Chapter 71

Epilepsy in Other Neurodegenerative Disorders: Huntington's and Parkinson's Diseases

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INTRODUCTION

Huntington's (HD) and Parkinson's diseases (PD) belong to a group of neurological disorders characterized by neuronal degeneration. In HD, striatal medium-sized spiny neurons (MSNs) are the most vulnerable, followed by cortical pyramidal neurons (Vonsattel and DiFiglia, 1998). In PD, dopamine (DA)-producing cells are the most susceptible to degeneration, but cells in the locus coeruleus and other regions also degenerate (Braak et al., 2002; Del Tredici and Braak, 2013). Generally speaking, HD and PD associate with aging, although juvenile forms also occur.

HD is caused by an unstable mutation in the short arm of chromosome 4. The mutation consists of an expansion of CAG (coding for glutamine) repeats in the *HTT* gene. When the number of repeats exceeds 36, patients will likely develop the symptoms of HD, consisting of abnormal dance-like movements (chorea), cognitive deficits, and psychiatric disturbances (Bates et al., 2002). Thus far, no effective treatment has been found and the disease is always fatal. DA-depleting drugs, for example, tetrabenazine (TBZ), have been used effectively to reduce chorea, but disease progression is not affected. In contrast, most cases of PD are idiopathic (sporadic) and genetics probably play a secondary role, except in a low percentage of cases caused by known genetic mutations. In general, HD and PD do not associate with epilepsy. However, comorbidity can occur in early-onset HD, a severe form of the disease occurring in children and adolescents carrying a very large number of CAG repeats. Early epidemiological studies indicated that epilepsy rarely occurs in PD patients and it was believed by some that PD may confer resistance to seizures. In fact, based on recent evidence, seizures are more common in PD patients than in the general age-matched population.

The incidence of epilepsy is age-dependent with peaks in early and late periods of life (Hauser, 1997). Multiple studies have demonstrated that the first year of life is a critical period for the development of seizures (Kramer, 1999; Moshe, 2000). This is probably due to the high sensitivity of young brains to environmental insults (e.g., temperature, as in febrile seizures). Likewise, brain malformations, such as cortical dysplasia (CD) usually culminate in epileptogenesis. According to our studies, about 50% of pediatric surgery cases are <2 years of age, and the anatomical substrate in most cases is CD (Lerner et al., 2009). Absence seizures and seizures caused by other pathologies, such as tuberous sclerosis complex and Rasmussen's encephalitis, also are common in infancy. After 10 years of age, the likelihood of developing epilepsy subsides, remaining stable for several decades, peaking again later in life (>60 years) when neurodegenerative diseases become more prevalent. Based on these facts, one might expect that in late-onset neurodegenerative diseases, the likelihood of developing epileptic seizures should increase. However, as shown later, this is not necessarily the case, and the occurrence of epileptic seizures largely depends on the specific neurological disease.

Genetic and toxin animal models of HD and PD have been developed and have helped understand underlying mechanisms (Levine et al., 2004). In this chapter we provide a review of the literature on the association between HD and PD with epilepsy, and discuss possible mechanisms leading to seizure activity in early-onset HD, and in sporadic or genetic forms of PD.

Models of Seizures and Epilepsy. http://dx.doi.org/10.1016/B978-0-12-804066-9.00073-0

HUNTINGTON'S DISEASE

General Description

Two main types of HD have been described, early-onset or juvenile HD and adult-onset HD (Table 71.1). Early-onset HD is extremely rare (less than 10% of cases), has a rapid progression, and preferentially associates with paternal transmission (Telenius et al., 1993). Early-onset HD has been further divided into childhood-onset and adolescence-onset (Letort and Gonzalez-Alegre, 2013). Symptom onset and severity are determined by the number of CAG repeats, as well as various genetic modifiers. In general, the greater the number of CAG repeats the earlier HD onset (Andrew et al., 1993; Stine et al., 1993). Also, the type and severity of symptoms differ between both HD types. In juvenile HD (Westphal variant), chorea rarely occurs, and rigidity, similar to that found in PD, is observed instead (Jervis, 1963). In contrast, in adult-onset HD, chorea is a telltale sign. Nevertheless, it is important that, as the disease progresses, choreatic movements tend to subside, being replaced by bradykinesia. Moreover, the evidence from HD patients indicates that increased DA release induces chorea, while a reduction in DA leads to akinesia (Bird, 1980; Spokes, 1980). In consequence, DA-depleting drugs have been used to reduce chorea, whereas L-DOPA has been used to treat bradykinesia and akinesia, not only in PD, but also in the rigid or akinetic form of HD (Racette and Perlmutter, 1998). Interestingly, one of the undesirable side-effects of L-DOPA is the occurrence of dyskinesias that, in a broad sense, resemble choreatic movements. However, the classification of HD in the group of hyperkinetic disorders is not completely accurate as, depending on the stage of the disease and the HD type, hypokinesia and rigidity may occur.

In general, HD and epilepsy do not associate except in severe, early-onset cases. In juvenile HD, particularly in childhood-onset (65–250 CAG repeats), epileptic seizures are a common symptom, whereas in adult-onset HD seizures almost never occur. Besides the epileptic syndrome, children with HD may display mental retardation, hyperactivity, and aggressive behavior. Some of these children also have microcephaly, suggesting a developmental rather than a neurodegenerative disorder as in adults (Gonzalez-Alegre and Afifi, 2006; Letort and Gonzalez-Alegre, 2013). With disease progression, dystonia, rigidity, and chorea may occur. Symptoms in adolescence-onset HD (45–80 CAG repeats) are somewhere in between those observed in children and those observed in adults.

