essential for the removal of aggregated proteins by delivering them to the lysosome for degradation (Nixon 2013). Htt has been found to function as an important regulator and substrate for selective autophagy (Gelman et al. 2015; Rui et al. 2015). Impairments of the autophagic process are associated with HD: in fact, a damaged ability of autophagic vacuoles to recognize cytosolic cargo has been demonstrated (Kiriyama and Nochi 2015; Martinez-Vicente et al. 2010). The resultant inferior activity of autophagy causes slower turnover and accumulation of mHtt. In support of the hypothesis that the clearance of mHtt is important, upregulation of autophagy produces beneficial effects (Jia et al. 2012; Koga et al. 2011; Martin et al. 2015; Sarkar et al. 2007; Williams et al. 2008).

12.1.5 Nonneuronal (Glial) and Peripheral Cells

mHtt is found in neurons and glial cells in the brains of HD (Hsiao and Chern 2010; Lee et al. 2013a, b; Shin et al. 2005; Yu et al. 2003). Although neuronal cells are preferentially damaged in HD, expression of mHtt in astrocytes and other glial cells causes age-dependent neurological symptoms and contributes to neuronal

excitotoxicity (Bradford et al. 2009; Crotti et al. 2014; Huang et al. 2015; Shin et al. 2005). mHtt in astrocytes clearly contributes to HD pathogenesis (Bradford et al. 2009, 2010; Chou et al. 2008; Hsiao et al. 2013). Specifically, mHtt alters several major astrocytic functions as follows: impaired glycolysis (Powers et al. 2007), lower expression of EAAT2 (GLT-1) that causes lower glutamate uptake (Chen et al. 2012; Shin et al. 2005), greater glutamate synthesis (Lee et al. 2013a, b), inferior GABA release (Wojtowicz et al. 2013), insufficient production and release of trophic factors (Chou et al. 2008; Wang et al. 2012), decreased expression of Kir4.1 potassium channel that eventually leads to neuronal excitotoxicity (Tong et al. 2014), dysfunctional calcium and glutamate signaling (Jiang et al. 2016), and higher inflammatory responses (Hsiao et al. 2013, 2014, 2015). Similar to the mechanism of other neurodegenerative diseases, microglia also play a critical role in HD pathogenesis. Abnormal functions of microglia have been implicated in overactivation of inflammatory response (Crotti et al. 2014; Hsiao et al. 2013). A recent study indicates that mHtt in glia can impart disease phenotype to normal mice, while normal glia can ameliorate disease phenotype in transgenic HD mice. This study suggests a causal role for glia in HD (Benraiss et al. 2016). mHtt is also expressed in peripheral cells and altered normal physiology. Specifically, mHtt is expressed in hepatocytes, suppresses the urea cycle activity, and causes high blood ammonia (Chiang et al. 2009; Chiu et al. 1975). The immune system is another important peripheral organ that expresses mHtt. It has been noted that enhanced immune activation in HD mice and patients could be detected in the early stage of HD. HD patients have elevated inflammatory cytokines and chemokines levels in plasma (Bjorkqvist et al. 2008). It has been proposed that mHtt levels of monocytes and T cells were significantly associated with disease progression in HD patients. The expression level of mHtt in immune cells might be used as a noninvasive disease biomarker (Weiss et al. 2012).

12.2 Dysfunction of Striatal Adenosine Receptors in HD

12.2.1 Striatal Adenosine Neurotransmission

Adenosine plays a fundamental role in the modulation of dopaminergic and glutamatergic neurotransmission in the striatum. Dopaminergic and glutamatergic afferents constitute the main extrinsic striatal inputs, which converge in the dendritic spines of the MSNs, the predominant striatal neuronal population (Gerfen 2004). Glutamatergic terminals make a tight synaptic contact with the head of the dendritic spines and astrocyte processes wrap the glutamatergic synapse, constituting the well-established tripartite synapse (Araque et al. 1999). On the other hand, dopaminergic terminals make a loose synaptic contact with the neck of the dendritic spine and allow volume transmission of dopamine to influence dopamine receptors located at the vicinity of the synapse (Rice et al. 2011). The dendritic spines, with their contacting glutamatergic and dopaminergic terminals and astrocyte process,

have been labelled as "striatal spine module" (Ferré et al. 2007), with "local module" being defined as an integrative functional unit of the central nervous system, a minimal portion of one or more neurons and/or one or more glial cells that operate as an independent integrative unit (Ferré et al. 2007). Within the striatal spine module, under normal conditions, extracellular adenosine originates predominantly from ATP released by a vesicular process from the astrocyte and rapidly converted to adenosine by ectonucleotidases (Pascual et al. 2005; Cunha 2016). The effects of extracellular adenosine are mediated by adenosine receptors, mostly adenosine A_1R (A_1Rs) and $A_{2A}Rs$, localized in the different elements of the striatal spine module. Both are G protein-coupled receptors, with A_1R and $A_{2A}R$ coupling to inhibitory Gi/o and excitatory Gs/olf proteins, respectively. Both receptors are co-localized in the glutamatergic terminals and astrocytes, where they form A_1R-$A_{2A}R$ heteromers (Ciruela et al. 2006). In the glutamatergic terminal, the A_1R-$A_{2A}R$ heteromers act as a "concentration-dependent switch" (Ciruela et al. 2006). The activation of A_1R and $A_{2A}R$ receptors by adenosine inhibits and stimulates glutamate release, respectively. Adenosine has more affinity for A_1R than $A_{2A}R$ receptors, and under basal conditions it tonically influences only presynaptic A_1Rs. Thus, gene-targeted vesicular release of astrocytic ATP leads to a loss of A_1R-mediated tonic inhibition of presynaptic hippocampal glutamatergic transmission (Pascual et al. 2005). Under physiological conditions, presynaptic $A_{2A}Rs$ are only activated by phasic increases of extracellular adenosine, which normally occurs upon strong glutamatergic input (which is associated to neuronal and glial co-release of ATP and its conversion to adenosine by 5-nucleotidases; Cunha 2016). Under these conditions, activation of $A_{2A}Rs$ negatively modulates A_1R signaling in the heteromer and, conversely, promotes glutamate release (Popoli et al. 1995; Solinas et al. 2002; Borycz et al. 2007; Quiroz et al. 2009, 2016). The same mechanism has also been described in cultured cortical astrocytes, where A_1R-$A_{2A}R$ heteromers modulate GABA uptake (Cristovao-Ferreira et al. 2013). A_1R, but not $A_{2A}R$, is also found in the dopaminergic terminals where it also exerts a tonic inhibitory modulation of dopamine release (Borycz et al. 2007). Finally, A_1R and $A_{2A}R$ are highly expressed postsynaptically, in the dendritic spines and in the rest of the somatodendritic region of the MSNs. Significantly, however, they are not co-localized but are segregated in the two phenotypically different striatal MSNs.

As stated above, two subtypes of MSNs give rise to the two striatal efferent pathways that connect the striatum with the output structures of the basal ganglia, which are the medial segment of the globus pallidus and the substantia nigra pars reticulata (Gerfen 2004). The striatonigral neurons constitutes the direct pathway, since it directly connects the striatum with the output structures and selectively expresses A_1R and D1R and also D3R in the ventral striatum (Ferré et al. 1997; Ferre et al. 1996; Sokoloff and Le Foll 2017). The striatopallidal neurons connects the striatum with the lateral segment of the globus pallidus and the ventral pallidum and selectively expresses $A_{2A}R$ and D2R (Ferré et al. 1993, 1997). A_1R and D1R and $A_{2A}R$ and D2R form specific receptor complexes, the A_1R-D1R and $A_{2A}R$-D2R heteromers (Ferré et al. 1997, 2016; Ginés et al. 2000; Hillion et al. 2002;

Canals et al. 2003), which act as molecular devices by which endogenous adenosine, by acting on the respective adenosine receptor, tonically inhibits the affinity and signaling of the respective dopamine receptor. Thus, differently from the striatal presynaptic $A_{2A}R$, under physiological conditions, postsynaptic $A_{2A}R$ is tonically activated by endogenous adenosine, as demonstrated by the significant behavioral and biochemical effects secondary to its blockade after the administration of $A_{2A}R$ antagonists (see below).

12.2.2 Adenosine Receptor Single Nucleotide Polymorphisms and Caffeine Intake

Considering the preferential vulnerability of the striatopallidal neurons in HD (Glass et al. 2000; Deng et al. 2004), not surprisingly, both D2R and $A_{2A}R$ were reported to be significantly and differentially downregulated, as compared to D1R, in early pathological stages of HD, but also in symptomatic patients with Vonsattel's pathological grade 0 (Glass et al. 2000), indicative of significant selective functional alterations of this MSN subpopulation. Downregulation of $A_{2A}R$ has also been reported in most studies using different HD mice, and several studies have provided possible molecular mechanisms (see below). On the other hand, although there is consensus about the decreased expression of $A_{2A}R$ in HD, as elaborated below, several studies imply the existence of an aberrant $A_{2A}R$ signaling, amplification, induced by mHtt in HD mice. The question is if those changes in $A_{2A}R$ expression and function are just markers of the selective degeneration of the indirect MSN or if they are involved in the pathogenetic process. Genetic studies would initially seem to reinforce the latter possibility, as a single nucleotide polymorphism (SNP) in *ADORA2A*, rs5751876 (C > T substitution in exon 5), has been associated to an earlier age at onset (AAO) of the disease (Dhaenens et al. 2009; Taherzadeh-Fard et al. 2010). Although rs5751876 constitutes a synonymous mutation (it does not change the encoded amino acid), it is linked by nearly complete linkage disequilibrium to other SNPs that could potentially modify $A_{2A}R$ transcription. Those include rs35320474, a T deletion in the 3′ untranslated region that includes U-rich motifs (which provide active sites of interaction with RNA-binding proteins), and rs2298383, a C > T substitution in a potential promoter region with a regulatory element predicted from alignment of human and other mammalian genes (Alsene et al. 2003; Childs et al. 2008; Rogers et al. 2010; Shinohara et al. 2013). Interestingly, the recent study by Shinohara et al. (2013) demonstrated a significant increase in the expression of $A_{2A}R$ in the brain of subjects homozygous for a rs5751876 polymorphic block (including rs35320474 and rs2298383) suggesting that, indeed, transcriptional dysregulation of $A_{2A}R$ is associated with HD. How these data reconcile with previous postmortem binding and expression studies in postmortem human brain and mouse models remains to be elucidated.

