Review Article

Underlying Mechanisms of Impulse Control Disorders and Dopamine Agonist Withdrawal Syndrome in Parkinson's Disease

Yasushi Shimo and Nobutaka Hattori*

Department of Neurology, Juntendo University, School of Medicine, Japan

INTRODUCTION

Recently, much attention has been paid to not only motor symptoms but also Non-Motor Symptoms (NMS) of Parkinson's disease [1]. NMS include sleep disorders, autonomic nervous system dysfunction, sensory impairment, and neuropsychiatric symptoms. Neuropsychiatric symptoms include depression, apathy, anxiety, anhedonia, attention deficit, hallucinations, confusion, Impulse Control Disorders (ICD), and cognitive dysfunction [1]. These symptoms are risk factors that influence a patient's quality of life, and the prevalence of NMS increases along with disease progression [2].

Among the NMS, ICD are socially devastating [3]. They can occur as a behavioral complication of dopaminergic therapy in PD, and are frequently observed as side effects of Dopamine Agonists (DA) [4]. There is no established treatment for ICD; however, some reports showed their improvement after reducing the dosage of DA [5,6] or sub thalamic deep brain stimulation [7-9], which may cause Dopamine Agonist Withdrawal Syndrome (DAWS) [10]. DAWS can protract ICD symptoms. Therefore, it is important to clarify the mechanisms of these psychiatric problems in order to perform appropriate treatment. .

In Parkinson's disease, the main pathological change is degeneration of dopamine-producing neurons in the Substantia Nigra pars Compacta (SNc). To alleviate motor symptoms of PD, Dopamine Replacement Therapy (DRT), which includes levodopa and DA, is a standard treatment, and ICD or DAWS usually occurs after long-term DRT. In this review, we will discuss the mechanisms of ICD and DAWS and the role of the dopaminergic system in each condition.

Possible mechanisms of ICD

ICD are defined as behaviors that are performed repetitively and compulsively and that interfere with the quality of life. The symptoms include pathological gambling, compulsive buying, punding, hobbyism, hypersexuality, and binge eating. The incidence of ICD in PD was found to be around 10~15% [11,12].

Dysfunction of the mesolimbic dopaminergic circuit, which includes the ventral tegmental area, ventral striatum (nucleus accumbens: NAc), ventral pallidum, and medial pre-frontal cortex, is considered to play a crucial role in the development of ICD, for which DA have a larger impact than levodopa [13]. According to recent studies in this field, it is considered that a hyperdopaminegic state in the mesolimbic dopaminergic circuit plays a critical role in ICD. Therefore, it is recommended that the dose of dopaminergic drugs be reduced for the treatment of ICD [14-16]. One possible mechanisms of ICD is dysfunction of negative feedback learning, which is mainly controlled by the mesolimbic dopamine system [17,18]. Dopamine neurons in the Substantia Nigra pars Compacta (SNc) or Ventral Tegmentum Area (VTA) are usually fired tonically at a rate lower than 10 Hz [19]. This tonic activity mainly stimulates D2 receptors, which are located on the medium spiny neurons of the striatum. If unexpected rewards are delivered or there are reward-indicating cues, dopaminergic neurons fire phasically, and the phasically released dopamine stimulates D1 receptors [20,21]. On the other hand, negative or aversive information causes a phasic pause response of dopaminergic neurons [22], which leads to excitation of D2-receptor-positive medium spiny neurons [21]. Such dopamine neurons, which convey information about motivational value, were mainly observed in VTA [22], which is part of the mesolimbic dopaminergic circuit. This phasic change of dopamine release plays a crucial role in both positive- and negative-outcome learning. By using DA, especially non-ergot DA, D2 receptors may be stimulated continuously. Therefore, PD patients treated with DA cannot appropriately learn the meaning of cues that indicate a positive or negative outcome [17,23,24] which may lead to the development of ICD. In support of this speculation, several studies indicate that DA increase risk-taking behavior in PD patients with ICD [17,25,26]. In addition, recent studies on drug addiction and compulsive eating showed relationships between these symptoms and dysfunction

of the D2 receptor [27-29]. The functions of D3 receptor which densely express in NAc are also considered to play pivotal role in developing ICD [30].