How and why a common mutation evolves into different symptomatology is unknown. However, age of onset can offer some clues, and the fact that younger brains are more susceptible to epilepsy could be one of the main reasons. Another possible cause is the spread of neuronal degeneration. It is possible that in juvenile HD structures besides the striatum, for example, cerebral cortex, hippocampus, and cerebellum, are more affected than in adult-onset HD. Accordingly, studies of HD pathology have emphasized the

TABLE 71.1 Epilepsy in Human HD and PD

Disease Type	Etiology	Age at Symptoms Onset	Phenotype	Seizure Type
Huntington's Disease				
Childhood onset	CAG repeat (65–250) expansion in the *HTT* gene	≤20 years	Rigidity, aggressive behavior, cognitive impairment	Generalized tonic–clonic and myoclonic seizures. Less common, complex partial seizures and staring spells
Adolescence onset	CAG repeat (45–80) expansion in the *HTT* gene			
Adultonset	CAG repeat (≥36) expansion in the *HTT* gene	>20 years	Chorea, psychiatric and cognitive symptoms, decreased weight	No seizures
Parkinson's Disease				
Genetic	Dominant: α-syn and LRRK2; Recessive: Parkin, PRK7, PINK1, and SYNJ1	~60 years. Younger cases can occur	Tremor, rigidity, bradykinesia, loss of the sense of smell, cognitive impairment	Generalized tonic–clonic seizures (SYNJ1)
Idiopathic/sporadic (environmental causes)	Pesticide or herbicide	~60 years	Similar motor and nonmotor features as seen in genetic forms of PD	Generalized tonic–clonic seizures, partial complex seizures, and simple partial motor seizures

α-syn, Alpha-synuclein; LRRK2, Leucine-rich repeat kinase 2; PINK1, PTEN-induced putative kinase 1; PRK7, protein deglycase DJ-1 or PD protein 7; SYNJ1, synaptojanin 1.

association between main symptoms and cortical degeneration. Thus, motor symptoms are preferentially associated with motor cortical degeneration, whereas mood changes or psychiatric symptoms relate to reduced motor cortex, but increased anterior cingulate cell loss (Nana et al., 2014; Thu et al., 2010; Waldvogel et al., 2012). It could be that widespread cortical and hippocampal degeneration facilitates the generation of epileptic activity in young HD brains. Although thalamic degeneration also occurs, it is not as widespread or severe as it is in the cortex.

Animal Models of Huntington's Disease: Methods of Generation

Animal models of HD have helped elucidate underlying mechanisms of the disease (Table 71.2). Although toxin models were prevalent before the discovery of the HD mutation, they have been largely replaced by genetic models. Toxin models used intrastriatal injections of excitatory amino acids, for example, glutamate, kainate (KA), and quinolinate [QA, a selective *N*-methyl-D-aspartate (NMDA) receptor agonist], to replicate neuronal loss observed in HD (DiFiglia, 1990). While these models provided insights into disease pathology, they had important limitations in that they could not replicate the progressive nature of HD. After the discovery of the *HTT* mutation (The Huntington's Disease Collaborative Research Group, 1993), efforts concentrated on the generation of a reliable animal model that could replicate disease phenotype, pathology, and progression.

The first transgenic mouse model created, the R6/2, expresses a 63 amino acid N-terminal fragment of mutant huntingtin (mHtt) with ~150 CAG repeats and its symptomatology closely resembles juvenile HD (Bates and Murphy, 2002; Mangiarini et al., 1996). Not surprisingly, symptomatic mice (over 5–7 weeks of age) display epileptic seizures that are frequently a cause of death (around 13–15 weeks). A related model, the R6/1, with ~110 CAG repeats also displays a severe but more protracted form of HD. Besides transgenic fragment mouse models, full-length and knock-in models have been generated (Chang et al., 2015;

TABLE 71.2 Epilepsy in Animal Models of HD and PD

Animal Model	Etiology	Phenotype	Seizure Type
Toxin Models of Huntington's Disease			
Excitotoxic models	Intrastriatal injections of EAAs	Motor alterations resembling those seen in HD patients	Varies as a function of the EAA used and site of injection. Generalized tonic–clonic seizures
Transgenic Models of Huntington's Disease			
R6/1 and R6/2	N-terminal fragment of mHTT with ~110 CAG repeats (R6/1) or ~150 CAG repeats (R6/2)	Decreased coordination, decreased weight, tremors, abnormal gait, cognitive impairment	Ectopic theta activity, reduced delta power, and epileptic discharges. Partial and generalized tonic–clonic seizures
Monkey	Exon 1 of N-terminal fragment of mHTT with 67 amino acids and 29 CAG repeats	Chorea and dystonia	Generalized tonic–clonic seizures
YAC	Full human mHTT with 72 (YAC72) or 128 (YAC128) CAG repeats	Hypoactivity, deficit in motor coordination, and increased weight	Susceptibility to epilepsy has been observed but requires further studies
BAC mouse, sheep, and rat	Full human mHTT with 97 (BAC mouse), 73 (sheep), and 51 (rat) CAG repeats	Varies depending on the model but all show motor alterations	No seizures
Toxin Models of Parkinson's Disease			
Neurotoxin and pesticide or herbicide	Neurotoxin: 6-OHDA or MPTP Pesticide or herbicide: rotenone or paraquat	Motor alterations resembling PD phenotype. Severity varies depending on extent of damage (i.e., unilateral vs. bilateral)	Generalized tonic–clonic seizures occur in rats bilaterally injected with 6-OHDA
Genetic Models of Parkinson's Disease			
Parkin, DJ-1 and PINK1	Parkin model (deletion of exons). DJ-1 model (deletion of exons and part of the promoter). KD or KO of PINK1 gene. α-syn OE	Minor motor abnormalities but no DA neuron loss	No seizures

EAAs, excitatory amino acids; KD, knockdown; KO, knockout; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropiridine; OE, overexpressor; 6-OHDA, 6-hydroxydopamine.

Menalled, 2005; Menalled and Brunner, 2014). These are closer models of adult-onset HD and, for the most part, they do not present with seizures, similar to human HD. It has been reported that YAC mice (with 72 or 128 CAG repeats) can display epileptic activity. However, this could be caused by their genetic background as FVB mice are more susceptible to neuronal degeneration and epileptic seizures, such as those induced by high-frequency noise (Goelz et al., 1998) and, compared with C57BL/6 mice, these mice are more sensitive to excitotoxins (Schauwecker, 2002).

Rat, sheep, and minipig genetic models of HD exist, but epileptic activity has not been reported (Baxa et al., 2013; Huntington's Disease Sheep Collaborative Research et al., 2013; Morton and Howland, 2013; von Horsten et al., 2003). A colony of transgenic HD rhesus monkeys also has been established, and longitudinal studies have been performed (Yang et al., 2008). One particular monkey, expressing exon 1 of the N-terminal fragment with 67 amino acids and 29 CAG repeats (normal repeat length in monkeys is ~10 CAG repeats) developed facial chorea and dystonia at around 18 months, and had his first seizure episode at 24 months. In contrast, three monkeys carrying exons 1–10 of the N-terminal fragment, with 508 amino acids and approximately 67–72 CAG repeats, did not display chorea, and seizures were not observed (Chan et al., 2015). Because of the distinct genotype (different gene fragments, promoters, and levels of expression), a more aggressive form of HD, similar to juvenile HD, was predicted in the first monkey, whereas the other three monkeys were more similar to the adult form of HD. This model thus replicates the differential symptomatology of juvenile and adult-onset human HD.

