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Effects of acute tryptophan depletion on cognition, memory and motor performance in Parkinson's disease

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Abstract

Background: Parkinson's disease (PD) is a neuropsychiatric disease, which is not only characterized by motor symptoms, but also by cognitive and psychiatric symptoms. It is hypothesized that some of the non-motor symptoms are related to the serotonergic deficiency that is present in PD.
Aim: To study the influence of serotonin on cognition, memory and motor performance in PD.
Methods: In a double blind, randomized, placebo-controlled, cross-over design, the effect of acute tryptophan depletion (ATD) on the Visual Verbal Learning Task (VVLT), the Concept Shifting Task (CST), Simple Reaction Time Task (SRT), Finger Precuing Task (FPT) and the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS, Section 3) was investigated in 15 PD patients in early stages of their disease and 15 healthy volunteers, matched for age, sex and educational status.
Results: With the exception of the absence of a differential effect for PD patients with the long interval of the SRT, ATD produced similar effects in PD patients and control subjects on all tasks. These included impairment of delayed recall and delayed recognition on the VVLT, and improved SRT and FPT for 'short intervals'. The UPDRS in patients remained unaffected after ATD.
Conclusion: Serotonin does not appear to play a disease-specific role in cognition and reaction time in early stage PD patients, nor does acute reduction of cerebral serotonin levels affect motor symptoms in a clinically relevant way.

Keywords: Parkinson's disease; Serotonin; Acute tryptophan depletion; Cognition; Memory; Motor symptoms

1. Introduction

The involvement of the serotonergic system in Parkinson's disease (PD) has been recognized for a long time. Degeneration of serotonergic neurons, decreased serotonin content and alterations in the activities of various serotonin receptor subtypes have all been demonstrated in post-mortem studies, using neurochemical and autoradiographic techniques [1–9]. In vivo studies of 5-hydroxyindoleacetic acid (5-HIAA) in the cerebrospinal fluid (CSF) of PD patients have confirmed the post-mortem findings of a reduced serotonergic tone. Reduced CSF 5-HIAA levels have been described in numerous studies concerning PD [10–12]. The impact of reduced serotonergic activity in PD, however, is still unclear. In animals, serotonin reduces the activity of dopaminergic cells in the substantia nigra pars compacta and reduces striatal DA release [13,14]. Based on these observations, a compensatory role for the reduced striatal dopamine (DA) activity is hypothesized [15]. Moreover, serotonin activity influences several cognitive functions, such as memory consolidation and attention shifting [16–18].

Recent paradigms have made it possible to study the relationship between cerebral serotonin levels, and cognition and motor behavior in vivo. A widely used method for studying serotonergic function is acute tryptophan depletion (ATD) [19,20]. ATD lowers the level of brain serotonin by depleting the body of its amino acid precursor l-tryptophan

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(TRP). This is achieved by two mechanisms. First, oral administration of an amino acid mixture devoid of TRP stimulates peripheral protein synthesis, which results in removal of circulating TRP from the blood. Second, the transportation of TRP over the blood–brain barrier is reduced because of a competition between TRP and an abundance of other large neutral amino acids (LNAAs: valine, leucine, isoleucine, phenylalanine and tyrosine) for the same active transport mechanism. Once in the brain, tryptophan is synthesized into 5-hydroxytryptophan (5-HTP) by the enzyme TRP hydroxylase, and this then is decarboxylated by the enzyme aromatic acid decarboxylase into 5-hydroxytryptamine (5-HT, serotonin). ATD, accompanied by a protein free diet, results in a decrease of central serotonin levels of up to 80% [20,21]. This method of acutely lowering central levels of serotonin has been widely used in healthy and in psychiatric populations to study the role of serotonin in cognition and psychomotor action, but never before in PD patients [22–27].

The aim of the present study was to investigate the role of serotonin in cognitive and motor function in PD patients by temporarily reducing the level of available serotonin in the brain by means of ATD. Based on results from earlier investigations, we hypothesized that ATD might have a negative effect on cognitive performance, but due to a reduced inhibition of striatal dopamine release, as based on results from preclinical data, a positive effect on aspects of motor performance.

2. Methods

2.1. Subjects

Fifteen PD patients were included in the ATD study. They were recruited from the neurological outpatient department of the University Hospital Maastricht. All patients were diagnosed with M. Parkinson, according to the United Kingdom Parkinson's Disease Society Brain Bank (UK PDS BB) criteria [28]. Participation in the study did not have any influence on the medical treatment patients were receiving. Excluded were those patients who were diagnosed with any neurological disease other than M. Parkinson, or with any psychiatric disorder, including depression, as defined by the criteria of the Diagnostic and Statistical Manual (DSM IV) of the American Psychiatric Association (APA) [29]. This was established in a psychiatric interview. Other exclusion criteria were the use of psychoactive medication, such as antidepressants and antipsychotics, the use of L-dopa, the dopamine agonist lisuride, selegeline, the abuse of alcohol or drugs, and dementia which was defined by a score on the Mini Mental State Examination (MMSE) of less than 23. A prior personal or family history of depression was also considered a ground for exclusion. Control subjects were recruited from an existing database of volunteer subjects of the Maastricht Aging Study (MAAS) [30], and individually matched with the PD patients concerning age, sex and education level. The same in- and exclusion criteria applied to the control subjects, with the exception of M. Parkinson. The study was approved by the Medical Ethics Committee of the Maastricht University Hospital. All subjects gave their written consent prior to participation and received a financial compensation for participating in the study.

2.2. Design

The study was conducted according to a double-blind, placebo-controlled, randomized cross-over design. Treatment consisted of a placebo and TRP depleted mixture. The treatment days were at least 7 days apart in order to rule out any carry-over effects.

2.3. Intervention

The TRP free amino acid mixture consisted of 75 g of a mixture of 15 amino acids in the same composition as was used in earlier experiments by our group [31,32]. The placebo amino acid mixture was identical in composition, but contained 3.0 g of TRP. Amino acid drinks were prepared prior to intake by adding 250 ml tap water. Subjects were instructed to consume the mixture as fast as possible.

2.4. Procedure

All subjects underwent a training session before the actual two test days to control for learning effects. Before this test session, the subjects underwent a short physical examination, to rule out any possible physical exclusion criteria. Furthermore, the Hamilton Rating Scale for Depression (HAMD) and the MMSE were obtained to characterize the population [33]. All patients were staged according to the Hoehn and Yahr staging system [34]. On the test days, subjects arrived at 9.00 a.m., after an overnight fast. Starting the day, a baseline measurement was obtained after which the subjects received the amino acid mixture. The measurements were performed again at the point of maximal depletion, which was about 5.5 h after consumption of the mixture. Blood samples were taken at three times during the day (baseline, 3 and 5.5 h after intake of the mixture), in order to check the TRP/LNAA ratio in the subjects' blood plasma. This ratio can be used as a peripheral measure for central serotonin depletion. Subjects were free to drink water, and were served a protein free bread meal at lunchtime.

2.5. Outcome measures

The Visual Verbal Learning Task (VVLT) and the Concept Shifting Task (CST) were administered to inves-