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Acute treatment with the PDE4 inhibitor roflumilast improves verbal word memory in healthy old individuals: a double-blind placebo-controlled study

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ABSTRACT

There is ample evidence that phosphodiesterase 4 (PDE4) inhibition can improve memory performance in animal studies. In the present study, we examined the acute effects of the PDE4 inhibitor roflumilast on memory performance in healthy individuals (60–80 years of age). We tested the effects of acute roflumilast administration (100, 250, 1000 μg) in a double-blind, placebo-controlled, 4-way crossover design. Participants were first screened for their verbal word memory performance to ensure normal memory performance (within 0.5 standard deviation from norm score; n = 20) Drug effects on memory performance were tested in a verbal memory test and a spatial memory test. Reported side effects of drug treatment were registered. Roflumilast (100 μg) improved the delayed recall performance of the participants (Cohen's d, 0.69). No effects were observed in the spatial memory task. Roflumilast was well tolerated at this low dose. Although no clear adverse side effects were reported at the low dose, mild adverse events (including headache, dizziness, insomnia, and diarrhea) were reported after the 1000 μg dose. The present study provides first evidence that the PDE4 inhibitor roflumilast improves verbal memory performance in old participants. The current data encourage further development of PDE4 inhibitors for improving memory.

1. Introduction

Various neurological and psychiatric conditions are associated with impaired cognitive functions. Despite an enormous research effort to identify targets and develop drugs to improve these cognitive functions, effective treatments are lacking (Millan et al., 2012). One drug target that has been associated with long-term potentiation (LTP), a neurophysiological correlate of memory formation, is cyclic adenosine monophosphate (cAMP), an intracellular second messenger. Many studies have shown beneficial effects on memory performance after induction of cAMP elevation in animal models (Lee, 2015).

Phosphodiesterases (PDEs) are enzymes that break down the cyclic nucleotides cAMP and cyclic guanosine monophosphate. There is a large superfamily of PDEs consisting of 11 different family members each having different isoforms (Bender and Beavo, 2006). The phosphodiesterase 4 (PDE4) subfamily is selective for degrading cAMP, and selective PDE4 inhibitors have been shown to increase neuronal cAMP levels. Accordingly, a vast number of studies have shown improved learning and memory performance and enhanced LTP after treatment with PDE4 inhibitors (e.g., Bollen et al., 2014; Peters et al., 2014; Richter et al., 2013). Moreover, PDE4 inhibition has been shown to ameliorate cognitive functions in different species (Rutten et al., 2008; Rutter et al., 2014) and disease models (e.g., Bourtchuladze et al., 1994; Sierksma et al., 2014).

Taken together, there is strong support from various models that PDE4 inhibition may improve memory performance via increased cAMP levels. The next step is to test the effects of a PDE4 inhibitor in humans. Unfortunately, it is well known that PDE4 inhibition is associated with emetic side effects, that is, nausea and emesis (e.g., Hebenstreit et al., 1989). This has prevented the development of PDE4 inhibitors as antidepressants or cognition enhancers. Roflumilast (Daliresp or Daxas) is a PDE4 inhibitor with a relative favorable therapeutic window. The drug has been approved by the

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FDA for the treatment of exacerbations in chronic obstructive pulmonary disease (COPD) in 2011 (Hebenstreit et al., 1989). For the dose of 500 μg, which is required to induce anti-inflammatory action for treatment of exacerbations in COPD, adverse side effects including nausea and diarrhea have been reported. Interestingly, different animal studies showed that roflumilast improved memory at nonemetic doses (Jabaris et al., 2015; Vanmierlo et al., 2016). Importantly, roflumilast has been shown to be a brain penetrant (Takano et al., 2018; Vanmierlo et al., 2016). These features of roflumilast make this PDE4 inhibitor an excellent drug to examine its possible cognition enhancing effects in humans.

