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Acute administration of roflumilast enhances immediate recall of verbal word memory in healthy young adults

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ABSTRACT

The need for new and effective treatments for dementia remains indisputably high. Phosphodiesterase inhibitors (PDE-Is) have proven efficacy as cognitive enhancers based on their positive effects in numerous preclinical studies. Especially the PDE4 subfamily is of interest due to its expression in the hippocampus, the key structure for memory formation. The current study investigates the memory enhancing effects of the clinically approved PDE4-I roflumilast in a test battery including the Verbal Learning Task (VLT) combined with electroencephalography (EEG) recording. This acute study was conducted according to a double-blind, randomized, placebo-controlled, 4-way crossover design. Three capsulated dosages of roflumilast HCl (Daxas) and a placebo were administered in four study periods. Administration occurred 1 h before testing to reach maximal plasma concentrations. Memory performance was assessed using a 30 word Verbal Learning Task. The number of words recalled both immediately and after 45 min and 24 h were included as outcome measures. EEG was recorded during the cognitive tasks on the first day. Different event-related potentials (ERPs) were considered with special emphasis on P600, as this peak has been related to word learning. Memory performance was significantly improved after acute administration of 100 μg roflumilast. Specifically, immediate recall performance on the VLT increased 2–3 words, accompanied by an enhanced P600 peak during word presentation at the third learning trial. No side effects typical for PDE4-Is were reported for the lowest and effective dose of 100 μg roflumilast. The current proof-of-concept study shows for the first time the potential of low-dose roflumilast administration as a memory enhancer in humans.

1. Introduction

Despite the awareness of the increasing impact of dementia on society in the upcoming ages, an unjustified discrepancy exists between the extent of investigations into its underlying pathological mechanisms and current treatment strategies. Part of this can be attributed to the multi-causal nature of dementia. Recently, the FDA has indicated to be open for considering treatments for dementia and in particular Alzheimer's Disease (AD), that focus on having an effect on cognitive impairment (Kozauer and Katz, 2013), which will positively affect the array of approved treatment options.

Phosphodiesterase inhibitors (PDE-Is) can be considered as cognitive enhancers based on their positive effect on cognitive processes in numerous animal studies (Reneerkens et al., 2009; Heckman et al., 2015a,b). PDE-Is exert their effects downstream via modulation of the cyclic nucleotides cGMP and cAMP. These second messengers transfer an extracellular signal, such as the binding of a neurotransmitter to its receptor, into nonstructural (e.g. increased neurotransmitter release, receptor mobilization) and structural (e.g. receptor generation and/or synapse formation) cellular responses (Wei et al., 1998; Lu and Hawkins, 2002). The former implicates the activation of protein kinases and the latter the additional activation of specific transcription factors. Both responses increase the efficacy of signal transduction and may underlie neuronal plasticity including long-term potentiation (LTP);

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the underlying physiological substrate of memory (Bliss and Collingridge, 1993).

PDE4 represents one of the eleven phosphodiesterase families (PDE1-PDE11), each of which shows a different distribution throughout the body. PDE4 is known to be widely distributed in the brain, both in rats and humans (Reneerkens et al., 2009; Lakics et al., 2010). More specifically, PDE4 is highly expressed in the frontal cortex and hippocampus, key structures in memory function (Mclachlan et al., 2007). PDE4-Is exert their actions by the selective inhibition of PDE4, an enzyme which degrades the second messenger cAMP (Bender and Beavo, 2006). cAMP activates protein kinase A (PKA), which can eventually result in the phosphorylation of the transcription factor cAMP response element binding protein (P-CREB). PKA as well as P-CREB, which induces expression of CREB responsive genes, are involved in synaptic plasticity, memory and cognition (Frey et al., 1993; Barad et al., 1998; Li et al., 2011). Improvements in LTP and memory performance in rodents after PDE4 inhibition can be attenuated by concomitant inhibition of hippocampal cAMP/PKA/CREB signaling (Bollen et al., 2014; Bernabeu et al., 1997). Taken together, animal studies show that central PDE4 inhibition and its effect on LTP underlies the memory enhancing effects of PDE4-Is.