Characteristics and Defining Features

The most common seizure types in human HD are; generalized tonic–clonic (grand mal), myoclonic, and, less commonly, complex partial seizures and staring spells (Cloud et al., 2012; Gonzalez-Alegre and Afifi, 2006; Jervis, 1963; Rasmussen et al., 2000). This suggests involvement of cortical and, to a minor degree, limbic structures (Fau et al., 1971; Gambardella et al., 2001), which agrees with pathological findings reporting profound cortical and striatal atrophy, with relative sparing of thalamic regions (Jervis, 1963). Atypical "absence" (staring) seizures were reported in one infant with extremely early onset (1 year of age) (Gonzalez-Alegre and Afifi, 2006). However, in this case the genetic mutation could not be documented, and the family history was negative for HD. In another multicenter study of juvenile HD with documented genetic mutations (mean CAG repeat length 82, and age of onset 10 years), staring spells were observed in some cases, but the EEG appeared normal in all but one case (Cloud et al., 2012), casting doubts that these were typical absence seizures.

In animal models of HD, injection of excitatory amino acids at high concentrations induces seizure activity. Interestingly, some genetic models of HD are protected against striatal injections of QA (Hansson et al., 1999, 2001). In contrast, direct application of glutamate in 14, but not in 10-week-old R6/2 mice produced the opposite effect, that is, increased toxicity as evidenced by larger lesion volume and number of fluoro-jade positive cells (Estrada-Sanchez et al., 2009). This effect appeared to depend on decreased levels of glutamate transporters in striatum. Clinically, the mice presented with head weaving, chewing, grooming, contralateral rotations, and tonic–clonic seizures. What could explain this apparent discrepancy? One possibility is that glutamate also activates other receptors, such as KA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and metabotropic glutamate receptors. Another possibility is that seizure activity plays a prominent role in nerve cell degeneration, as only R6/2 animals showed paroxysmal discharges and seizures after glutamate application. Further, while seizures can also be induced by QA, its epileptogenic potency is inferior to that of KA. Similarly, while QA lesions are localized, distant lesions are observed after KA (and presumably also glutamate) injections (Schwarcz et al., 1983). Finally, excitotoxic effects of QA appear to be more dependent than other toxins on excitatory inputs to the striatum, and it is well known that in HD mice excitatory input from cortex and thalamus is markedly reduced as the disease progresses (Cepeda et al., 2003, 2007).

Age of disease progression also plays a critical role. In presymptomatic R6/2 animals, systemic injections of KA are less toxic and seizures are less intense than in wild-type (WT) animals (Morton and Leavens, 2000), suggesting that the mutation triggers compensatory mechanisms even before full manifestation of symptoms. In contrast, R6/2 mice at 12 weeks are more vulnerable to 3-nitropropionic (3-NP) acid than WTs (Bogdanov et al., 1998). Again, this effect is age-dependent, as increased susceptibility to 3-NP did not occur between 7 and 10 weeks and, if anything, R6/2 mice appeared to be more resistant than WTs (Hickey and Morton, 2000). In the YAC72 model, the precursor of the YAC128 model, with a more protracted development of symptoms, QA injected in 6- or 10-month-old animals produced larger lesions, suggesting specific involvement of NMDA receptors (Zeron et al., 2002). In contrast, in YAC128 mice the effect of QA was age-dependent as in older mice (10 mo) resistance to QA also developed (Graham et al., 2009). In general, regardless of the HD model utilized, presymptomatic animals display similar or enhanced sensitivity to QA, whereas symptomatic animals develop resistance to the excitotoxin, corresponding to electrophysiological findings demonstrating biphasic changes in glutamatergic neurotransmission (Cepeda et al., 2003; Graham et al., 2009; Joshi et al., 2009). How

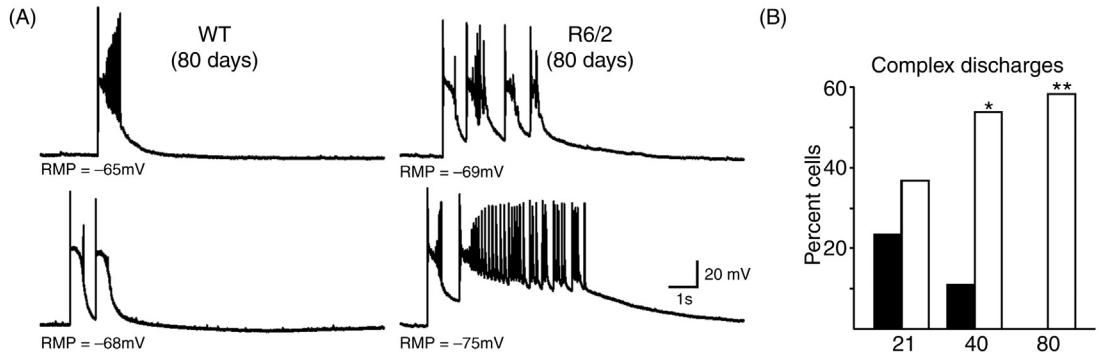

FIGURE 71.1 Epileptiform activity induced by bath application of bicuculline (20 μM) in cortical slices from WT and symptomatic R6/2 mice (aged 80 days). (A) Whole-cell patch clamp recordings in current clamp mode show that application of bicuculline induces paroxysmal discharges in both WT and R6/2 mice. However, R6/2 cells showed more complex discharges than WT cells. (B) Proportion of cells displaying complex discharges is greater in R6/2 mice and becomes more frequent with age (three groups were included: 21, 40, and 80 days). *(Adapted from Cummings, D.M., Andre, V.M., Uzgil, B.O., Gee, S.M., Fisher, Y.E., Cepeda, C., Levine, M.S., 2009. Alterations in cortical excitation and inhibition in genetic mouse models of Huntington's disease. J. Neurosci. 29, 10371–10386.)*

the HD mutation affords resistance to certain excitotoxins is unknown, however, it has been observed that symptomatic R6/2 mice are relatively more tolerant to ischemia than controls, suggesting that the mutation triggers compensatory mechanisms, for example, ischemic preconditioning (Hickey and Morton, 2000; Klapstein and Levine, 2005).