Another epidemiological study linking adenosine receptors to HD is the association of habitual consumption of caffeine with earlier AAO of HD (Simonin et al. 2013). Although caffeine is a nonselective $A_1R/A_{2A}R$ antagonist, the authors suggested $A_{2A}R$ blockade as the most probable explanation for the apparent caffeine-mediated increased acceleration of neurodegeneration. This assumption was based on the preferential tolerance to the A_1R versus $A_{2A}R$ blocking effects with chronic caffeine exposure (Karcz-Kubicha et al. 2003) and on the experimental evidence that indicates that high doses of $A_{2A}R$ antagonists or global $A_{2A}R$ blockade worsen disease progression in HD models (Blum et al. 2003a, b; Mievis et al. 2011), while $A_{2A}R$ agonists produce beneficial effects (Chou et al. 2005). However, A_1R blockade was not discarded as alternative mechanism, and an A_1R agonist has also been shown to protect against neurodegeneration in a rat HD model (Blum et al. 2002). A way to reconcile some of these findings could be the recently described evidence of alterations of adenosine metabolism in animal models of HD, a striatal hypoadenosinergic tone (see below), which could be mimicked by chronic caffeine exposure. Interestingly, an association between the *ADORA2A* rs5751876 polymorphism and caffeine intake was reported by Cornelis et al. (2007), which could have established a possible connection between this polymorphism, caffeine intake, and HD progression. However, this association has not been confirmed in a recent genome-wide meta-analysis of polymorphisms and habitual coffee intake (Coffe and Caffeine Genetics Consortium et al. 2015).

12.2.3 Alterations of A_1R Function During HD Progression

The stimulation of A_1R exerts a clear neuroprotective effect in different conditions (Paul et al. 2011; von Lubitz et al. 1988), including HD models. Thus, A_1R activation has been demonstrated to attenuate limb dystonia and striatal degeneration in the 3NP model of HD (Blum et al. 2002). These findings are in line with other data showing that an A_1R agonist prevented 3NP-induced seizures in mice (Zuchora et al. 2001) and that A_1R blockade was deleterious in another metabolic model of HD induced by malonate (Alfinito et al. 2003). Although no changes of A_1R density were observed in an HD rat model (Tg51 HD rats; see below and Bauer et al. 2005), binding studies in frankly symptomatic R6/2 mice, a widely used transgenic model of HD, revealed a decrease in density but not antagonist affinity, of cortical and striatal A1Rs (Ferrante et al. 2014). Interestingly, however, despite the reduced density of A_1Rs, the same authors found an increased effect of the agonist CPA in reducing synaptic transmission and glutamate release in the striatum of R6/2 versus WT mice, a. The decrease density and increased functionality of A_1Rs were further confirmed in a striatal cell line expressing mHtt (Ferrante et al. 2014). These results are in line with a noninvasive PET imaging study in HD patients in which the level of A_1R was found significantly reduced with respect to non-HD subjects in the symptomatic stages of the disease (Matusch et al. 2014; see 2.5).

12.2.4 Alterations of $A_{2A}R$ During HD Progression

Downregulation of the $A_{2A}R$ has been consistently reported in patients and in animal models, even before the onset of motor dysfunctions (Glass et al. 2000), and in animal models that do not show neuronal loss (Cha et al. 1999; Ishiwata et al. 2002; Bauer et al. 2005; Mievis et al. 2011; Orrù et al. 2011). The first evidence of a downregulation of $A_{2A}R$ in HD was obtained by autoradiography in tissue sections of the human brain (Martinez-Mir et al. 1991) and was later confirmed in the basal ganglia of early, intermediate, and advanced grades of HD patients (Glass et al. 2000). A downregulation of $A_{2A}R$ at the protein and transcript levels has been also found in most of the animal and cell models of HD (with the exception of H46, YAC72, and Tg51 transgenic models; Cha et al. 1999; Chan et al. 2002; Chou et al. 2005; Chiang et al. 2005; Tarditi et al. 2006; Villar-Menendez et al. 2013; Guitart et al. 2016), and these models have been fundamental for the identification of the molecular mechanisms through which a mHtt results in reduction of $A_{2A}R$ expression. It is well documented that aggregated mHtt causes aberrant protein-protein interactions with several transcription factors, which result in changes in gene expression profiles (Steffan et al. 2000; Nucifora et al. 2001; Dunah et al. 2002; Li et al. 2002). These changes appear to be specific since no changes in the expression of several important genes (cytoskeleton proteins, enzymes of metabolism, mitochondrial proteins, caspases, and others) have been reported. As for $A_{2A}R$, Chiang and collaborators (2005a, b) found that expression of mHtt significantly reduces the transcript levels of the endogenous $A_{2A}R$ in PC12 cells and striatal neurons in culture. They identified an atypical CRE site located in the core promoter of the $A_{2A}R$ gene that mediates the suppression of the $A_{2A}R$ gene by mHtt, by preventing CREB binding (Chiang et al. 2005). Interestingly, stimulation of the $A_{2A}R$ restored the reduced CREB binding caused by the mutation and reduced mHtt aggregation. The length of poly(Q)-expanded Htt seems to be critical for the downregulation of $A_{2A}R$ transcript: in HD models that express an extended N-terminal fragment or a full-length mHtt as in HD46 and YAC72 mice, respectively (Chan et al. 2002), a reduction in the expression of $A_{2A}R$ and of other mHtt-sensitive genes has not been found, and it is hypothesized that transcriptional dysfunctions only occur in the presence of a short N-terminal fragment (<171 amino acids) of mHtt.

Interestingly, DNA methylation has been proposed as a key mechanism for the reduced striatal $A_{2A}R$ levels observed in the brain from HD patients and from R6/1 and R6/2 mice (Villar-Menendez et al. 2013; Mangiarini et al. 1996; Vonsattel 2008). DNA methylation (5-methylcytosine, 5mC, and 5-hydroxymethylcytosine, 5hmC) is an important mechanism for epigenetic silencing, and it has been demonstrated to regulate basal $A_{2A}R$ level in the human brain (Buira et al. 2010). In their study, Villar-Menendez and collaborators (2013) found an increase in 5mC levels and a reduction in 5hmC levels in the 5′ untranslated region (5'UTR) of $A_{2A}R$ gene, and these findings were closely associated with the downregulation of the $A_{2A}R$ transcript in R6/2 mice and in the putamen of HD patients. This finding appears to be particularly interesting since it could open new approaches to treat HD by modulating $A_{2A}Rs$.

While the expression of the $A_{2A}R$ has been demonstrated to be reduced in the presence of mHtt (although with some exceptions), an amplification of its signaling has also been reported during the progression of HD. Data from Varani et al. (2001) reported an aberrant amplification of $A_{2A}R$-mediated stimulation of adenylyl cyclase in striatal-derived cells engineered to express mHtt, a result confirmed in the striatum of R6/2 mice (Chou et al. 2005; Tarditi et al. 2006). The amplification of the $A_{2A}R$ signaling was also found in peripheral blood cells from HD subjects, where overstimulation of $A_{2A}R$-mediated cAMP production was associated with aberrant increase in $A_{2A}R$ function and density (Varani et al. 2007). Moreover, $A_{2A}R$ density in blood platelets has been found to correlate with age at onset and CAG repeat expansion in HD patients (Maglione et al. 2006). These findings suggested that $A_{2A}R$ in peripheral blood cells could be used as a biomarker for the prediction of HD prognosis and drug efficacy. However, despite an initial enthusiasm, further studies are needed to ultimately validate this receptor as a biomarker and used for the disease prognosis.

12.2.5 Positron Emission Tomography (PET) Imaging for Adenosine Receptor Occupancy in HD

Positron emission tomography (PET) allows in vivo imaging of regional receptor-binding capacity and, together with magnetic resonance, identifies minimal changes in brain activity, greatly helping in the comprehension of the natural history of several diseases, including HD (Roussakis and Piccini 2015). Different radiotracers have been used with PET to measure brain metabolism, dopaminergic function, neuroinflammation, phosphodiesterases, and other targets in HD (Roussakis and Piccini 2015). However, few adenosine analogue radiotracers have been developed and employed with PET in the noninvasive imaging of A_1R and $A_{2A}R$. The A_1R is ubiquitously expressed in the human brain and can be imaged in vivo with [18F] CPFPX-PET (Bauer et al. 2003; Holschbach et al. 2002; Meyer et al. 2007). A cross-sectional study using [18F]CPFPX-PET and MRI was performed to assess differences in A_1R density between controls and HD patients at different stages of the disease (premanifest patients far from predicted symptoms onset, premanifest patients near to predicted symptoms onset, and manifest patients; Matusch et al. 2014). In this study a 25% reduction in [18F]CPFPX binding in the caudate of manifest HD patients was found. Interestingly, in premanifest patients far from symptoms onset, [18F]CPFPX binding in the thalamus was 31% higher than in healthy controls, while in premanifest patients near to symptoms onset, thalamic [18F]CPFPX binding was similar to the levels in healthy controls, suggesting that A1R switch from upregulation to downregulation during HD progression. Thus, A_1Rs seem to be involved in the pathophysiology of HD, and [18F]CPFPX and PET can be considered useful tools to explore these receptors in preclinical and clinical trials (Matusch et al. 2014).

$A_{2A}R$ antagonist PET tracers have been developed and tested with PET imaging. However, xanthine ligands, including [11C]TMSX, [11C]KF17837, [11C]TMSX, [11C]KF21213, [11C]KF19631, and [11C]KW6002, proved to be not very suitable for molecular imaging mainly because of low signal to noise ratio and high degree of non-specific binding (Khanapur et al. 2014). [11C]SCH442416 was the first non-xanthine ligand being suitable for mapping of $A_{2A}R$ using PET (Moresco et al. 2005). In general, radioligands that lack the xanthine structure appear to offer better specificity for the $A_{2A}R$ subtype and allow quantitative imaging of $A_{2A}R$ in the mammalian striatum but not in other areas of the brain (for an updated review, see van Waarde et al. 2018). Recently, [11C]preladenant has been demonstrated to be a suitable PET tracer for the quantification of $A_{2A}R$ binding sites in the rat brain. The tracer displayed high uptake in striatum and low and homogenous uptake in all extra-striatal regions, and the regional distribution of [11C]preladenant is in agreement with the known $A_{2A}R$ expression in the rat brain (Zhou et al. 2017a). The suitability [11C]preladenant for imaging of $A_{2A}Rs$ in the brain has been confirmed in monkey and human brains (Zhou et al. 2017b; Sakata et al. 2017). Very few studies have been conducted for $A_{2A}R$ in PET images and in particular in HD. In a rat model of HD (intrastriatal injection of quinolinic acid resulting in loss of striatopallidal GABAergic enkephalin neurons), the binding potential of [11C]TMSX in the striatum and globus pallidus was reduced by 25%, similar to the loss of D2R ([11C] raclopride) (Ishiwata et al. 2002). Hopefully, the availability of new and more suitable radiotracers will prompt PET studies of $A_{2A}R$ in HD.

