The role of dopamine and serotonin in cervical dystonia

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GENERAL INTRODUCTION
Dystonia is a movement disorder characterized by involuntary, sustained muscle contractions causing twisting movements and abnormal postures. Dystonia has an estimated prevalence somewhere in the wide range of 32-7,370/million making it the third most common movement disorder, after Parkinson’s disease and tremor. Dystonia can be subdivided based on different characteristics. One of the most used classifications is based on topographic distribution: focal, segmental, multifocal, hemi- and generalized dystonia. This classification partly overlaps with a more causal classification. Generalized and multifocal dystonia usually present at young age (<25 years) and most commonly have a genetic cause. Focal and segmental dystonia usually present at a higher age (>25 years) and are in most cases considered to be idiopathic. Cervical dystonia (CD), dystonia of the neck, is the most common form of focal dystonia with an estimated prevalence of 20-4,100/million. The range is wide since it is likely that many patients do not visit a neurologist or are not properly diagnosed. Dystonic jerks or tremor of the head is present in approximately 50% of CD patients.

**History**

Although the term dystonia was first used in 1911 by Oppenheimer, several reports of torticollis, an old name for CD, were already published between the sixteenth and nineteenth century. Torticollis was the first type of dystonia to be identified and published on. Especially in the nineteenth century, several well-known neurologists in different European counties, including Bell, Romberg, Erb and Duchenne, published cases of patients with torticollis. One of the symptoms that gained a lot of attention was the ‘sensory trick’ or ‘geste antagonistique’. This symptom consists of a slight touch of the head or neck that can alleviate the abnormal posture of the head. In 1894, Brissaud, a pupil of Charcot, published a case series of patients with torticollis and a ‘sensory trick’. He described this as childish behavior and considered it the most important argument to consider torticollis as a mental disorder. After this, in several European countries cases of “mental torticollis” (Brissaud’s disease) were published. Even though, several neurologists including Babinski and Guillain over the years openly doubted the psychological origin of torticollis, it took until the extensive work of Marsden around 1975 before dystonia was accepted to be a neurological disorder. Nowadays, the presence of a sensory trick is an extra argument for “organic” dystonia.

**Non-motor symptoms**

The past years more attention has been given to symptoms that often accompany CD, the non-motor symptoms. Patients often mention pain (up to 75% of CD patients) and fatigue. There is an increasing awareness for psychiatric symptoms, mainly depressive symptoms and anxiety, that have a lifetime prevalence of 40-70% in CD patients.
Quality of life is usually impaired in patients with CD compared to controls and appears to be related to non-motor symptoms, particularly psychiatric symptoms, pain, fatigue and sleep disturbances, rather than motor symptoms (dystonia, tremor and jerks).

**Current treatment**

For CD and most other forms of focal dystonia the current state of the art treatment is with local botulinum neurotoxin (BoNT) injections. BoNT is a locally acting neurotoxin that blocks neuromuscular signal transmission, thereby paralyzing the injected muscles for approximately three months. Treatment with BoNT is highly effective for dystonic symptoms and pain and there are indications that treatment with BoNT improves quality of life. From clinical practice we know that dystonic jerks and tremor of the neck are more difficult to treat with BoNT. The results of BoNT treatment on fatigue and psychiatric symptoms are inconsistent. BoNT is an expensive therapy and because of the repeated injections in the cervical muscles also patient-unfriendly. To be able to develop a treatment that has an effect on the cause of CD, rather than only focusing on the reductions of symptomatology, a better understanding of the pathophysiology is required.