Few studies have focused on examination of epileptic activity in transgenic mice. In a detailed report of EEG abnormalities in R6/1 mice, ectopic theta activity, reduced delta power, and epileptic discharges were observed (Pignatelli et al., 2012). The cholinergic antagonist atropine reduced ectopic theta and also restored delta activity but did not influence epileptic discharges. Spontaneous generalized seizures also were observed. In contrast, the majority of EEG studies do not report spontaneous paroxysmal discharges. However, in the presence of proconvulsant agents, for example, the $GABA_A$ receptor antagonists bicuculline or picrotoxin, epileptic activity in hippocampal structures was observed (Cepeda-Prado et al., 2012; Parievsky et al., 2012). Complex paroxysmal discharges resembling ictal activity also were reported in the cerebral cortex in the presence of a $GABA_A$ receptor antagonist (Cummings et al., 2009) (Fig. 71.1). These observations confirm cortical and hippocampal involvement. Clinically, however, seizures appear to be generalized tonic–clonic and not limbic seizures. Similarly, spike and wave discharges have not been reported, suggesting no thalamic involvement. As for possible triggers or facilitators of seizures, high-frequency noise (around 20 kHz, e.g., that produced by a sonicator) can easily trigger seizures. Stress also seems to facilitate seizures. Substrates involved in seizure activity thus seem to concentrate in cortical and limbic regions. These regions, besides the striatum, contain large numbers of mHtt aggregates (Murphy et al., 2000). In fact, the cortex seems to contain more aggregates than the striatum (Fusco et al., 1999).

Response to Antiepileptic Drugs

Most treatments for HD patients are palliative and focus on reducing choreatic movements. TBZ, a drug that depletes DA from intracellular stores, has been used to control chorea in humans (Huntington Study Group, 2006) and in a rat model that shows abnormal (choreatic-like) movements and increased DA expression in striatum (Zeef et al., 2014). The efficacy of TBZ relies on the observation that hyperkinesia is caused by increased DA levels in striatum and that hypokinesia is caused by reduced DA levels, as in PD. Studies in animal models have shown biphasic changes in DA levels, corresponding to biphasic changes in motor activity (Cepeda et al., 2014; Dallerac et al., 2015). In R6/2 mice, DA levels are reduced during the late symptomatic stage (Johnson et al., 2006). Reduced DA levels could facilitate the occurrence of seizure activity. In childhood-onset HD (the rigid or Westphal variant) chorea does not occur and it is possible that DA levels are reduced, similar to symptomatic R6/2 or R6/1 mice (Ortiz et al., 2011). If this is the case, then DA should confer antiepileptic properties. However, this issue is more complex as the effects of DA are mediated by different receptor subtypes with sometimes opposite actions. This will be elaborated further in the section on epilepsy and PD.

Besides TBZ, several drugs have been shown to ameliorate HD symptoms. For example, regularizing circadian rhythms with a short-acting anxiolytic of the benzodiazepine class, Alprazolam (Xanax) improves motor deficits in R6/2 mice (Pallier et al., 2007). Tiagabine (R(-)-N-[4,4-bis(3-methylthien-2-yl)but-3-enyl]nipecotic acid), a centrally acting GABA reuptake inhibitor, also had positive effects in two HD models (Masuda et al., 2008). Further, systemic injections of tiagabine significantly reversed 3-NP-induced alterations in various behavioral and biochemical measures

(Dhir et al., 2008). Importantly, in the present context, both drugs have potent anticonvulsant properties (Nielsen et al., 1991), suggesting that positive effects could be mediated by reduction of cortical and hippocampal hyperexcitability. The question then is whether antiepileptic drugs can also be effective for adult-onset HD, where no overt seizures occur.

In spite of showing different symptoms, adult-onset HD could be considered a subdued version of juvenile HD. In that sense, both HD types may be amenable to similar pharmacological approaches (Gil and Rego, 2009; Woodman et al., 2007). Although seizures are rarely observed in adult-onset HD, cortical hyperexcitability may be a common denominator. In favor of this assumption, there is a subgroup of relatively young adult-onset patients, usually with paternal inheritance, who develop cortical myoclonus without full-blown seizures, and respond to valproate and benzodiazepines, although chorea is not affected (Adam and Jankovic, 2008; Funakawa et al., 2004; Thompson et al., 1994). Therefore, in this subgroup of HD patients, treatment with valproic acid may be advised (Saft et al., 2006; Vogel et al., 1991). However, in adult-onset HD the efficacy of antiepileptic drugs is not as evident. Lamotrigine, a drug that inhibits glutamate release, does not prevent HD progression, although more patients reported symptomatic improvement and a trend toward reduced chorea, compared to the placebo group (Kremer et al., 1999). Similarly, valproate does not ameliorate involuntary movements in adult-onset HD (Pearce et al., 1977; Symington et al., 1978). Thus, chorea seems to depend more on DA changes in basal ganglia structures than on cortical hyperexcitability.

A role for endocannabinoids also has been suggested. Downregulation of total CB1 receptor expression in the basal ganglia of HD patients and animal models before symptom onset is firmly established (Dowie et al., 2009; Fernandez-Ruiz, 2009; Glass et al., 2000). *CNR1* mRNA and CB1 receptor expression are decreased in the striatum of presymptomatic R6/1 and R6/2 mice (Denovan-Wright and Robertson, 2000). CB1 receptor expression is downregulated in MSNs of the indirect pathway and also in neuropeptide Y/nitric oxide synthase (NPY/NOS)-expressing interneurons, but not in parvalbumin (PV)- and calretinin-expressing interneurons of HD mice and human patients (Horne et al., 2013). Decreases in CB1 receptor expression are probably due to disruption of *CNR1* mRNA transcription by mHtt (Blazquez et al., 2011). Further, modulation of endocannabinoids affects the expression of seizures in HD mice. For example, inhibition of ABHD6, the enzyme that hydrolyzes the endogenous CB1 agonist 2-arachidonoylglycerol (2-AG), blocks spontaneous seizures in R6/2 mice (Naydenov et al., 2014).

Mechanisms and Insights into Human Disorders

Although a number of mechanisms have been invoked to explain epileptic activity in general, reduced inhibition and/or increased excitation are some of the generally accepted mechanisms. In HD, loss of PV-containing GABAergic interneurons has been reported (Reiner et al., 2013). In addition, reduced inhibition in the cerebral cortex of HD mouse models also was demonstrated electrophysiologically (Cummings et al., 2009; Spampanato et al., 2008). It is important to note that interneuron degeneration in the cerebral cortex is heterogeneous, and depends on the HD symptomatology. In the primary motor cortex, there is a significant loss of calbindin interneurons in cases with predominant motor symptoms. In contrast, the anterior cingulate cortex shows a significant loss of calbindin, calretinin, and PV interneurons, in cases with a predominant mood phenotype (Kim et al., 2014). It is likely that loss of some groups of GABAergic interneurons leads to cortical hyperexcitability and increased seizure susceptibility in HD. Reduced inhibition in cortical regions in conjunction with increased excitation (Cummings et al., 2009) combine to facilitate seizure susceptibility in HD.