12.2.6 Alterations in Striatal Adenosine Tone in HD

In a recent study on the Tg51 transgenic rat model of HD (von Hörsten et al. 2003), we found a clue for an alteration of the adenosinergic system independent of alterations in $A_{2A}R$ expression (Guitart et al. 2016). Tg51 rats offer a model with a slower neurodegenerative progression as compared to other animal models, which in principle allow an easier evaluation of possible biomarkers during initial stages of HD (von Hörsten et al. 2003). Using methods of analysis of the function of striatal pre- and postsynaptic $A_{2A}R$, it was initially suggested that Tg51 rats had a selective functional impairment of striatal postsynaptic $A_{2A}R$ during early pathological stages (Orrú et al. 2011). This was based on the observation of a complete loss of locomotor-activating effects of $A_{2A}R$ antagonists, without changing their efficacy at modulating presynaptic corticostriatal neurotransmission (Orrú et al. 2011). It was then assumed that the most probable mechanism was the previously demonstrated down-regulation of $A_{2A}R$ in both HD and HD animal models. However, a more extensive pharmacological characterization of the Tg51 indicated that postsynaptic striatal $A_{2A}R$ function was not altered after all. Thus, there was no difference in the locomotor depression induced by an $A_{2A}R$ agonist (which depends on the integrity of postsynaptic $A_{2A}R$) in Tg51 rats as compared to WT littermates (Guitart et al. 2016). More convincingly, radioligand-binding experiments showed no differences in the number of striatal $A_{2A}R$ antagonist binding sites or affinity between Tg51 (homo- or

heterozygous) and WT rats (Guitart et al. 2016). Altogether, the pharmacological results (effect with agonist and lack of effect of the antagonist) suggested a low adenosinergic tone, a decrease in the ability of endogenous adenosine to activate postsynaptic $A_{2A}R$. This would also explain the ability of $A_{2A}R$ antagonists to act presynaptically, blocking corticostriatal transmission (Orrú et al. 2011), which depends on phasic increases of extracellular adenosine (see above). In fact, we could demonstrate a significant reduction in the extracellular striatal concentration of adenosine both in Tg51 rats and in zQ175 knock-in mice (Guitart et al. 2016), a more recently obtained animal model of HD (Menalled et al. 2012). Nevertheless, differently from Tg51 rats, $A_{2A}R$ downregulation was also observed in zQ175 mice, with a hypoadenosinergic tone representing the common striatal alteration (Guitart et al. 2016).

The next step was, therefore, to find the alteration in the mechanisms that regulate the extracellular concentrations of adenosine. It is now well accepted that astroglial vesicular release of ATP is the main source of extracellular adenosine under physiological conditions (Pascual et al. 2005). Extracellular ATP is rapidly converted to adenosine by a series of ectonucleotidases; the extracellular levels of adenosine, the adenosinergic tone, is mostly maintained by the ability ofequilibrative transporters and astrocytic adenosine kinase (ADK) to respectively uptake and metabolize adenosine (Boison et al. 2010; Cunha 2016). In mammals, there are two types of nucleoside transporters, equilibrative and concentrative, which mediate a bidirectional equilibrative transport driven by chemical gradient and a unidirectional concentration transport driven by sodium electrochemical gradient, respectively (Parkinson et al. 2011). Adenosine uptake in the brain occurs primarily by facilitated diffusion via equilibrative transporters, which pharmacological blockade is associated with an accumulation of adenosine in the extracellular space (Parkinson et al. 2011; Dulla and Masino 2013; Cunha 2016). From the four types of equilibrative transporters so far identified (ENT1, ENT2, ENT3, and ENT4), ENT1 and ENT2 are the most expressed in the brain, both by neurons and astrocytes (Parkinson et al. 2011). Nevertheless, some studies suggest that ENT1 has a more salient role in determining the concentration of extracellular adenosine in the brain and its dependence on glutamate receptor activation (Alanko et al. 2006; Bicket et al. 2016). Using the ENT1 selective inhibitor [3H]-S-(4-nitrobenzyl)-6-thioinosine ([3H]NBTI), we found a significant upregulation of the transporter in zQ175 mice (Guitart et al. 2016). More importantly, ENT1 gene (SLC29A1) transcript was significantly upregulated in HD disease patients at an early neuropathological severity stage, but not those with a higher severity stage, relative to non-demented controls (Guitart et al. 2016). Furthermore, SLC29A1 transcript was differentially co-expressed (gained correlations) with several other genes in HD disease subjects compared to the control group, demonstrating that ENT1 constitutes a biomarker of the initial stages of neurodegeneration in HD disease (Guitart et al. 2016). It was also postulated that adenosine could constitute another biomarker and, in fact, in a more recent study, CSF adenosine levels were found significantly lower in HD patients (Kao et al. 2017). In addition, the CSF concentration of ATP was inversely correlated with the number of CAG repeats, and the adenosine/ATP ratio was negatively correlated with the disease duration of HD patients (Kao et al. 2017).

12.3 Adenosine Neurotransmission as a Therapeutic Target in HD

12.3.1 Targeting A_1R in Phenotypic HD Models

Modulation of A_1R has not been largely evaluated. We have previously tested the A_1R agonist ADAC in the 3NP model of HD (Blum et al. 2002). We interestingly observed that the acute administration of this compound completely prevented the development of hindlimb dystonia related to striatal degeneration in this particular model and reduced the size of 3NP-induced striatal lesions, as well as the ongoing process of striatal degeneration. The protective effect of A1R activation was in line with other data showing that another A_1R agonist was able to prevent 3NP-induced seizures in mice (Zuchora et al. 2001) and that A_1R blockade was deleterious in another metabolic model of HD induced by malonate (Alfinito et al. 2003). The protective effects of ADAC were ascribed to its presynaptic ability to reduce glutamate release within the striatum (Blum et al. 2002). Although the therapeutic potential of A_1R activation in HD has remained difficult to extrapolate, mostly due to potential cardiovascular side effects associated with A_1R activation (see Blum et al. 2003b for review), the new studies targeting the adenosine tone (see below) might reinvigorate A_1R as a direct or indirect target in HD.

12.3.2 Targeting $A_{2A}R$ in Chemical- and Lesion-Induced HD Models

Compelling evidence suggests that inactivation of $A_{2A}R$ in rodents by pharmacological (e.g., antagonists) or genetic (e.g., knockout) approaches ameliorates the striatal damage evoked by an N-methyl-D-aspartate (NMDA) receptor agonist, quinolinic acid (QA), a mitochondrial toxin 3-nitropropionic acid (3-NP), and a mitochondrial complex II inhibitor (malonate) (Lee and Chern 2014). The intrastriatal injection of QA and systemic administration of 3-NP can mimic the anatomical and behavioral deficits of HD, produce the direct and indirect excitotoxicity of HD, and trigger the selective loss of MSN in the striatum (Alston et al. 1977; Brouillet et al. 1993, 2005; Jacobson et al. 2012; Shear et al. 1998). Malonate is a competitive inhibitor of succinate dehydrogenase. Intrastriatal injection of malonate results in significant lesions in the striatum and has been used to create a HD model (Andreassen et al. 2000; Beal et al. 1993; Messam et al. 1995). Several $A_{2A}R$ antagonists (DMPX, SCH58261, ZM241385, ST1535, MSX-3, and CSC) have been shown to elicit multiple beneficial effects in these chemical- and lesion-induced HD models by reducing the striatal atrophy or degeneration, EEG abnormality, and motor hyperactivity, improving the loss of the GABA content, lowering the glutamate outflow, and increasing the life-span (Alfinito et al. 2003;

Blum et al. 2003a, b; Fink et al. 2004; Galluzzo et al. 2008; Popoli et al. 2002; Reggio et al. 1999; Scattoni et al. 2007; Tebano et al. 2004). On the contrary, an $A_{2A}R$ agonist (CGS21680) was shown to increase the 3-NP-induced striatal lesion size (Blum et al. 2003a, b). In addition, different $A_{2A}R$-null mice models were developed to reveal the cell-type-specific functions of $A_{2A}Rs$ in the 3-NP-evoked striatal damage. Surprisingly, global $A_{2A}R$ knockout mice show opposite effects on the 3-NP-induced neurological deficit behaviors and striatal damage at different disease dosages (Blum et al. 2003a, b; Fink et al. 2004; Huang et al. 2006), suggesting the potential involvement of diverse cell types. The selective depletion of $A_{2A}R$ in forebrain neurons does not contribute to the 3-NP-evoked striatal damage (Huang et al. 2006). However, the selective removal of $A_{2A}R$ in bone marrow-derived cells (BMDCs) recapitulates the enhanced 3-NP-induced striatal damage in global A2AR knockout mice. These findings argue against the importance of $A_{2A}R$-mediated glutamate release in the 3-NP-induced striatal damage (Huang et al. 2006). The possible role of $A_{2A}R$ in controlling nonneuronal cells (e.g., glia) might also contribute to the function of $A_{2A}R$ in the brain, which requires further evaluation. In summary, inactivation of $A_{2A}R$ appears to be beneficial in the chemical- and lesion-induced HD models.

12.3.3 Targeting A2AR in Phenotypic HD Models

The first genetic mouse model of HD was developed and characterized two decades ago (Mangiarini et al. 1996). Since then, multiple genetic mouse models of HD (including transgenic, conditional transgenic, and knock-in mice) have been created for in-depth investigations (Ferrante 2009; Li et al. 2005; Menalled 2005; Menalled and Chesselet, 2002). More than 30 genetic mouse models of HD are available from various sources (Lee et al. 2013a, b; Pouladi et al. 2013). It is of great interest to find that modulation of $A_{2A}R$ in HD mice might result in different effects, as opposed to those in wild-type mice. The role of $A_{2A}R$ in HD had been evaluated in two different mouse models (R6/2 and N171-82Q) of HD. R6/2 mice express the exon 1 of the human huntingtin gene (Mangiarini et al. 1996) and show a speedy progression with many major HD symptoms (e.g., motor impairment, aggregate formation, body weight loss) (Cha et al. 1998, 1999; Luthi-Carter et al. 2000). Chronic treatment with an $A_{2A}R$ agonist (CGS21680) has been shown to have beneficial effects in R6/2 mice by reducing the accumulation of mHtt aggregates, lowering the NMDA toxicity, improving the brain atrophy, increasing the rotarod performance, and enhancing proteasome activity (Cepeda et al. 2010; Chiang et al. 2009; Chou et al. 2005; Ferrante et al. 2010; Huang et al. 2011a, b; Ju et al. 2011; Lin et al. 2013; Martire et al. 2007, 2013). Treatment with another $A_{2A}R$ agonist (T1–11) also produces beneficial effects in R6/2 mice by enhancing the rotarod performance and proteasome activity (Huang et al. 2011a, b).