**Pathophysiology**

Not much is known regarding the pathophysiology of CD. About 10-20% of patients with focal dystonia have a positive family history for dystonia. The phenotype in family members with focal dystonia can be heterogeneous, suggesting a multifactorial pathophysiological mechanism with genetic and environmental factors. Thus far, several genes, including ANO3, GNAL, THAP1 and TOR1A, have been associated with CD but are all only present in a small percentage of CD patients. Neuroimaging studies have significantly contributed to the understanding of the underlying pathophysiological processes of dystonia. Over the years different techniques have been used and information gathered has led to the hypothesis of dystonia as a network disorder with involvement of the basal ganglia, cerebellum, thalamus and different cortical regions, for example the somatosensory cortex. Both the basal ganglia and the cerebellum are thought to have an increased level of activity. The abnormalities found in cortical regions are more difficult to interpret. One theory is that there is reduced surround inhibition in cortical motor areas, like the primary and premotor cortex. This would lead to an increased activated area on the motor cortex which causes too much muscle activation. This has for example been shown using functional MRI (fMRI) in patients with writer’s cramp, where there is a larger area of activation on the motor cortex during simple hand tasks. Another theory is that there is sensory-motor disintegration, in which sensory and motor information needed to initiate a voluntary movement is not
combined properly. One argument to support this theory is the frequently present sensory trick in patients with dystonia. Several studies have found abnormalities in processing of sensory input information using fMRI in patients with writer’s cramp.\textsuperscript{20, 21} Similar mechanisms are thought to underlie other types of dystonia, but these are more difficult to investigate as they are not task-specific.

**Dopamine**

As mentioned above, the basal ganglia are an important structure in the network model of dystonia, even though it is unclear whether the abnormalities in the basal ganglia are the cause of the dystonia or a compensating mechanism. Several studies have used positron emission tomography (PET) and single photon emission computed tomography (SPECT) to focus on different neurotransmitters in the brain.\textsuperscript{22-26} Historically, dopamine has received most attention when studying neurotransmitters in dystonia, as it is one of the most important neurotransmitters in the basal ganglia and CD has been hypothesized to be a disorder with increased levels of synaptic dopamine, e.g. a hyperdopaminergic disorder. One of the arguments is that neuroleptics, that mainly block dopamine D2 receptors and thereby increase synaptic levels of dopamine (by blocking dopamine D2 autoreceptors), can cause acute dystonic reactions and tardive dystonia.\textsuperscript{27} Furthermore, dopa-responsive dystonia (DRD) is a genetic form of dystonia that is associated with defects in the dopamine synthesis and responds well to levodopa. Neuroimaging studies using PET or SPECT and dopamine D2 receptor tracers have reported decreased striatal binding. However, it is difficult to determine whether reduced tracer binding is caused by competition with endogenous dopamine or by reduced binding sites, thus reduced number of dopamine receptors, or a combination of both. This question cannot be answered when a single tracer is used in a cohort. Far less studies investigated the presynaptic dopamine transporter (DAT) that is related to dopamine reuptake. The studies that have been performed were in small heterogeneous groups and did not investigate a possible relation between DAT binding and symptomatology.\textsuperscript{28}

**Serotonin**

The past years other neurotransmitters, such as serotonin and acetylcholine, have also gained interest in research on dystonia. Over the years decreased levels of 5-HIAA, the main metabolite of serotonin, have been found in the cerebrospinal fluid of patients with different forms of dystonia, including focal dystonia and DRD.\textsuperscript{29, 30} One of the most important reasons to investigate the role of the serotonin system is the high prevalence of psychiatric symptoms, especially depressive symptoms and anxiety, in patients with dystonia.\textsuperscript{8} Particularly these psychiatric conditions have been linked to the serotonin...
system and are usually treated with serotonergic drugs, for example selective serotonin reuptake inhibitors (SSRIs). On the one hand, in different forms of dystonia beneficial effects on motor symptoms have been described when patients were prescribed SSRIs, but on the other hand worsening of dystonia and dystonic reactions in patients who did not have dystonia before treatment with SSRIs have also been described. It has also been debated that most side effects of SSRIs, including dystonic reactions, are caused by an effect on other neurotransmitter systems, including the dopamine system. This would indicate that in patients with dystonia, when there is an indication for an SSRI, it would be wise to use an SSRI with the least effect on the dopamine system, e.g. escitalopram.