Other potential mechanisms could involve trophic factors. Although the function of normal Htt is not completely elucidated, it is proposed to act as a general facilitator of neuronal gene transcription (Zuccato et al., 2003). In HD, reduced brain-derived neurotrophic factor (BDNF) levels and altered function of TrkB receptors have been observed (Plotkin et al., 2014; Zuccato et al., 2001). WT Htt stimulates the production of BDNF and the HD mutation leads to loss of this stimulatory activity (Cattaneo et al., 2005). BDNF in the striatum is produced in the cerebral cortex and transported to MSNs by the corticostriatal pathway (Altar et al., 1997). This transport is reduced in HD (Gauthier et al., 2004). The present evidence indicates that a BDNF deficit is one of the major contributors to HD pathogenesis (Zuccato and Cattaneo, 2014). Supporting this idea, conditional Emx-BDNF knockout mice, deficient in BDNF production in cortical neurons develop behavioral and anatomical abnormalities reminiscent of those observed in mouse models of HD (Baquet et al., 2004). In addition, inactivation of one BDNF allele in transgenic R6/1 mice exacerbates the HD phenotype and pathology of enkephalin-containing MSNs, whereas exogenous administration of BDNF prevents cell dysfunction and delays disease progression (Canals et al., 2004).

In epilepsy, BDNF also plays an important but complex role. Although it may display neuroprotective properties, for the most part BDNF appears to promote seizure activity (Binder et al., 2001) and uncoupling TrkB receptors from phospholipase C prevents epilepsy after status epilepticus (Gu et al., 2015). Besides the well-known effects of BDNF on dendritic elaboration and axonal sprouting, evidence also indicates that acute application of BDNF increases glutamatergic responses (Li et al., 1998) and decreases GABAergic responses (Tanaka et al., 1997). This could be one mechanism by which BDNF promotes epileptic activity. In HD, the levels of BDNF are reduced, at least in the striatum.

In the cerebral cortex, the region expected to be more implicated in epileptogenesis, the evidence is more tenuous (Zuccato and Cattaneo, 2014). However, there also is evidence that BDNF can have antiepileptic effects. For example, chronic infusion of BDNF delays hippocampal kindling (Larmet et al., 1995; Reibel et al., 2000a). Interestingly, this effect appears to be mediated by increased production of NPY (Reibel et al., 2000b, 2003), a peptide with recognized antiepileptic properties (Colmers and El Bahh, 2003; Klapstein and Colmers, 1997; Pezet and Malcangio, 2004). Although the role of NPY in HD is not well known, several studies have reported interesting findings. First, NPY/somatostatin interneurons not only are spared, but increased in HD patients (Dawbarn et al., 1985). Second, the concentrations of NPY and other peptides are increased in the cerebral cortex of HD cases (Mazurek et al., 1997). Third, a study of single nucleotide polymorphisms in NPY and its receptors found a significant association between NPY2 receptor promoter variations and age of HD onset, suggesting that NPY, acting on NPY2 receptors, slows down the course of HD (Kloster et al., 2014). In agreement, intracerebral injection of NPY improved behavior and reduced striatal atrophy in R6/2 mice (Decressac et al., 2010). These changes in NPY expression appear to support the idea that, before the cortex becomes hyperexcitable, compensatory mechanisms may occur.

Overall, seizure activity in HD models involves cerebral cortex and hippocampus. However, it is doubtful that seizures are solely of the limbic or temporal lobe type. The fact that no epileptic cortical or hippocampal foci have been described in these models suggests that seizures are generalized, with participation of subcortical structures. This, in addition to the fact that high-frequency sounds can trigger seizures in R6/2 mice (Cepeda-Prado et al., 2012), indicates heightened susceptibility to reflex epilepsy. Audiogenic seizures in epilepsy-prone rats involve the inferior colliculus, medial geniculate, as well as other subcortical and cortical areas (Faingold and Randall, 1995; Faingold et al., 1988, 1994). Some mouse strains have also been shown to be prone to auditory stimuli (e.g., DBA/1 or 2 mice) (Le Gal La Salle and Naquet, 1990). Interestingly, the maximal response to auditory challenge in DBA/2 mice is about 20 KHz (Schreiber, 1978), similar to the frequency produced by a sonicator. At present it is unknown if HD animal models also display photosensitivity, another common form of reflex epilepsy. In photosensitive epilepsy, a prominent role of the motor cortex has been emphasized, in particular the fronto-rolandic area (Naquet et al., 1995; Silva-Barrat et al., 1986).

While all these are valid mechanisms of epileptogenicity in HD, there is a consensus that probably one of the most determinant factors involved in the increased susceptibility of early-onset-HD brains is age itself. As already stated, young brains are more vulnerable to external insults and to intrinsic errors of development, as those that may be induced by the presence of the HD mutation. The idea that HD is not solely a neurodegenerative, but also a developmental disease, is gaining momentum (Humbert, 2010; Kerschbamer and Biagioli, 2015). It is well-known that normal Htt plays an important role during development as lack of this protein is lethal (Zeitlin et al., 1995). The Htt protein may alter different aspects of chromatin regulation and transcription during neural development and specification (Kerschbamer and Biagioli, 2015). Htt also regulates critical steps of mouse embryonic corticogenesis. Studies have shown that in vivo inactivation of Htt by RNA interference, or by deletion of the gene, affects spindle orientation and cell fate of cortical progenitors of the ventricular zone in mouse embryos (Godin et al., 2010). It is thus predictable that the mutant form of Htt could also alter corticogenesis. In fact, mHtt affects spindle orientation in dividing mouse cortical progenitors, altering the thickness of the developing cortex, and the polarization and migration processes of newly generated neurons (Molina-Calavita et al., 2014). This observation is reminiscent of the cortical maldevelopment found in CD. Thus, we could hypothesize that the presence of mHtt in neuronal progenitors affects cortical organization, and induces diffuse architectural changes, similar to those occurring in CD type I (dyslamination and pyramidal neuron misorientation), and result in cortical hyperexcitability and eventual epileptiform activity (Blumcke et al., 2011).