According to a previous report, Deep Brain Stimulation (DBS) of the STN more frequently induces ICD-like symptoms than DBS of the internal part of the Globus Pallidus (GPi) [31-34], although most of these symptoms are transient. Medial part of the STN receives inputs from anterior cingulate cortex and sends outputs to ventral pallidum [35]. Modulating the activity of this area in the STN may leads to appearance of ICD. These results support the dysfunction of mesolimbic dopaminergic system in ICD patients. However, ICD is one possible therapeutic target for STNDBS to reduce DA administration [7-9] which may leads to improve ICD symptoms.. Therefore, more precise mechanisms of ICD should be clarified to achieve good outcomes after both DRT and functional neurosurgery.

Possible mechanisms of DAWS

The symptoms of DAWS have been reported to be similar to those of psychostimulant addiction withdrawal [10]. Acute reduction of DA after their long-term treatment may induce these syndromes. The symptoms include panic attacks, depression, diaphoresis, agitation, fatigue, pain, orthostatic hypotension, and drug craving [10]. The most common reason for a reduction of DA was shown to be the presence of ICD [10,36] and DAWS can protract ICD symptoms.

The mechanisms of DAWS are still unclear [37]. Recent studies have reported that DAWS can occur not only in PD, but also in other pathophysiologic situations such as restless legs syndrome [38] and microprolactinoma with DA treatment [39]. These results indicate that DAWS does not occur specifically in association with PD, and disproportionate dysfunction of mesolimbic vs. nigrostriatal motor systems [10] is not only a pathophysiology of this syndrome.

To understand the mechanisms of DWAS, it is important to understand the mechanisms of psychostimulant withdrawal syndrome (PWS), which has similar symptoms to DAWS. Psychostimulants that can induce addiction increase dopamine in the NAc [40]. The NAc receives dopaminergic input from VTA, and imbalance of tonic dopamine levels and phasic change of dopamine levels in the synaptic cleft have been suggested as mechanisms behind PWS [41,42]. According to this theory, psychostimulants induce a high concentration of dopamine in the synaptic cleft, by blocking dopamine transporters (cocaine, amphetamine), by disinhibition of VTA dopamine neurons (opioids), or by directly activating VTA dopamine neurons (tobacco products). A high concentration of dopamine in the synaptic cleft leads to stimulation of post-synaptic D2 receptors and a decrease of phasically released dopamine by stimulation of dopamine autoreceptors, which are located on dopaminergic nerve terminals. This leads to a consistently high concentration of dopamine in the synaptic cleft, which sets a high threshold of dopamine responsiveness in the striatum [43]. After a long period in this steady state, acute cessation of psychostimulants causes further imbalance of the tonic/phasic dopamine level (more tonic dopamine release by activation of cortical glutamatergic input to the VTA and less phasic dopamine release by activation

of autoreceptors of the dopaminergic nerve terminal), which leads to drug cravings and a dysphoric mood [42,44]. Although there is no evidence on DAWS patients and increasing activity of the cortex in humans, and many other neurotransmitters such as glutamate [45], serotonin [46], and acetylcholine [47] play pivotal roles in drug addiction and withdrawal syndrome, it would be interesting to determine the relationships between brain activity of the frontal cortex or neurotransmitters and DAWS in order to establish a treatment and to identify patients at a higher risk of developing DAWS.

Before characterizing the phenomenon of DAWS, we frequently experienced cases of depression after STNDBS in both the short and the long term [48,49] in up to 37.4% of patients [50]. A certain number of DAWS patients might be included among these because reduction of anti-parkinsonian drugs is one therapeutic target of STNDBS in advanced Parkinson's disease. After establishment of diagnosis of the syndrome, it is recommended to avoid acute reduction of dopaminergic drugs, especially DA, which can cause DAWS. Therefore, it is important to establish the pathophysiological mechanisms of DAWS and therapeutic mechanisms of STNDBS in order to develop better pharmacological therapy after surgical intervention for PD.

CONCLUSION

Since the 1990s, after Schultz's group identified the role of dopamine in reward systems [20], research in this field has mainly focused on the role of dopamine in reward and learning systems. On the other hand, after DeLong's group identified the role of the basal ganglia in movement disorders [51], research in this area has intensively focused on functional abnormality of the basal ganglia in motor dysfunction. After much attention focused on the non-motor symptoms of PD, studies on the role of dopamine and basal ganglia in PD have advanced markedly. Future research, on both animals and humans, should clarify the role of dopamine in each behavioral subtype of non-motor symptoms, including punding, hobbyism, and compulsive drug use.

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Shimo et al. (2014)
Email: nhattori@juntendo.ac.jp

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