On the other hand, injection of an $A_{2A}R$ antagonist (SCH58261) was shown to reduce the glutamate and adenosine outflow, normalize the alteration in the emotional response, and reduce the NMDA-induced toxicity (Domenici et al. 2007; Gianfriddo et al. 2004). However, SCH58261 exhibited no effect on motor capability (Cipriani et al. 2008; Domenici et al. 2007). Genetic and pharmacological inactivation of $A_{2A}R$ was also found to reduce working memory deficits in R6/2 mice (Li et al. 2015). Interestingly, combined blockade of D1Rs and A2ARs improved cognitive dysfunction in another HD mouse model (R6/1, a transgenic HD mouse model similar to R6/2) (Tyebji et al. 2015). Taken together, results of these studies suggest that $A_{2A}R$ blockade may be beneficial for the impaired cognitive function in HD mice. Genetic inhibition of $A_{2A}R$ in HD was also tested in another mouse model (N171-82Q) that expresses mHtt only in neurons (Mievis et al. 2011). Removal of $A_{2A}R$ shortens the survival and worsens the motor impairment of N171-82Q mice. Together with the earlier studies showing that activation of $A_{2A}R$ improved motor function of HD mice (R6/2 (Chou et al. 2005)), $A_{2A}R$ blockade might be of concern for HD patients. Given that activation and inactivation of $A_{2A}R$ are beneficial on different symptoms (motor functions and cognitive function, respectively) and apparently depends on the model used, the symptom-specific effects of $A_{2A}R$ need to be further investigated.

12.3.4 Targeting ENT1 in Phenotypic HD Models

The results, demonstrating upregulation of ENT1 and reduced adenosinergic tone in both animal models and HD patients, predict that ENT1 could constitute a new therapeutic target to delay the progression of HD. In complete support, pharmacological blockade with the low-affinity ENT1 inhibitor JMF1907 (Chen et al. 2011) or genetic blockade of ENT (global ENT1 knockout) in HD mice led to a significant increase in the mean survival time in the R6/2 mouse model of HD (Kao et al. 2017). In the same study, evidence could also be obtained for an increased expression and activity of ENT1 and ENT2, and decreased striatal adenosine levels could be demonstrated in R6/2 mice and still another animal model of HD, the knock-in Hdh(CAG)150 mouse (Lin et al. 2001). The expression of ectonucleotidases and ADK was also analyzed in both models, and only ADK transcript was found to be upregulated, but only in R6/2 mice (Kao et al. 2017), indicating that alterations in the equilibrative transporters are more likely to represent a key pathogenetic mechanism in HD. ENT1 and less selective ENT1/ENT2 inhibitors should then be considered as potentially new therapeutic drugs to decrease the progression of the disease. Although blood-brain barrier permeable, JMF1907 is still under preclinical evaluation and belongs to a group of multifunctional adenosine compounds that are both ENT1 inhibitors and $A_{2A}R$ agonists (Chen et al. 2011; Huang et al. 2011a, b). Given that inhibitors of ENT1 such as dipyridamole, ticagrelor, or

dilazep have already been used to treat different pathological conditions related to vascular relaxation and platelet aggregation or the NSAID sulindac sulfide for its anti-inflammatory effects, it has been suggested that they should be clinically studied in HD patients in order to evaluate their ability to delay the progression of the disease or the age of onset (Guitart et al. 2017). The main caveat is their purported low brain penetrability.

Using the classical reserpinized mice model, we recently evaluated the ability of the systemic administration of dipyridamole to decrease locomotor activation by dopamine receptor agonists. This model has been very useful for the discovery of the specific antagonistic interactions between adenosine and dopamine receptor ligands that led to the discovery the A_{2A}R-D2R and A_1R-D1R heteromers (Ferré et al. 1991, 1994). At a minimal dose of 30 mg/kg, dipyridamole significantly decreased the locomotor-activating effect of equipotent doses of selective D1R and D2R agonists, and the depressant effect of dipyridamole was totally counteracted by caffeine (Ferré et al. 2017). The results could then be entirely explained by the ability of systemically administered dipyridamole to promote an increase in the basal extracellular levels of striatal adenosine that normally exert a tonic-activating effect of postsynaptic A_1R and A_{2A}R. Such an increase should lead to the observed ability to depress both D1R and D2R agonist-mediated locomotor activation in reserpinized mice. Also, such an increase should be expected to increase the tonic activation of postsynaptic A_{2A}R and A_1R, but also presynaptic A_1R, leading to a decrease in glutamate release, hopefully promoting a therapeutic effect in HD patients.

12.4 Concluding Remarks

Adenosine receptors, and especially A_{2A}R, are clearly linked to HD pathophysiology as attested by a large number of genetic, epidemiological, and experimental studies. Several aspects concerning its pathophysiological involvement remain however to be further deciphered. The pre−/postsynaptic aspects deserve further investigation using specific ligands as well as genetic murine tools. Also, how A_{2A} receptors interact with glial dysfunctions promoted by mHtt has been largely underestimated. Furthermore, given that A_{2A}R heteromerize with several other GPCRs, such as D2R or A_1R, that play a presumable role in striatal dysfunctions and degeneration in HD, one may consider A_{2A}R heteromers as targets for drug development. Finally, since HD is a chronically progressive disease, the multiple mechanisms involving A_{2A}Rs may play different relative roles along the degenerative process. The role of A_1R in HD pathogenesis has been largely understudied, but it is becoming clear that this field deserves to be reconsidered. This is because of new developments on the role of low adenosine tone in HD, with the upregulation of ENT1, which recent studies indicating it could become a new target for drug development in HD.

References

Alanko L, Porkka-Heiskanen T, Soinila S (2006) Localization of equilibrative nucleoside transporters in the rat brain. J Chem Neuroanat 31:162–168

Alfinito PD, Wang SP, Manzino L et al (2003) Adenosinergic protection of dopaminergic and GABAergic neurons against mitochondrial inhibition through receptors located in the substantia nigra and striatum, respectively. J Neurosci 23(34):10982–10987

Alsene K, Deckert J, Sand P et al (2003) Association between A2a receptor gene polymorphisms and caffeine-induced anxiety. Neuropsychopharmacology 28:1694–1702

Alston TA, Mela L, Bright HJ (1977) 3-Nitropropionate, the toxic substance of Indigofera, is a suicide inactivator of succinate dehydrogenase. Proc Natl Acad Sci U S A 74(9):3767–3771

Andreassen OA, Ferrante RJ, Hughes DB et al (2000) Malonate and 3-nitropropionic acid neurotoxicity are reduced in transgenic mice expressing a caspase-1 dominant-negative mutant. J Neurochem 75(2):847–852

Araque A, Parpura V, Sanzgiri RP et al (1999) Tripartite synapses: glia, the unacknowledged partner. Trends Neurosci 22:208–215

Bantubungi K, Blum D (2007a) Mechanisms of neuronal death in Huntington's disease. First part: general considerations and histopathological features. Rev Med Brux 28:413–421

Bantubungi K, Blum D (2007b) Mechanisms of neuronal death in Huntington's disease. Second part: therapeutic challenges. Rev Med Brux 28:487–494

Barnat M, Le Friec J, Benstaali C et al (2017) Huntingtin-mediated multipolar-bipolar transition of newborn cortical neurons is critical for their postnatal neuronal morphology. Neuron 93:99–114

Bauer A, Holschbach MH, Meyer PT et al (2003) In vivo imaging of adenosine A1 receptors in the human brain with [18F]CPFPX and positron emission tomography. NeuroImage 19:1760–1769

Bauer A, Zilles K, Matusch A et al (2005) Regional and subtype selective changes of neurotransmitter receptor density in a rat transgenic for the Huntington's disease mutation. J Neurochem 94:639–650

Beal MF, Kowall NW, Ellison DW et al (1986) Replication of the neurochemical characteristics of Huntington's disease by quinolinic acid. Nature 321:168–171

Beal MF, Brouillet E, Jenkins B et al (1993) Age-dependent striatal excitotoxic lesions produced by the endogenous mitochondrial inhibitor malonate. J Neurochem 61:1147–1150

Benchoua A, Trioulier Y, Zala D et al (2006) Involvement of mitochondrial complex II defects in neuronal death produced by N-terminus fragment of mutated huntingtin. Mol Biol Cell 17:1652–1663

Benchoua A, Trioulier Y, Diguet E et al (2008) Dopamine determines the vulnerability of striatal neurons to the N-terminal fragment of mutant huntingtin through the regulation of mitochondrial complex II. Hum Mol Genet 17:1446–1456

Bennett EJ, Shaler TA, Woodman B et al (2007) Global changes to the ubiquitin system in Huntington's disease. Nature 448:704–708

Benraiss A, Wang S, Herrlinger S et al (2016) Human glia can both induce and rescue aspects of disease phenotype in Huntington disease. Nat Commun 7:11758

Bicket A, Mehrabi P, Naydenova Z et al (2016) Novel regulation of equilibrative nucleoside transporter 1 (ENT1) by receptor-stimulated Ca2+−dependent calmodulin binding. Am J Physiol Cell Physiol 310:C808–C820

Bjorkqvist M, Wild EJ, Thiele J et al (2008) A novel pathogenic pathway of immune activation detectable before clinical onset in Huntington's disease. J Exp Med 205:1869–1877

Blum D, Gall D, Galas MC et al (2002) The adenosine A_1 receptor agonist adenosine amine congener exerts a neuroprotective effect against the development of striatal lesions and motor impairments in the 3-nitropropionic acid model of neurotoxicity. J Neurosci 22:9122–9133

Blum D, Galas MC, Pintor A et al (2003a) A dual role of adenosine A_{2A} receptors in 3-nitropropionic acid-induced striatal lesions: implications for the neuroprotective potential of A_{2A} antagonists. J Neurosci 23:5361–5369