PARKINSON'S DISEASE

General Description

PD is a chronic, progressive neurodegenerative condition that, like HD, compromises the patient's movements, but in a different way. While adult-onset HD is characterized by involuntary dance-like movements, PD patients mainly develop tremor, rigidity, and bradykinesia. Together, these motor symptoms impair posture, coordination, and balance (Poewe and Wenning, 1996). In addition, PD patients also display nonmotor symptoms, such as loss of the sense of smell, hallucinations, and cognitive impairment culminating in dementia (Cosgrove et al., 2015). In general, early clinical symptoms of PD may go unnoticed; however, they worsen gradually, and eventually impair daily activities (Poewe and Wenning, 1996). Typically, onset of motor signs in PD occurs around 60 years of age. However, early-onset Parkinsonism also has been reported. It is important to mention that Parkinsonism refers to a clinical condition characterized by the main motor signs observed in PD, although its origins are more heterogeneous (Bohlhalter and Kaegi, 2011). Regardless of their origin, prototypic PD and other forms of Parkinsonism show similar motor and nonmotor features and, interestingly, both conditions can show atypical signs, such as epileptic seizures and status epilepticus (Feddersen et al., 2014; Petrov, 2006).

Two main factors determine PD onset, the first is related to mutations in specific genes and the second comprises environmental causes, such as exposure to pesticides (Bohlhalter and Kaegi, 2011). In both PD types, α-synuclein, a presynaptic protein, and the principal component of Lewy bodies, seems to play a critical role, hence the idea that PD is a synucleinopathy. Misfolding and aggregates of α-synuclein occur in vulnerable neuronal types of the human central, peripheral, and enteric nervous systems and are crucial for the development of sporadic PD (Braak et al., 2002; Del Tredici and Braak, 2015). Importantly, progression of PD pathology follows a predictable sequence throughout six stages (Braak and Braak, 2000; Braak et al., 2002). In addition, aggregates appear to be able to propagate trans-synaptically from cell to cell. Initially, α-synuclein aggregation occurs in the olfactory bulb or the enteric nervous system and then proceeds in a caudo-rostral direction via viscero- and somatomotor brainstem centers to the midbrain, forebrain, and ultimately reaching the cerebral cortex (Del Tredici and Braak, 2015).

Animal Models of Parkinson's Disease: Methods of Generation

As the etiology of PD comprises both environmental and genetic factors, the study of the mechanisms underlying PD neuropathology has been done in animal models that fall into two main groups: toxin models and genetic models. Toxin models can be categorized according to the type of toxin used. Neurotoxin models are mainly generated by administration of 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenyl-1,2,3,6-tetrahydropiridine (MPTP). Both toxins cause DA-producing neurons to degenerate (Bohlhalter and Kaegi, 2011; Le et al., 2014). Pesticide or herbicide models mostly use rotenone and 1,1'-Dimethyl-4-4'-bypiridinium dichloride (paraquat) (Le et al., 2014). In order to reproduce behavioral changes similar to PD, toxin models have to induce more than 50% DA neuron loss in the substantia nigra. As with other neurodegenerative disorders, toxin models are somewhat imperfect and do not replicate all the behavioral and neuropathological hallmarks of PD (Levine et al., 2004). However, the identification of gene mutations linked to familial PD has brought an opportunity of developing more reliable PD models.

Although only about 20% of PD cases originate from genetic mutations, the identification of familial PD-related genes has allowed the development of genetic models, a powerful tool to understand the underlying causes of PD neuropathology. Mutations in various genes have been described and can be grouped into two main categories: (1) autosomal dominant mutations that include α-synuclein, perhaps the most well-known protein associated with PD, and the Leucine-rich repeat kinase 2 (LRRK2), and (2) autosomal recessive mutations that include mutations in the protein called parkin, protein deglycase DJ-1 also known as PD protein 7, PTEN-induced putative kinase 1 (PINK1), and SYNJ1, the most recently described PD-related gene (Dawson et al., 2010; Klein and Westenberger, 2012; Krebs et al., 2013; Quadri et al., 2013).

In the case of the autosomal dominant mutations, manipulation of both α-synuclein and LRRK2 genes have been used to create genetic models. However, these models have failed to develop clear PD-like motor signs and/or nigrostriatal degeneration (Dawson et al., 2010; Le et al., 2014). In the striatum of a mouse model overexpressing the human α-synuclein, MSNs showed decreased frequency of spontaneous excitatory postsynaptic currents. Moreover, at corticostriatal synapses, decreased neurotransmitter release was observed, and this might be related to altered presynaptic plasticity (Watson et al., 2009; Wu et al., 2010). These results indicate that α-synuclein PD models display altered neuronal functioning that extends beyond the substantia nigra and possibly changes in corticostriatal activity might be related to preclinical manifestations. In LRRK2 knockout mice, no changes in corticostriatal glutamatergic transmission, cognitive, or motor deficits were observed. However, these mice showed changes in the short-term synaptic plasticity mediated by DA D2 receptors, correlating with hypoactivity and impaired recognition memory (Beccano-Kelly et al., 2015).

For the autosomal recessive mutations, parkin, DJ-1, and PINK1 genetic models also have been developed (Dawson et al., 2010) and again, despite the fact that genetic models show mild nigrostriatal deficits, no apparent DA neuronal loss and only slight motor changes have been observed (Dawson et al., 2010; Le et al., 2014). For example, the parkin-deficient mouse model shows normal brain morphology and no degeneration of DA neurons is detected in the substantia nigra (Goldberg et al., 2003). However, microdialysis studies showed an increase in DA levels in the striatum where MSNs displayed a reduction in synaptic excitability (Goldberg et al., 2003; Lam et al., 2011). Thus, although several genetic PD animal models have been developed, models that closely resemble the classic hallmarks of PD neuropathology and clinical signs are still lacking. There is no doubt that the study of these models has increased our understanding of the molecular and cellular mechanisms underlying DA neuronal loss and also they represent powerful tools in the search for novel therapeutic strategies.

Characteristics and Defining Features

Initial studies reported that development of PD symptoms in patients previously suffering from epilepsy leads to a decreased frequency of seizure activity (Vercueil, 2000; Yakovlev, 1928). Based on a cross calculation of the prevalence of epilepsy and idiopathic PD, it was reported that one or two PD patients out of 100,000 would develop epilepsy

(Vercueil, 2006). However, such a low prevalence might be biased since the report was based on the prevalence of each disorder. In addition, it also is possible that pharmacological treatment of PD affected the incidence of seizures. For example, apomorphine, amphetamines, L-DOPA, and other drugs used to treat PD have antiepileptic effects (Bozzi and Borrelli, 2013; Bozzi et al., 2000). Current evidence indicates that epilepsy may develop in either genetic or idiopathic PD.