**Dopamine-serotonin imbalance**

The dopamine and serotonin systems in the brain are closely related and influence each other and it has been established that dopaminergic neurons contain serotonin receptors and vice versa. For example, serotonin $1_A$ receptor agonists influence serotonergic firing rate in the raphe nuclei, but also influence dopaminergic signaling. Recent studies in Parkinson's disease (PD), another common movement disorder, have shown dopamine-serotonin imbalance in relation to levo-dopa induced dyskinesias (LIDs). After 5-10 years, patients with PD often develop LIDs. These LIDs are associated with relatively intact serotonergic nerve terminals and PD patients with more available serotonin nerve terminals are more likely to develop LIDs. The main hypothesis is that serotoninergic neurons are able to produce dopamine, but not to regulate its synaptic release, causing considerable swings in dopamine concentrations. On molecular imaging studies these patients have a higher serotonin transporter (SERT) to DAT ratio in the striatum and it is likely that this imbalance leads to LIDs. In a mouse model of myoclonus dystonia, an inherited form of dystonia associated with myoclonus and psychiatric symptoms, the hypothesis of a dysbalanced dopamine-serotonin system has been confirmed. Neurochemical studies in the striata of these mice showed increased levels of dopamine metabolites, which correlated with motor performance (dystonia and jerks). In the same mice the level of serotonin metabolites, that was not significantly different from wild-type mice, inversely correlated with motor performance. The myoclonus in myoclonus-dystonia resembles the jerks that are often present in CD. This might indicate that the jerks in CD may also be related to comparable alterations of the serotonin and dopamine system. It is believed that the motor symptoms and psychiatric symptoms in dystonia have a common underlying biochemical pathophysiology, possibly expressed as dysbalanced dopamine and serotonin systems.
Nuclear imaging of neurotransmitter systems using spect

SPECT is a nuclear imaging technique that uses radiopharmaceuticals. These radiopharmaceuticals consist of 2 parts: a pharmaceutical that is aimed to bind to a specific receptor or transporter and a radioactive isotope. Radioactive decay leads to emission which can be detected by a SPECT camera. By positioning a collimator between the subject and the camera most photons are discarded and only photons that can pass the collimator under certain angles will reach the crystal of the camera. So, a collimator is used to estimate properly where a certain photon detected by the crystal of the camera came from. For brain imaging, usually scanners with multiple camera heads are used and reconstruction techniques, very similar to CT techniques, are used to reconstruct the images. The most commonly used SPECT tracers for brain imaging are coupled to either technetium-99 (99mTc) or iodine-123 (123I), both of which are stable enough to allow preparation, transportation and injection of the tracer with adequate image acquisition minutes to hours after injection. In SPECT brain imaging 99mTc-labeled tracers are most commonly used to study regional cerebral blood flow, with the exception of 99mTc-TRODAT that is used to study the DAT. 123I-labeled tracers are commonly used to study both the presynaptic DAT (e.g. [123I]FP-CIT or [123I]β-CIT) as well as postsynaptic dopamine receptors (e.g. [123I]IBZM). The last years it has become clear that [123I]FP-CIT and [123I]β-CIT can also be used to study the SERT and this technique is now well validated.36

Aim and outline of this thesis

In the first part of this thesis, the existing evidence regarding neuroimaging abnormalities in the brain of patients with focal dystonia is summarized in an extensive review (Chapter 2). Hereafter, the role of dopamine and serotonin are investigated using SPECT. For the first time, abnormalities in tracer binding to SERT, DAT and dopamine D2/3 receptors are investigated in a group of patients with CD compared to controls. Differences in tracer binding are studied in relation to clinical symptoms, both motor and psychiatric symptoms (Chapters 3 and 4). To attempt to restore neurotransmitter (especially dopamine-serotonin) balance, we conducted a double-blind, randomized, crossover trial with escitalopram, an SSRI. In this study, patients with CD and jerks received escitalopram and placebo and motor (dystonia and jerks) and non-motor (depression and anxiety) were scored and compared (Chapter 5). Finally, the results of treatment with the highly selective SSRI escitalopram on SERT occupancy, as well as on the dopaminergic system in relation to the clinical effects, is reported (Chapter 6).
REFERENCES


Chapter 1