Blum D, Hourez R, Galas MC et al (2003b) Adenosine receptors and Huntington's disease: implications for pathogenesis and therapeutics. Lancet Neurol 2:366–374
Boison D, Chen JF, Fredholm BB (2010) Adenosine signaling and function in glial cells. Cell Death Differ 17:1071–1082
Borrell-Pages M, Canals JM, Cordelieres FP et al (2006) Cystamine and cysteamine increase brain levels of BDNF in Huntington disease via HSJ1b and transglutaminase. J Clin Invest 116:1410–1424
Borycz J, Pereira MF, Melani A et al (2007) Differential glutamate-dependent and glutamate-independent adenosine A1 receptor-mediated modulation of dopamine release in different striatal compartments. J Neurochem 101:355–363
Bradford J, Shin JY, Roberts M et al (2009) Expression of mutant huntingtin in mouse brain astrocytes causes age-dependent neurological symptoms. Proc Natl Acad Sci U S A 106:22480–22485
Bradford J, Shin JY, Roberts M et al (2010) Mutant huntingtin in glial cells exacerbates neurological symptoms of Huntington disease mice. J Biol Chem 285:10653–10661
Brouillet E, Jenkins BG, Hyman BT et al (1993) Age-dependent vulnerability of the striatum to the mitochondrial toxin 3-nitropropionic acid. J Neurochem 60:356–359
Brouillet E, Conde F, Beal MF et al (1999) Replicating Huntington's disease phenotype in experimental animals. Prog Neurobiol 59:427–468
Brouillet E, Jacquard C, Bizat N et al (2005) 3-Nitropropionic acid: a mitochondrial toxin to uncover physiopathological mechanisms underlying striatal degeneration in Huntington's disease. J Neurochem 95:1521–1540
Browne SE, Bowling AC, MacGarvey U et al (1997) Oxidative damage and metabolic dysfunction in Huntington's disease: selective vulnerability of the basal ganglia. Ann Neurol 41:646–653
Buira SP, Dentesano G, Albasanz JL et al (2010) DNA methylation and Yin Yang-1 repress adenosine A2A receptor levels in human brain. J Neurochem 115:283–295
Canals M, Marcellino D, Fanelli F et al (2003) Adenosine A2A-dopamine D2 receptor-receptor heteromerization: qualitative and quantitative assessment by fluorescence and bioluminescence energy transfer. J Biol Chem 278:46741–46749
Cepeda C, Ariano MA, Calvert CR et al (2001) NMDA receptor function in mouse models of Huntington disease. J Neurosci Res 66:525–539
Cepeda C, Cummings DM, Hickey MA et al (2010) Rescuing the corticostriatal synaptic disconnection in the R6/2 mouse model of Huntington's disease: exercise, adenosine receptors and Ampakines. PLoS Curr 2:RRN1182
Cha JH, Kosinski CM, Kerner JA et al (1998) Altered brain neurotransmitter receptors in transgenic mice expressing a portion of an abnormal human Huntington disease gene. Proc Natl Acad Sci U S A 95:6480–6485
Cha JH, Frey AS, Alsdorf SA et al (1999) Altered neurotransmitter receptor expression in transgenic mouse models of Huntington's disease. Philos Trans R Soc Lond Ser B Biol Sci 354:981–989
Chan EY, Luthi-Carter R, Strand A et al (2002) Increased huntingtin protein length reduces the number of polyglutamine-induced gene expression changes in mouse models of Huntington's disease. Hum Mol Genet 11:1939–1951
Chao MV (2003) Neurotrophins and their receptors: a convergence point for many signalling pathways. Nat Rev Neurosci 4:299–309
Chen N, Luo T, Wellington C et al (1999) Subtype-specific enhancement of NMDA receptor currents by mutant huntingtin. J Neurochem 72:1890–1898
Chen JB, Liu EM, Chern TR (2011) Design and synthesis of novel dual-action compounds targeting the adenosine A(2A) receptor and adenosine transporter for neuroprotection. Chem Med Chem 6:1390–1400
Chen LL, Wu JC, Wang LH et al (2012) Rapamycin prevents the mutant huntingtin-suppressed GLT-1 expression in cultured astrocytes. Acta Pharmacol Sin 33:385–392
Chiang MC, Lee YC, Huang CL et al (2005) cAMP-response element-binding protein contributes to suppression of the A2A adenosine receptor promoter by mutant Huntingtin with expanded polyglutamine residues. J Biol Chem 280:14331–14340

Chiang MC, Chen HM, Lai HL et al (2009) The A2A adenosine receptor rescues the urea cycle deficiency of Huntington's disease by enhancing the activity of the ubiquitin-proteasome system. Hum Mol Genet 18:2929–2942
Childs E, Hohoff C, Deckert J et al (2008) Association between ADORA2A and DRD2 polymorphisms and caffeine-induced anxiety. Neuropsychopharmacology 33:2791–2800
Chiu E, Mackay IR, Bhathal PB (1975) Hepatic morphology in Huntington's chorea. J Neurol Neurosurg Psychiatry 38(10):1000–1002
Choo YS, Johnson GV, MacDonald M et al (2004) Mutant huntingtin directly increases susceptibility of mitochondria to the calcium-induced permeability transition and cytochrome c release. Hum Mol Genet 13:1407–1420
Chou SY, Lee YC, Chen HM et al (2005) CGS21680 attenuates symptoms of Huntington's disease in a transgenic mouse model. J Neurochem 93:310–320
Chou SY, Weng JY, Lai HL et al (2008) Expanded-polyglutamine huntingtin protein suppresses the secretion and production of a chemokine (CCL5/RANTES) by astrocytes. J Neurosci 28(13):3277–3290
Cipriani S, Bizzoco E, Gianfriddo M et al (2008) Adenosine A2A receptor antagonism increases nNOS-immunoreactive neurons in the striatum of Huntington transgenic mice. Exp Neurol 213:163–170
Ciruela F, Casadó V, Rodrigues RJ et al (2006) Presynaptic control of striatal glutamatergic neurotransmission by adenosine A1-A2A receptor heteromers. J Neurosci 26:2080–2087
Coffee and Caffeine Genetics Consortium, Cornelis MC, Byrne EM et al (2015) Genome-wide meta-analysis identifies six novel loci associated with habitual coffee consumption. Mol Psychiatry 20:647–656
Colin E, Zala D, Liot G et al (2008) Huntingtin phosphorylation acts as a molecular switch for anterograde/retrograde transport in neurons. EMBO J 27:2124–2134
Cornelis MC, El-Sohemy A, Campos H (2007) Genetic polymorphism of the adenosine A2A receptor is associated with habitual caffeine consumption. Am J Clin Nutr 86:240–244
Costa V, Giacomello M, Hudec R et al (2010) Mitochondrial fission and cristae disruption increase the response of cell models of Huntington's disease to apoptotic stimuli. EMBO Mol Med 2:490–503
Cristóvão-Ferreira S, Navarro G, Brugarolas M et al (2013) A1R-A2AR heteromers coupled to Gs and G i/0 proteins modulate GABA transport into astrocytes. Purinergic Signal 9:433–449
Crotti A, Benner C, Kerman BE et al (2014) Mutant Huntingtin promotes autonomous microglia activation via myeloid lineage-determining factors. Nat Neurosci 17(4):513–521
Cunha RA (2016) How does adenosine control neuronal dysfunction and neurodegeneration? J Neurochem 139:1019–1055
del Toro D, Canals JM, Gines S et al (2006) Mutant huntingtin impairs the post-Golgi trafficking of brain-derived neurotrophic factor but not its Val66Met polymorphism. J Neurosci 26:12748–12757
Demartino GN, Gillette TG (2007) Proteasomes: machines for all reasons. Cell 129(4):659–662
Deng YP, Albin RL, Penney JB et al (2004) Differential loss of striatal projection systems in Huntington's disease: a quantitative immunohistochemical study. J Chem Neuroanat 27:143–164
Dhaenens CM, Burnouf S, Simonin C et al (2009) A genetic variation in the ADORA2A gene modifies age at onset in Huntington's disease. Neurobiol Dis 35:474–476
Domenici MR, Scattoni ML, Martire A et al (2007) Behavioral and electrophysiological effects of the adenosine A2A receptor antagonist SCH 58261 in R6/2 Huntington's disease mice. Neurobiol Dis 28:197–205
Dompierre JP, Godin JD, Charrin BC et al (2007) Histone deacetylase 6 inhibition compensates for the transport deficit in Huntington's disease by increasing tubulin acetylation. J Neurosci 27:3571–3583
Dragatsis I, Efstratiadis A, Zeitlin S (1998) Mouse mutant embryos lacking huntingtin are rescued from lethality by wild-type extraembryonic tissues. Development 125:1529–1539