In a previous study with young healthy volunteers, we showed improved immediate recall performance after roflumilast treatment (Van Duinen et al., 2018). Based on these findings, we tested the effects of roflumilast in old participants with no apparent memory impairment. The level of the memory performance was based on normative data of the verbal word learning task (VLT) (Van der Elst et al., 2005). The individuals were tested according to a double-blind placebo-controlled four-way crossover design. We tested 3 different doses to determine the dose dependency of the drug. As described in the protocol (see Trial Registration ISRCTN96013814), the primary outcome measures were the number of words remembered and recognized in a VLT. We also assessed the effects of roflumilast in a spatial memory task (SMT) and a Stroop test which assess other aspect of the memory domain and attention/response inhibition, respectively. Finally, the reported adverse side effects were evaluated to determine the therapeutic window of roflumilast.

2. Methods

2.1. Participants

All procedures were approved by the local Medical Ethical Committee and were in accordance with the Helsinki Declaration of 1975 (as revised in 1983). The study was monitored by the contract research organization Quintiles (current name IQVIA) to implement quality assurance and quality control. Healthy old individuals (60–80 years of age) were recruited through advertisements. The individuals were screened using a VLT to determine their memory performance. We used normative data of the VLT (based on 1855 healthy participants Van der Elst et al., 2005) to assign the individuals to a “normal” performance group. According to the normative data, scores were corrected for age, sex, and education level. The education level was categorized as 1, 2, or 3, which refers to an average of 8.6, 11.4, and 15.3 years of full-time education (Van der Elst et al., 2005). Performance was considered normal when individuals scored within 0.5 standard deviation of the predicted normative score. For screening purposes, we also administered the Mini-Mental State Examination. The score on this test had to be at least 24 to exclude severe memory complaints. After screening, 20 participants with normal memory performance were enrolled in our study (see Consort flow diagram in Supplementary Material). All participants signed an informed consent to participate in the study, and they received financial compensation for their participation.

Exclusion criteria included current or history of cardiac, hepatic, renal, pulmonary, neurological, gastrointestinal, or hematological illness. Further exclusion criteria were orthostatic hypotension, lactose intolerance, and any sensory or motor deficits which could reasonably be expected to affect test performance. Participants with current or a history of psychiatric illness and psychoactive medication were excluded (e.g., cholinesterase inhibitors, memantine, antidepressants, and benzodiazepines), which was partly based on the outcomes of a semistructured neuropsychiatric interview (Sheehan et al., 1998). Furthermore, the use of illicit drugs (e.g., amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, and opiates) was considered as an exclusion criterion if they were detected in the blood and urine screening.

The physical health of the remaining participants was evaluated by a physician by means of a medical questionnaire and medical examination, including electrocardiogram, blood, and urine screening.

2.2. Treatment

Roflumilast HCl (Daliresp or Daxas) capsules were manufactured and prepared by Takeda according to Good Manufacturing Practice guidelines. The capsules containing placebo and the different doses were identical with regard to the shape and color. The capsules were coded by Fisher Clinical Services (Horsham, UK). Next to placebo, 3 different doses were used, that is, 100, 250, and 1000 μg. Roflumilast was administered orally 1 hour before testing to result in maximum plasma concentrations (Hauns et al., 2006). The study was conducted according to a double-blind, placebo-controlled, 4-way crossover design. The order of treatments was predefined and balanced over the test days. Test days were separated by a washout period of at least 12 days. This was required on the basis of the half-life of roflumilast N-oxide, the active metabolite of roflumilast. After the experiment was completed, the data sets were locked. Then the treatment order was decoded for statistical analyses.

2.3. Cognitive testing

Before the participants were subjected to the actual testing, they were familiarized with the setting and the cognitive test battery on a separate training day. After each test day, participants returned 24 hours later to repeat 3 cognitive tasks.