The development of PDE4-Is as cognition-enhancing drugs has been hampered by the dose-limiting emetic side effects in humans, particularly nausea and even vomiting (Hebenstreit et al., 1989; Puhan, 2011), as was evident with rolipram. Currently, PDE4-Is are being developed with a strongly improved therapeutical window by reducing the emetic side effects. Roflumilast (Daliresp or Daxas) is such an example which was approved by the FDA for the treatment of Chronic Obstructive Pulmonary Disease (COPD) in 2011 (Izquierdo and Aparicio, 2010; Chong et al., 2011). Recently, we (Vanmierlo et al., 2016) and others (Jabaris et al., 2015) have shown that roflumilast is brain penetrant and improves short-term and long-term memory in rodents. Importantly, a PET study with the ligand [18F]B9302-107 for roflumilast confirmed that the currently marketed dose for COPD is also brain penetrant in humans (Ji, 2009). On basis of these data, and the low emetic effects of roflumilast, this offered an excellent opportunity to investigate the cognitive effects of a PDE4-I in humans in a neuropsychological test battery.

In order to find the optimal acute dose for cognition enhancement in human subjects, we estimated the dose on basis of animal data (Vanmierlo et al., 2016). In addition, the dose should not induce emetic effects in humans. For COPD treatment, a daily dose of 500 μg roflumilast is prescribed which causes mild to moderate nausea in approximately 5% of the COPD patients (Rabe, 2011).

The performance on the verbal word learning task was the primary outcome measure. In addition, electroencephalography (EEG) recordings were included to examine whether the drug affected information processing in the brain. For the current study, we specifically expected potential memory improvements to be reflected in altered P600 amplitude since this Event-Related Potential (ERP) peak has been related to word learning (Balass et al., 2010).

2. Methods

2.1. Subjects

Forty-four healthy young university students were recruited through advertisements. The age-range for inclusion was 18–35 years of age. Informed consent was obtained from all volunteers and they received financial compensation. Exclusion criteria included current or history of cardiac, hepatic, renal, pulmonary, neurological, gastrointestinal, or hematological illness. In addition, volunteers with a first-degree relative with a psychiatric disorder including history of depressive disorder with or without suicidal risk were excluded as well. Other exclusion criteria were excessive drinking (>20 glasses of alcohol containing beverages a week), pregnancy or lactation, use of chronic medication other than oral contraceptives, use of recreational drugs from 2 weeks before until the end of the experiment, smoking, orthostatic hypotension, lactose intolerance, and sensory or motor deficits which could reasonably be expected to affect test performance. Subjects with current or a history of psychiatric illness were excluded as well based on the outcomes of a semi-structured neuropsychiatric interview (Apa, 1994). Two subjects were excluded because of psychopathology. The physical health of the remaining subjects was evaluated by a physician by means of a medical questionnaire and medical examination, including ECG, and blood and urine screening.

Out of this group, twenty-two subjects were selected for participation, based on their performance in the verbal learning task (VLT; Van Der Elst et al., 2005). Subjects performing in the lower and upper quartile were excluded in order to minimize floor- or ceiling effects (cf. Reneerkens et al., 2013). All procedures were approved by the local Medical Ethical Committee and in accordance with the declaration of Helsinki.

2.2. Design

This acute study was conducted according to a double-blind, randomized, placebo-controlled, 4-way crossover design. Order of treatments was balanced over the test days using orthogonal Latin square design. Test days were separated by a washout period of at least 10 days. Beforehand, subjects were familiarized with the setting and the cognitive test battery. After each test day, participants returned 24 h later to perform two cognitive tasks. EEG was recorded during the first day of testing only.

2.3. Treatment

Roflumilast HCl (Daxas) 500 μg tablets were grinded, and the appropriate quantities (i.e., 100, 300, 1000 μg) were distributed over capsules with lactose monohydrate as the principle constituent. The placebo capsules contained lactose monohydrate in an equivalent amount and the appearance was identical to the roflumilast capsules. The capsules were manufactured, blinded, and labelled by Basic Pharma Technologies BV (Geleen, the Netherlands) according to GMP regulations. Roflumilast was administered orally 1 h before testing based on maximum plasma concentrations (EMA, 2010).

2.4. Cognitive assessment

2.4.1. verbal learning task

The VLT is an adapted version of the original 15 word Rey auditory verbal learning test (Lezak, 1995), which assesses short- and long-term memory function for verbal information. The current task was developed to maximize the possibility of measuring enhancement rather than only impairment, by means of prolonging the list to 30 words (Riedel et al., 1999). The test consists of a list of 30 Dutch monosyllabic words (18 nouns and 12 adjectives). For each test day, a different validated version was used in each period. The use of the different versions was counterbalanced over the four periods. Words were shown on a computer screen for 1 s which was followed by a 2 s inter-trial interval. Each trial ended with a free recall of the words (immediate recall). Forty-five minutes after the first exposure, the participants were asked to recall as many words as possible (delayed recall). EEG was recorded during the learning