Dulla CG, Masino SA (2013) Physiology and metabolic regulation of adenosine: mechanisms. In: Masino S, Boison D (eds) Adenosine. A key link between metabolism and brain activity. Springer, New York, pp 87–107
Dunah AW, Jeong H, Griffin A et al (2002) Sp1 and TAFII130 transcriptional activity disrupted in early Huntington's disease. Science 296:2238–2243
Faideau M, Kim J, Cormier K et al (2010) In vivo expression of polyglutamine-expanded huntingtin by mouse striatal astrocytes impairs glutamate transport: a correlation with Huntington's disease subjects. Hum Mol Genet 19:3053–3067
Fan MM, Raymond LA (2007) N-methyl-D-aspartate (NMDA) receptor function and excitotoxicity in Huntington's disease. Prog Neurobiol 81:272–293
Ferrante RJ (2009) Mouse models of Huntington's disease and methodological considerations for therapeutic trials. Biochim Biophys Acta 1792(6):506–520
Ferrante A, Martire A, Armida M et al (2010) Influence of CGS 21680:a selective adenosine A(2A) receptor agonist, on NMDA receptor function and expression in the brain of Huntington's disease mice. Brain Res 1323:184–191
Ferrante A, Martire A, Pepponi R et al (2014) Expression, pharmacology and functional activity of adenosine A1 receptors in genetic models of Huntington's disease. Neurobiol Dis 71:193–204
Ferré S, Herrera-Marschitz M, Grabowska-Andén M et al (1991) Postsynaptic dopamine/adenosine interaction:I. Adenosine analogues inhibit dopamine D2-mediated behaviour in short-term reserpinized mice. Eur J Pharmacol 192:25–30
Ferré S, O'Connor WT, Fuxe K et al (1993) The striopallidal neuron: a main locus for adenosine-dopamine interactions in the brain. J Neurosci 13:5402–5406
Ferré S, Popoli P, Giménez-Llort L et al (1994) Postsynaptic antagonistic interaction between adenosine A1 and dopamine D1 receptors. Neuroreport 6:73–76
Ferre S, O'Connor WT, Svenningsson P et al (1996) Dopamine D1 receptor-mediated facilitation of GABAergic neurotransmission in the rat strioentopenduncular pathway and its modulation by adenosine A1 receptor-mediated mechanisms. Eur J Neurosci 8:1545–1553
Ferré S, Fredholm BB, Morelli M et al (1997) Adenosine–dopamine receptor–receptor interactions as an integrative mechanism in the basal ganglia. Trends Neurosci 20:482–487
Ferré S, Agnati LF, Ciruela F et al (2007) Neurotransmitter receptor heteromers and their integrative role in 'local modules': the striatal spine module. Brain Res Rev 55:55–67
Ferré S, Bonaventura J, Tomasi D et al (2016) Allosteric mechanisms within the adenosine A2A-dopamine D2 receptor heterotetramer. Neuropharmacology 104:154–160
Ferré S, Quiroz C, Guitart X et al (2017) Pivotal role of adenosine neurotransmission in restless legs syndrome. Front Neurosci 11:722
Fink JS, Kalda A, Ryu H et al (2004) Genetic and pharmacological inactivation of the adenosine A2A receptor attenuates 3-nitropropionic acid-induced striatal damage. J Neurochem 88(3):538–544
Finkbeiner S, Mitra S (2008) The ubiquitin-proteasome pathway in Huntington's disease. ScientificWorldJournal 8:421–433
Galluzzo M, Pintor A, Pezzola A et al (2008) Behavioural and neurochemical characterization of the adenosine. A2A receptor antagonist ST1535 Eur J Pharmacol 579(1–3):149–152
Gauthier LR, Charrin BC, Borrell-Pages M et al (2004) Huntingtin controls neurotrophic support and survival of neurons by enhancing BDNF vesicular transport along microtubules. Cell 118:127–138
Gelman A, Rawet-Slobodkin M, Elazar Z (2015) Huntingtin facilitates selective autophagy. Nat Cell Biol 17(3):214–215
Gerfen CR (2004) Basal ganglia. In: Paxinos G (ed) The rat nervous system. Elsevier Academic Press, Amsterdam, pp 445–508
Gharami K, Xie Y, An JJ et al (2008) Brain-derived neurotrophic factor over-expression in the forebrain ameliorates Huntington's disease phenotypes in mice. J Neurochem 105:369–379
Gianfriddo M, Melani A, Turchi D et al (2004) Adenosine and glutamate extracellular concentrations and mitogen-activated protein kinases in the striatum of Huntington transgenic mice.

Selective antagonism of adenosine A2A receptors reduces transmitter outflow. Neurobiol Dis 17:77–88
Ginés S, Hillion J, Torvinen M et al (2000) Dopamine D1 and adenosine A1 receptors form functionally interacting heteromeric complexes. Proc Natl Acad Sci U S A 97:8606–8611
Giralt A, Friedman HC, Caneda-Ferron B et al (2010) BDNF regulation under GFAP promoter provides engineered astrocytes as a new approach for long-term protection in Huntington's disease. Gene Ther 17:1294–1308
Glass M, Dragunow M, Faull RL (2000) The pattern of neurodegeneration in Huntington's disease: a comparative study of cannabinoid, dopamine, adenosine and GABA(A) receptor alterations in the human basal ganglia in Huntington's disease. Neuroscience 97:505–519
Godin JD, Colombo K, Molina-Calavita M et al (2010) Huntingtin is required for mitotic spindle orientation and mammalian neurogenesis. Neuron 67:392–406
Goldberg AL (2003) Protein degradation and protection against misfolded or damaged proteins. Nature 426(6968):895–899
Gourfinkel-An I, Cancel G, Trottier Y et al (1997) Differential distribution of the normal and mutated forms of huntingtin in the human brain. Ann Neurol 42:712–719
Gu M, Gash MT, Mann VM et al (1996) Mitochondrial defect in Huntington's disease caudate nucleus. Ann Neurol 39:385–389
Guidetti P, Luthi-Carter RE, Augood SJ et al (2004) Neostriatal and cortical quinolinate levels are increased in early grade Huntington's disease. Neurobiol Dis 17:455–461
Guidetti P, Bates GP, Graham RK et al (2006) Elevated brain 3-hydroxykynurenine and quinolinate levels in Huntington disease mice. Neurobiol Dis 23:190–197
Guitart X, Bonaventura J, Rea W et al (2016) Equilibrative nucleoside transporter ENT1 as a biomarker of Huntington disease. Neurobiol Dis 96:47–53
Guitart X, Chern Y, Ferré S (2017) Targeting the equilibrative nucleoside transporter ENT1 in Huntington disease. Oncotarget 8:12550–12551
Guo X, Disatnik MH, Monbureau M et al (2013) Inhibition of mitochondrial fragmentation diminishes Huntington's disease-associated neurodegeneration. J Clin Invest 123(12):5371–5388
Gusella JF, MacDonald ME (2006) Huntington's disease: seeing the pathogenic process through a genetic lens. Trends Biochem Sci 31(9):533–540
Hershko A, Ciechanover A (1998) The ubiquitin system. Annu Rev Biochem 67:425–479. https://doi.org/10.1146/annurev.biochem.671425
Hillion J, Canals M, Torvinen M et al (2002) Coaggregation, cointernalization, and codesensitization of adenosine A2A receptors and dopamine D2 receptors. J Biol Chem 277:18091–11807
Holschbach MH, Olsson RA, Bier D et al (2002) Synthesis and evaluation of no-carrier-added 8-cyclopentyl-3-(3-[(18)F]fluoropropyl)-1-propylxanthine ([(18)F]CPFPX): a potent and selective A(1)-adenosine receptor antagonist for in vivo imaging. J Med Chem 45:5150–5156
Hsiao HY, Chern Y (2010) Targeting glial cells to elucidate the pathogenesis of Huntington's disease. Mol Neurobiol 41(2–3):248–255
Hsiao HY, Chen YC, Chen HM et al (2013) A critical role of astrocyte-mediated nuclear factor-kappaB-dependent inflammation in Huntington's disease. Hum Mol Genet 22(9):1826–1842
Hsiao HY, Chiu FL, Chen CM et al (2014) Inhibition of soluble tumor necrosis factor is therapeutic in Huntington's disease. Hum Mol Genet 23(16):4328–4344
Hsiao HY, Chen YC, Huang C (2015) Aberrant astrocytes impair vascular reactivity in Huntington disease. Ann Neurol 78(2):178–192
Huang QY, Wei C, Yu L et al (2006) Adenosine A2A receptors in bone marrow-derived cells but not in forebrain neurons are important contributors to 3-nitropropionic acid-induced striatal damage as revealed by cell-type-selective inactivation. J Neurosci 26:11371–11378
Huang NK, Lin JH, Lin JT et al (2011a) A new drug design targeting the adenosinergic system for Huntington's disease. PLoS One 6:e20934

Huang CL, Yang JM, Wang KC et al (2011b) Gastrodia elata prevents huntingtin aggregations through activation of the adenosine A(2)A receptor and ubiquitin proteasome system. J Ethnopharmacol 138(1):162–168

Huang B, Wei W, Wang G et al (2015) Mutant huntingtin downregulates myelin regulatory factor-mediated myelin gene expression and affects mature oligodendrocytes. Neuron 85(6):1212–1226

Ishiwata K, Ogi N, Hayakawa N et al (2002) Adenosine A2A receptor imaging with [11C]KF18446 PET in the rat brain after quinolinic acid lesion: comparison with the dopamine receptor imaging. Ann Nucl Med 16:467–475

Jacobson KA, Balasubramanian R, Deflorian F et al (2012) G protein-coupled adenosine (P1) and P2Y receptors:ligand design and receptor interactions. Purinergic Signal 8(3):419–436

Jacquard C, Trioulier Y, Cosker F et al (2006) Brain mitochondrial defects amplify intracellular [Ca2+] rise and neurodegeneration but not Ca2+ entry during NMDA receptor activation. FASEB J 20:1021–1023

Jenkins BG, Rosas HD, Chen YC et al (1998) 1H NMR spectroscopy studies of Huntington's disease:correlations with CAG repeat numbers. Neurology 50:1357–1365

Jeon J, Kim W, Jang J et al (2016) Gene therapy by proteasome activator, PA28gamma, improves motor coordination and proteasome function in Huntington's disease YAC128 mice. Neuroscience 324:20–28

Jia H, Kast RJ, Steffan JS et al (2012) Selective histone deacetylase (HDAC) inhibition imparts beneficial effects in Huntington's disease mice: implications for the ubiquitin-proteasomal and autophagy systems. Hum Mol Genet 21(24):5280–5293

Jiang R, Diaz-Castro B, Looger LL et al (2016) Dysfunctional calcium and glutamate signaling in striatal astrocytes from Huntington's disease model mice. J Neurosci 36(12):3453–3470

Ju TC, Chen HM, Lin JT et al (2011) Nuclear translocation of AMPK-alpha1 potentiates striatal neurodegeneration in Huntington's disease. J Cell Biol 194(2):209–227

Kao YH, Lin MS, Chen CM, Wu YR, Chen HM, Lai HL, Chern Y, Lin CJ (2017) Targeting ENT1 and adenosine tone for the treatment of Huntington's disease. Hum Mol Genet 26:467–478

Karcz-Kubicha M, Antoniou K, Terasmaa A et al (2003) Involvement of adenosine A1 and A2A receptors in the motor effects of caffeine after its acute and chronic administration. Neuropsychopharmacology 28:1281–1291

Khanapur S, Waarde A, Ishiwata K et al (2014) Adenosine A(2A) receptor antagonists as positron emission tomography (PET) tracers. Curr Med Chem 21:312–328

Kim W, Seo H (2014) Baclofen, a GABAB receptor agonist, enhances ubiquitin-proteasome system functioning and neuronal survival in Huntington's disease model mice. Biochem Biophys Res Commun 443(2):706–711

Kim J, Moody JP, Edgerly CK et al (2010) Mitochondrial loss, dysfunction and altered dynamics in Huntington's disease. Hum Mol Genet 19:3919–3935

Kiriyama Y, Nochi H (2015) The function of autophagy in neurodegenerative diseases. Int J Mol Sci 16(11):26797–26812

Koga H, Martinez-Vicente M, Arias E et al (2011) Constitutive upregulation of chaperone-mediated autophagy in Huntington's disease. J Neurosci 31(50):18492–18505

Kopito RR (2000) Aggresomes, inclusion bodies and protein aggregation. Trends Cell Biol 10(12):524–530

Lee CF, Chern Y (2014) Adenosine receptors and Huntington's disease. Int Rev Neurobiol 119:195–232