A recent study reported that 2.6% of PD patients develop epilepsy (Feddersen et al., 2014), similar to a previous report describing a prevalence of 2.4% (Bodenmann et al., 2001). These figures are slightly higher than those expected in the general population aged ~60 years (1%), but much less than the prevalence of epilepsy in Alzheimer's disease that is about 10% (Vercueil, 2006). While the relative incidence of epileptic seizures in PD is low, the likelihood of presenting with status epilepticus appears to be very high. By comparing the rate of epilepsy and status epilepticus in patients with and without PD, it was reported that PD patients are more likely to develop status epilepticus relative to age-matched non-PD patients (Feddersen et al., 2014). Likewise, another study showed that 10 out of 250 patients with Parkinsonism showed episodes of epileptic seizures, ranging from generalized tonic–clonic seizures, to complex partial seizures, and simple motor partial seizures (Petrov, 2006). In some patients, the EEG showed irregular brain activity, and the presence of focal, intermittent rhythmic delta activity. In a group that developed secondarily generalized seizures, the EEG showed focal activity with biphasic discharges, bilateral paroxysmal activity, and irregular theta waves (Petrov, 2006). Of interest, PD patients seem to be more vulnerable to induced epilepsy when they are subjected to hyperventilation or photostimulation (Henneberg et al., 1998). Under these conditions, EEG recordings showed the presence of polyspikes and polyspike-waves. A recent study described a genetic-related Parkinsonism with early onset signs that also included generalized seizures (Krebs et al., 2013; Quadri et al., 2013). Two siblings from a consanguineous Iranian family showed generalized seizures during childhood, and onset of Parkinsonism around 20 years of age. Homozygosity mapping and whole-exome sequencing revealed a homozygous mutation within the N-terminal domain of the synaptojanin 1 gene (SYNJ1) (Krebs et al., 2013). Together, these studies indicate that epilepsy is more closely related with Parkinsonism and PD than previously thought. Obviously, more studies are necessary to understand the underlying causes of epilepsy, and the exact incidence among the worldwide population suffering from PD and Parkinsonism. Further, a more systematic investigation on the role of DA and the basal ganglia in the generation and/or modulation of epileptic activity is warranted.

It is interesting that none of the animal models created thus far, either toxin or genetic, has been reported to develop seizures; this might not be surprising as, at least for genetic models, most do not display marked DA neuron degeneration (Goldberg et al., 2003; Le et al., 2014). In the case of toxin models, we are not aware of studies examining seizure susceptibility in aged animals, when seizures are more commonly observed in human sporadic PD. However, when 6-OHDA is bilaterally injected and severe lesions occur, animals often die of seizures (Bourn et al., 1972), supporting again antiepileptogenic effects of DA. It might be worth evaluating epileptic susceptibility to proconvulsant agents in these models. On the other hand, SYNJ1 could be a strong candidate for developing a new genetic model that might develop seizure-like activity, since patients showing homozygotic mutations in the SYNJ1 gene develop seizures (Krebs et al., 2013).

Response to Antiepileptic Drugs

PD patients that develop seizures have been treated with conventional antiepileptic medications, such as carbamazepine, a blocker of Na^+ channels, benzodiazepines, agonists of $GABA_A$ receptors, and other enhancers of GABAergic activity, like valproate and phenytoin (Feddersen et al., 2014; Macdonald and Kelly, 1995; Petrov, 2006). In the case of the patients carrying the homozygous mutation in the SYNJ1 protein that developed epileptic seizures during childhood, epilepsy was controlled with phenobarbital (Krebs et al., 2013). Another option for PD patients developing epilepsy is deep brain stimulation (DBS). Neurostimulation has been used effectively to treat movement disorders and it makes sense to expand this technique to PD patients with epilepsy (Vercueil et al., 1998). As for potential target structures, antiepileptic effects have been seen by stimulation of the caudate nucleus, the subthalamic nucleus, and the anterior thalamus (Fisher and Velasco, 2014). Recent advances have indicated that closed-loop neurostimulation that allows stimulation after sensing abnormal discharges is more effective at stopping ongoing epileptic activity (Sun and Morrell, 2014). Finally, the advent of optogenetics has opened new avenues for more selective and precise manipulation of antiepileptic regions, at least in animal models (Paz and Huguenard, 2015; Paz et al., 2013). For example, in a rat model of cortical stroke and seizures, thalamo-cortical neurons displayed changes in hyperpolarization-activated cyclic nucleotide-gated (HCN) channels and hyperexcitability. Reducing their activity with closed-loop optogenetics was able to interrupt seizure activity (Paz et al., 2013).

Mechanisms and Insight into Human Disorders

Role of DA and Other Neurotransmitters

In order to understand the outcome of DA cell loss on epileptic manifestations in PD patients, a clear understanding of the role of DA in the modulation of epileptic discharges

in general is necessary. Overall, it is believed that DA per se is antiepileptic. As already mentioned, drugs used to treat PD also have antiepileptic effects (Bozzi and Borrelli, 2013; Bozzi et al., 2000). Neuroimaging studies in human patients with epilepsy have shown changes in several DA-related proteins, including DA receptors and the dopamine transporter (DAT). According to these studies, a decrease in the binding of [18F]-fluoro-L-DOPA, indicating reduced DAT levels, appears to be a common alteration in patients with various forms of epilepsy (Bozzi and Borrelli, 2013). Reduced DAT activity causes increases in DA concentration and overactivation of DA receptors that could modulate the occurrence of epileptic discharges. However, this modulation is complex due to the existence of different DA receptor subtypes.

There are five DA receptor subtypes that can be grouped into two main families, D1-like (D_1 and D_5) and D2-like (D_2, D_3, and D_4). Their effects can be opposite, as D1 family receptors increase cAMP production, whereas D2 family receptors decrease cAMP (Missale et al., 1998). D1 and D2 family receptors produce differential effects on glutamate receptor-mediated responses (Cepeda et al., 1993). It is interesting that, besides producing opposite effects on intracellular signaling pathways and glutamate responses, activation of DA receptors also exerts opposite effects on epileptogenic activity. Based on studies performed in pharmacologic animal models, it was shown that, while activation of D1-like receptors leads to the generation of epileptic events, activation of D2-like receptors suppresses epileptogenic activity (al-Tajir et al., 1990; Bozzi and Borrelli, 2013; Starr, 1996). In agreement, a study evaluating the electrophysiological changes induced by either D1 or D2 receptors in cortical tissue samples from children with pharmacoresistant epilepsy demonstrated that activation of D1 receptors enhanced cortical excitability, and facilitated the development of epileptic activity, while D2 receptor agonists had the opposite effect (Cepeda et al., 1999).