Lee CY, Cantle JP, Yang XW (2013a) Genetic manipulations of mutant huntingtin in mice: new insights into Huntington's disease pathogenesis. FEBS J 280(18):4382–4394

Lee W, Reyes RC, Gottipati MK et al (2013b) Enhanced Ca(2+)-dependent glutamate release from astrocytes of the BACHD Huntington's disease mouse model. Neurobiol Dis 58:192–199

Li SH, Cheng AL, Zhou H et al (2002) Interaction of Huntington disease protein with transcriptional activator Sp1. Mol Cell Biol 22:1277–1287

Li JY, Popovic N, Brundin P (2005) The use of the R6 transgenic mouse models of Huntington's disease in attempts to develop novel therapeutic strategies. NeuroRx 2(3):447–464
Li W, Silva HB, Real J et al (2015) Inactivation of adenosine A2A receptors reverses working memory deficits at early stages of Huntington's disease models. Neurobiol Dis 79:70–80
Lievens JC, Woodman B, Mahal A et al (2001) Impaired glutamate uptake in the R6 Huntington's disease transgenic mice. Neurobiol Dis 8:807–821
Lin CH, Tallaksen-Greene S, Chien WM et al (2001) Neurological abnormalities in a knock-in mouse model of Huntington's disease. Hum Mol Genet 10:137–144
Lin JT, Chang WC, Chen HM et al (2013) Regulation of feedback between protein kinase A and the proteasome system worsens Huntington's disease. Mol Cell Biol 33(5):1073–1084
Liot G, Valette J, Pépin J, Flament J, Brouillet E (2017) Energy defects in Huntington's disease: why "in vivo" evidence matters. Biochem Biophys Res Commun 483(4):1084–1095
Liu Y, Hettinger CL, Zhang D et al (2014) Sulforaphane enhances proteasomal and autophagic activities in mice and is a potential therapeutic reagent for Huntington's disease. J Neurochem 129(3):539–547
Luthi-Carter R, Strand A, Peters NL et al (2000) Decreased expression of striatal signaling genes in a mouse model of Huntington's disease. Hum Mol Genet 9(9):1259–1271
Lynch G, Kramar EA, Rex CS et al (2007) Brain-derived neurotrophic factor restores synaptic plasticity in a knock-in mouse model of Huntington's disease. J Neurosci 27:4424–4434
Maglione V, Cannella M, Martino T et al (2006) The platelet maximum number of A2A-receptor binding sites (Bmax) linearly correlates with age at onset and CAG repeat expansion in Huntington's disease patients with predominant chorea. Neurosci Lett 393:27–30
Mangiarini L, Sathasivam K, Seller M et al (1996) Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. Cell 87(3):493–506
Martin DD, Ladha S, Ehrnhoefer DE et al (2015) Autophagy in Huntington disease and huntingtin in autophagy. Trends Neurosci 38(1):26–35
Martinez-Mir MI, Probst A, Palacios JM (1991) Adenosine A2 receptors: selective localization in the human basal ganglia and alterations with disease. Neuroscience 42(3):697–706
Martinez-Vicente M, Talloczy Z, Wong E et al (2010) Cargo recognition failure is responsible for inefficient autophagy in Huntington's disease. Nat Neurosci 13(5):567–576
Martire A, Calamandrei G, Felici F et al (2007) Opposite effects of the A2A receptor agonist CGS21680 in the striatum of Huntington's disease versus wild-type mice. Neurosci Lett 417(1):78–83
Martire A, Ferrante A, Potenza RL et al (2010) Remodeling of striatal NMDA receptors by chronic A(2A) receptor blockade in Huntington's disease mice. Neurobiol Dis 37:99–105
Martire A, Pepponi R, Domenici MR et al (2013) BDNF prevents NMDA-induced toxicity in models of Huntington's disease:the effects are genotype specific and adenosine A2A receptor is involved. J Neurochem 125(2):225–235
Matusch A, Saft C, Elmenhorst D et al (2014) Cross sectional PET study of cerebral adenosine A_1 receptors in premanifest and manifest Huntington's disease. Eur J Nucl Med Mol Imaging 41:1210–1220
McColgan P, Tabrizi SJ (2018) Huntington's disease: a clinical review. Eur J Neurol 25(1):24–34
Menalled LB (2005) Knock-in mouse models of Huntington's disease. NeuroRx 2(3):465–470
Menalled LB, Chesselet MF (2002) Mouse models of Huntington's disease. Trends Pharmacol Sci 23(1):32–39
Menalled LB, Kudwa AE, Miller S et al (2012) Comprehensive behavioral and molecular characterization of a new knock-in mouse model of Huntington's disease: zQ175. PLoS One 7(12):e49838
Messam CA, Greene JG, Greenamyre JT et al (1995) Intrastriatal injections of the succinate dehydrogenase inhibitor, malonate, cause a rise in extracellular amino acids that is blocked by MK-801. Brain Res 684(2):221–224

Meyer PT, Elmenhorst D, Boy C et al (2007) Effect of aging on cerebral A1 adenosine receptors: A [18F]CPFPX PET study in humans. Neurobiol Aging 28:1914–1924
Mievis S, Blum D, Ledent C (2011) A2A receptor knockout worsens survival and motor behaviour in a transgenic mouse model of Huntington's disease. Neurobiol Dis 41(2):570–576
Milakovic T, Johnson GV (2005) Mitochondrial respiration and ATP production are significantly impaired in striatal cells expressing mutant huntingtin. J Biol Chem 280:30773–30782
Milnerwood AJ, Gladding CM, Pouladi MA et al (2010) Early increase in extrasynaptic NMDA receptor signaling and expression contributes to phenotype onset in Huntington's disease mice. Neuron 65:178–190
Moresco RM, Todde S, Belloli S et al (2005) In vivo imaging of adenosine A2A receptors in rat and primate brain using [11C]SCH442416. Eur J Nucl Med Mol Imaging 32:405–413
Nixon RA (2013) The role of autophagy in neurodegenerative disease. Nat Med 19(8):983–997
Nucifora FC Jr, Sasaki M, Peters MF et al (2001) Interference by huntingtin and atrophin-1 with cbp-mediated transcription leading to cellular toxicity. Science 291:2423–2428
Orrú M, Zanoveli JM, Quiroz C et al (2011) Functional changes in postsynaptic adenosine A(2A) receptors during early stages of a rat model of Huntington disease. Exp Neurol 232:76–80
Ortega Z, Lucas JJ (2014) Ubiquitin-proteasome system involvement in Huntington's disease. Front Mol Neurosci 7:77
Panov AV, Gutekunst CA, Leavitt BR et al (2002) Early mitochondrial calcium defects in Huntington's disease are a direct effect of polyglutamines. Nat Neurosci 5:731–736
Parkinson FE, Damaraju VL, Graham K et al (2011) Molecular biology of nucleoside transporters and their distributions and functions in the brain. Curr Top Med Chem 11:948–972
Pascual O, Casper KB, Kubera C et al (2005) Astrocytic purinergic signaling coordinates synaptic networks. Science 310:113–116
Paul S, Elsinga PH, Ishiwata K et al (2011) Adenosine A(1) receptors in the central nervous system:their functions in health and disease, and possible elucidation by PET imaging. Curr Med Chem 18:4820–4835
Peng Q, Masuda N, Jiang M et al (2008) The antidepressant sertraline improves the phenotype, promotes neurogenesis and increases BDNF levels in the R6/2 Huntington's disease mouse model. Exp Neurol 210:154–163
Popoli P, Betto P, Reggio R et al (1995) Adenosine A2A receptor stimulation enhances striatal extracellular glutamate levels in rats. Eur J Pharmacol 287:215–217
Popoli P, Pintor A, Domenici MR et al (2002) Blockade of striatal adenosine A2A receptor reduces, through a presynaptic mechanism, quinolinic acid-induced excitotoxicity: possible relevance to neuroprotective interventions in neurodegenerative diseases of the striatum. J Neurosci 22:1967–1975
Popoli P, Blum D, Domenici MR et al (2008) A critical evaluation of adenosine A2A receptors as potentially "druggable" targets in Huntington's disease. Curr Pharm Des 14:1500–1511
Pouladi MA, Morton AJ, Hayden MR (2013) Choosing an animal model for the study of Huntington's disease. Nat Rev Neurosci 14(10):708–721
Powers WJ, Videen TO, Markham J et al (2007) Selective defect of in vivo glycolysis in early Huntington's disease striatum. Proc Natl Acad Sci U S A 104(8):2945–2949
Quiroz C, Luján R, Uchigashima M et al (2009) Key modulatory role of presynaptic adenosine A2A receptors in cortical neurotransmission to the striatal direct pathway. ScientificWorldJournal 9:1321–1344
Quiroz C, Orrú M, Rea W et al (2016) Local control of extracellular dopamine levels in the medial nucleus Accumbens by a glutamatergic projection from the Infralimbic cortex. J Neurosci 36:851–859
Reggio R, Pezzola A, Popoli P (1999) The intrastratial injection of an adenosine A(2) receptor antagonist prevents frontal cortex EEG abnormalities in a rat model of Huntington's disease. Brain Res 831(1–2):315–318