Loss of DA neurons in the substantia nigra is one of the defining neuropathological features of PD. Also, in postmortem PD brains, surviving neurons show deposits of α-synuclein forming the Lewy bodies. It is interesting that besides the main affected area, PD brains also show Lewy bodies in the nucleus basalis of Meynert, locus coeruleus, and dorsal raphe nuclei (Gesi et al., 2000). Accordingly, postmortem studies of advanced PD patients revealed a widespread reduction in the levels of the corresponding neurotransmitters acetylcholine, norepinephrine, and serotonin. Particularly, a dramatic reduction in norepinephrine was detected, suggesting a major loss of innervating neurons from the locus coeruleus (Buddhala et al., 2015). This is a very important finding that could be related to PD clinical signs, in particular cognitive impairment and depression as previously described (Szot et al., 2012). Similarly, reduction in norepinephrine could contribute to the development of epileptic seizures in PD as norepinephrine is known to modulate neuronal excitability. In fact, anticonvulsant effects of the noradrenergic system have been described (Szot, 2012; Szot et al., 2001; Weinshenker and Szot, 2002). Animals with lesions of the noradrenergic system with 6-OHDA are more vulnerable to seizures induced by electroconvulsive shock and hippocampal kindling (Weinshenker and Szot, 2002). In a genetically epilepsy-prone rat, increased vulnerability to audiogenic seizures occurs along with decreased norepinephrine content and alterations in the norepinephrine synthesis pathway (Dailey and Jobe, 1986; Dailey et al., 1991). However, the relationship between changes in norepinephrine and the vulnerability to epilepsy in PD is still not well known.

Compelling evidence indicates that besides DA neurons, PD brains show changes in PV-expressing fast-spiking interneurons (FSIs). The prefrontal cortex of PD postmortem brains shows decreased levels of PV mRNA and glutamic acid decarboxylase (GAD) (Lanoue et al., 2013). It is interesting, however, that despite the reduction of both PV and GAD, no loss of PV-positive interneurons is detected in the frontal cortex, suggesting that, rather than neuronal loss, PV-positive interneurons undergo functional changes that may also occur in other brain regions. FSIs in hemi-parkinsonian rats were evaluated in striatum by measuring spontaneous activity and responsiveness to cortical stimulation. Results suggested that, while FSI activity did not change, MSNs from the direct pathway were more strongly inhibited by FSIs, whereas MSNs from the indirect pathway were not affected. Thus, FSI activity strongly contributes to the imbalance observed in MSNs in PD (Mallet et al., 2006).

Role of the Basal Ganglia

In both HD and PD, structures of the basal ganglia play a critical role. Loss of MSNs in HD and loss of substantia nigra DA neurons in PD are hallmarks of each disease, respectively. Further, epileptic manifestations and altered DA function occur in both pathologies. This means that basal ganglia structures have the potential of modulating epileptic activity. A large number of studies have demonstrated this to be the case. Electrical stimulation of the caudate nucleus reduces limbic epileptic discharges (La Grutta and Sabatino, 1988; Sabatino et al., 1989). Similarly, electrical stimulation of the substantia nigra has antiepileptic effects on a cortical focus (Sabatino et al., 1988). In addition, activation of the striatum with NMDA or bicuculline protects against pilocarpine- or kindling-induced limbic seizures (Cavalheiro and Turski, 1986; Cavalheiro et al., 1987; Turski et al., 1987). Also, activation of striatal D1 MSNs or direct application of muscimol, a GABA agonist, in the substantia nigra is antiepileptic (Deransart and Depaulis, 2002; Iadarola and Gale, 1982; Sperber et al., 1989; Veliskova and Moshe, 2006). This is opposite to results showing that excitotoxins, such as glutamate, NMDA, and KA, or the

glutamate uptake inhibitor TBOA injected in the rat striatum induce epileptic activity (Estrada-Sanchez et al., 2009; Montiel et al., 2005; Schwarcz et al., 1983). How can these effects be reconciled? The vast majority of striatal neurons are inhibitory, thus they are not likely to serve as generators of epileptic discharges. Further, local injections of glutamate receptor agonists in the striatum or globus pallidus induce turning behavior or motor alterations, but not motor seizures (Deransart and Depaulis, 2002). Perhaps the proconvulsant effects of excitatory amino acids are indirect due to either diffusion to epileptogenic areas, or to changes in the excitability of cortical and hippocampal terminals, known to possess AMPA and KA receptors capable of modulating glutamate release (Fujiyama et al., 2004; Lerma, 2003). On hippocampal terminals, presynaptic KA receptors can facilitate glutamate release (Lauri et al., 2001).

In a comprehensive review, it was concluded that, rather than a generator region, the basal ganglia work as a propagation structure, and their participation depends on the type and intensity of seizure activity (Deransart and Depaulis, 2002). In addition to changes in neuronal activity induced by seizure occurrence, the basal ganglia can modulate ongoing seizure activity. For example, studies have shown that inhibition of the substantia nigra suppresses EEG changes and behavioral alterations observed during generalized epileptic seizures (Depaulis et al., 1994). Likewise, DBS of substantia nigra pars reticulata can be an effective anticonvulsant (Velisek et al., 2002). Thus, it is natural that neurodegenerative disorders involving different regions of the basal ganglia affect the course of epileptogenicity.

CONCLUSIONS

HD and PD are two neurodegenerative disorders caused by genetic (HD), and a combination of environmental and genetic susceptibility (PD) factors. Central to both disorders is the cell loss in basal ganglia and cortical regions. In early-onset HD, epileptic seizures occur frequently, whereas in adult-onset HD seizure manifestations are rare. In PD the occurrence of seizures is becoming more recognized. The causes of seizures in these disorders remain unknown, but cortical, hippocampal, and brain stem alterations, plus atrophy could play an important role. Age of disease onset appears to be a determinant factor to explain the propensity for epilepsy in HD. Reduced DA levels may also be a precipitating factor in both disorders. Recent advances in neurostimulation and optogenetics have opened interesting venues for the treatment of epileptic manifestations in these disorders.

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