Reiner A, Medina L, Veenman CL (1998) Structural and functional evolution of the basal ganglia in vertebrates. Brain Res Brain Res Rev 28:235–285
Rice ME, Patel JC, Cragg SJ (2011) Dopamine release in the basal ganglia. Neuroscience 198:112–137
Rogers PJ, Hohoff C, Heatherley SV et al (2010) Association of the anxiogenic and alerting effects of caffeine with ADORA2A and ADORA1 polymorphisms and habitual level of caffeine consumption. Neuropsychopharmacology 35:1973–1983
Ross CA, Tabrizi SJ (2011) Huntington's disease: from molecular pathogenesis to clinical treatment. Lancet Neurol 10:83–98
Roussakis AA, Piccini P (2015) PET imaging in Huntington's disease. J Huntington's Dis 4:287–296
Rui YN, Xu Z, Patel B et al (2015) Huntingtin functions as a scaffold for selective macroautophagy. Nat Cell Biol 17(3):262–275
Sakata M, Ishibashi K, Imai M et al (2017) Initial evaluation of an adenosine A(2A) receptor ligand, (11)C-preladenant, in healthy human subjects. J Nucl Med 58:1464–1470
Sarkar S, Perlstein EO, Imarisio S et al (2007) Small molecules enhance autophagy and reduce toxicity in Huntington's disease models. Nat Chem Biol 3(6):331–338
Saudou F, Humbert S (2016) The biology of huntingtin. Neuron 89(5):910–296
Scattoni ML, Valanzano A, Pezzola A et al (2007) Adenosine A2A receptor blockade before striatal excitotoxic lesions prevents long term behavioural disturbances in the quinolinic rat model of Huntington's disease. Behav Brain Res 176:216–221
Schiffmann SN, Vanderhaeghen JJ (1993) Adenosine A2 receptors regulate the gene expression of striatopallidal and striatonigral neurons. J Neurosci 13:1080–1087
Seo H, Sonntag KC, Isacson O (2004) Generalized brain and skin proteasome inhibition in Huntington's disease. Ann Neurol 56(3):319–328
Seo H, Sonntag KC, Kim W et al (2007) Proteasome activator enhances survival of Huntington's disease neuronal model cells. PLoS One 2(2):e238
Seong IS, Ivanova E, Lee JM, Choo YS, Fossale E, Anderson M, Gusella JF, Laramie JM, Myers RH, Lesort M et al (2005) HD CAG repeat implicates a dominant property of huntingtin in mitochondrial energy metabolism. Hum Mol Genet 14:2871–2880
Shear DA, Dong J, Gundy CD et al (1998) Comparison of intrastriatal injections of quinolinic acid and 3-nitropropionic acid for use in animal models of Huntington's disease. Prog Neuro-Psychopharmacol Biol Psychiatry 22(7):1217–1240
Shehadeh J, Fernandes HB, Zeron Mullins MM et al (2006) Striatal neuronal apoptosis is preferentially enhanced by NMDA receptor activation in YAC transgenic mouse model of Huntington disease. Neurobiol Dis 21:392–403
Shin JY, Fang ZH, Yu ZX et al (2005) Expression of mutant huntingtin in glial cells contributes to neuronal excitotoxicity. J Cell Biol 171(6):1001–1012
Shinohara M, Saitoh M, Nishizawa D et al (2013) ADORA2A polymorphism predisposes children to encephalopathy with febrile status epilepticus. Neurology 80:1571–1576
Shirendeb U, Reddy AP, Manczak M et al (2011) Abnormal mitochondrial dynamics, mitochondrial loss and mutant huntingtin oligomers in Huntington's disease: implications for selective neuronal damage. Hum Mol Genet 20:1438–1455
Simmons DA, Rex CS, Palmer L et al (2009) Up-regulating BDNF with an ampakine rescues synaptic plasticity and memory in Huntington's disease knockin mice. Proc Natl Acad Sci U S A 106:4906–4911
Simonin C, Duru C, Salleron J et al (2013) Association between caffeine intake and age at onset in Huntington's disease. Neurobiol Dis 58:179–182
Sokoloff P, Le Foll B (2017) The dopamine D3 receptor, a quarter century later. Eur J Neurosci 45:2–19
Solinas M, Ferré S, You ZB et al (2002) Caffeine induces dopamine and glutamate release in the shell of the nucleus accumbens. J Neurosci 22:6321–6324

Stack EC, Dedeoglu A, Smith KM et al (2007) Neuroprotective effects of synaptic modulation in Huntington's disease R6/2 mice. J Neurosci 27:12908–12915
Steffan JS, Kazantsev A, Spasic-Boskovic O et al (2000) The Huntington's disease protein interacts with p53 and CREB-binding protein and represses transcription. Proc Natl Acad Sci U S A 97:6763–6768
Stopschinski BE, Diamond MI (2017) The prion model for progression and diversity of neurodegenerative diseases. Lancet Neurol 16(4):323–332
Sun Y, Savanenin A, Reddy PH et al (2001) Polyglutamine-expanded huntingtin promotes sensitization of N-methyl-D-aspartate receptors via post-synaptic density 95. J Biol Chem 276:24713–24718
Tabrizi SJ, Cleeter MW, Xuereb J et al (1999) Biochemical abnormalities and excitotoxicity in Huntington's disease brain. Ann Neurol 45:25–32
Taherzadeh-Fard E, Saft C, Wieczorek S et al (2010) Age at onset in Huntington's disease: replication study on the associations of ADORA2A, HAP1 and OGG1. Neurogenetics 11:435–439
Tarditi A, Camurri A, Varani K et al (2006) Early and transient alteration of adenosine A2A receptor signaling in a mouse model of Huntington disease. Neurobiol Dis 23:44–53
Tebano MT, Pintor A, Frank C et al (2004) Adenosine A2A receptor blockade differentially influences excitotoxic mechanisms at pre- and postsynaptic sites in the rat striatum. J Neurosci Res 77:100–107
The Huntington's Disease Collaborative Research Group (1993) A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell 72:971–983
Tong X, Ao Y, Faas GC et al (2014) Astrocyte Kir41 ion channel deficits contribute to neuronal dysfunction in Huntington's disease model mice. Nat Neurosci 17(5):694–703
Trottier Y, Devys D, Imbert G et al (1995) Cellular localization of the Huntington's disease protein and discrimination of the normal and mutated form. Nat Genet 10:104–110
Tyebji S, Saavedra A, Canas PM et al (2015) Hyperactivation of D1 and A2A receptors contributes to cognitive dysfunction in Huntington's disease. Neurobiol Dis 74:41–57
van Waarde A, Dierckx RAJO, Zhou X et al (2018) Potential therapeutic applications of adenosine A(2A) receptor ligands and opportunities for A(2A) receptor imaging. Med Res Rev 38:5–56
Varani K, Rigamonti D, Sipione S et al (2001) Aberrant amplification of A(2A) receptor signaling in striatal cells expressing mutant huntingtin. FASEB J 15:1245–1247
Varani K, Bachoud-Levi AC, Mariotti C et al (2007) Biological abnormalities of peripheral A(2A) receptors in a large representation of polyglutamine disorders and Huntington's disease stages. Neurobiol Dis 27:36–43
Villar-Menéndez I, Blanch M, Tyebji S et al (2013) Increased 5-methylcytosine and decreased 5-hydroxymethylcytosine levels are associated with reduced striatal A2AR levels in Huntington's disease. NeuroMolecular Med 15:295–309
von Hörsten S, Schmitt I, Nguyen HP et al (2003) Transgenic rat model of Huntington's disease. Hum Mol Genet 12:617–624
von Lubitz DK, Dambrosia JM, Kempski O et al (1988) Cyclohexyl adenosine protects against neuronal death following ischemia in the CA1 region of gerbil hippocampus. Stroke 19:1133–1139
Vonsattel JP (2008) Huntington disease models and human neuropathology: similarities and differences. Acta Neuropathol 115:55–69
Vonsattel JP, DiFiglia M (1998) Huntington disease. J Neuropathol Exp Neurol 57:369–384
Walker FO (2007) Huntington's disease. Lancet 369:218–228
Wang J, Wang CE, Orr A et al (2008) Impaired ubiquitin-proteasome system activity in the synapses of Huntington's disease mice. J Cell Biol 180(6):1177–1189
Wang L, Lin F, Wang J et al (2012) Expression of mutant N-terminal huntingtin fragment (htt552-100Q) in astrocytes suppresses the secretion of BDNF. Brain Res 1449:69–82
Weiss A, Trager U, Wild EJ et al (2012) Mutant huntingtin fragmentation in immune cells tracks Huntington's disease progression. J Clin Invest 122(10):3731–3736

Weydt P, Pineda VV, Torrence AE et al (2006) Thermoregulatory and metabolic defects in Huntington's disease transgenic mice implicate PGC-1alpha in Huntington's disease neurodegeneration. Cell Metab 4:349–362

Williams A, Sarkar S, Cuddon P et al (2008) Novel targets for Huntington's disease in an mTOR-independent autophagy pathway. Nat Chem Biol 4(5):295–305

Wojtowicz AM, Dvorzhak A, Semtner M et al (2013) Reduced tonic inhibition in striatal output neurons from Huntington mice due to loss of astrocytic GABA release through GAT-3. Front Neural Circuits 7:188

Wong HK, Bauer PO, Kurosawa M et al (2008) Blocking acid-sensing ion channel 1 alleviates Huntington's disease pathology via an ubiquitin-proteasome system-dependent mechanism. Hum Mol Genet 17(20):3223–3235

Wu LL, Fan Y, Li S et al (2010) Huntingtin-associated protein-1 interacts with pro-brain-derived neurotrophic factor and mediates its transport and release. J Biol Chem 285:5614–5623

Xie Y, Hayden MR, Xu B (2010) BDNF overexpression in the forebrain rescues Huntington's disease phenotypes in YAC128 mice. J Neurosci 30:14708–14718

Yu ZX, Li SH, Evans J et al (2003) Mutant huntingtin causes context-dependent neurodegeneration in mice with Huntington's disease. J Neurosci 23(6):2193–2202

Zeron MM, Hansson O, Chen N et al (2002) Increased sensitivity to N-methyl-D-aspartate receptor-mediated excitotoxicity in a mouse model of Huntington's disease. Neuron 33:849–860

Zheng Q, Huang T, Zhang L et al (2016) Dysregulation of ubiquitin-proteasome system in neurodegenerative diseases. Front Aging Neurosci 8:303

Zhou X, Khanapur S, de Jong JR et al (2017a) In vivo evaluation of [(11)C]preladenant positron emission tomography for quantification of adenosine A(2A) receptors in the rat brain. J Cereb Blood Flow Metab 37:577–589

Zhou X, Boellaard R, Ishiwata K et al (2017b) In vivo evaluation of (11)C-preladenant for PET imaging of adenosine A(2A) receptors in the conscious monkey. J Nucl Med 58:762–767

Zuccato C, Cattaneo E (2007) Role of brain-derived neurotrophic factor in Huntington's disease. Prog Neurobiol 81:294–330

Zuccato C, Cattaneo E (2009) Brain-derived neurotrophic factor in neurodegenerative diseases. Nat Rev Neurol 5:311–322

Zuccato C, Ciammola A, Rigamonti D et al (2001) Loss of huntingtin-mediated BDNF gene transcription in Huntington's disease. Science 293:493–498

Zuccato C, Tartari M, Crotti A et al (2003) Huntingtin interacts with REST/NRSF to modulate the transcription of NRSE-controlled neuronal genes. Nat Genet 35:76–83

Zuccato C, Valenza M, Cattaneo E (2010) Molecular mechanisms and potential therapeutical targets in Huntington's disease. Physiol Rev 90:905–981

Zuchora B, Turski WA, Wielosz M et al (2001) Protective effect of adenosine receptor agonists in a new model of epilepsy--seizures evoked by mitochondrial toxin, 3-nitropropionic acid, in mice. Neurosci Lett 305:91–94