2.3.1. Verbal learning task

The VLT is an adapted version of the original 15-word Rey auditory verbal learning test, which assesses short- and long-term memory function for verbal information (e.g., Van der Elst et al., 2005). 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). The stimuli were presented on a 17-inch computer screen controlled by a PC. The words were displayed in capital letters of the font “Times” size 72, in white against a black background and in the center of the screen. We used different word lists for each session. Furthermore, we used different list versions that were counterbalanced over the 4 treatment conditions. Words were shown on a computer screen for 1 second which was followed by a 2-s intertrial interval. Each trial ended with a free recall of the words (immediate recall). This list of 30 words was presented 3 times in total and followed by an immediate recall test. Forty-five minutes after the first presentation, the participants were asked to recall as many words as possible (delayed recall). During the 45-min interval, the participants did other cognitive tests (see below). The next day, the participants came back to the laboratory and were tested for the 24-h delay performance.

2.3.2. Spatial memory task

The SMT assesses spatial memory and is based on the object relocation task by Kessels et al., 1999. It consists of 1 immediate and 2 delay conditions. In the immediate condition, a set of 10 pictures was presented 1 by 1 on different locations within a white square on a computer screen. All pictures were everyday, easy-to-name objects presented in grayscale (about 3.5 × 5 cm). Each picture

was presented for 2 seconds with an interstimulus interval of 1 second. This was followed by a "relocation" part, which consists of the presentation of a picture in the middle of the screen, followed by a "1" and a "2" being presented on 2 different locations. The participants' task is to decide where the picture was originally presented, in location "1" or location "2." The "1" and "2" remain on the screen until the participant responds. After relocation, which is accomplished by a button press, the next picture is presented followed by the "1/2" choice option. This continues until all 10 pictures are relocated. Thereafter, the next set of 10 pictures was presented. A total of 6 sets of 10 pictures were displayed. Forty-five minutes later, participants perform the first delayed relocation version. The original locations are not presented again. Twenty-four hours after the immediate condition, participants returned to the laboratory to perform the task again. This time, the SMT only included a recognition phase. They were shown 60 old pictures (from the SMT task) and 60 new pictures (not seen before in the SMT task) in 6 blocks of 20 pictures each (each block contains 10 old and 10 new pictures). Within 2 seconds, they had to decide whether these pictures were presented in the learning trials by a "yes/no" response. If participants indicated that they had seen a picture before, they were again presented with a "1" and a "2" on 2 different locations, regardless of the correctness of their response. Once more, they had to decide whether the picture was previously presented in location "1" or location "2." The "1" and "2" remained on the screen until the participant responded. If the participant indicated that the picture presented was new, no reply with regard to the original location was made. In that case, participants had to press the space bar and the next picture was presented. The number of correctly localized items was collected during the immediate and 2 delay periods. Reaction times to make a response were also registered.

2.3.3. Stroop

The Stroop task is well known for its ability to induce interference and assesses response inhibition and focused attention (Van der Elst et al., 2006). In this task, color names (in Dutch) are presented on a computer screen in colored font colors; in the congruent category, the color name and the color font are the same, in the incongruent category they are not. Participants have to indicate the font color by pressing a corresponding button (i.e., correct or not correct), not the meaning of the words. However, because of the automatic tendency to read words, interference occurs. Because the written words and ink font differ in the incongruent category, interference is larger in this category than in the congruent category; this is called the "Stroop effect" and is known to remain even after extended practice. The colors used in this task are blue, red, green, and yellow. The color of the font has to be indicated by pressing 1 of 4 buttons, with each representing one of the colors. In total, 144 stimuli are presented; 72 congruent and 72 incongruent items. The main performance measures are the reaction time and the correct responses. The Stroop task was also presented at the 24-h measurement.

2.4. Pharmacokinetics

Blood samples were collected for measurement of roflumilast and roflumilast N-oxide concentrations just before and after the cognitive battery measurements and on the next day (i.e., 1.17, 2.33, and 24.5 hours after administration, respectively). Plasma concentrations of roflumilast and roflumilast N-oxide were determined using a validated assay using high-performance liquid chromatography with tandem mass spectrometry method (Knebel et al., 2012). Average drug concentrations were calculated at the 3 different time points. If in an experimental group a sample measurement was below the detection limit, yet other samples showed a value (which was always the case), then a value of zero was used. Missing values were not included when calculating such averages.

2.5. Subjective (adverse) effects

At baseline and during cognitive testing, a Bond and Lader questionnaire was administered to assess subjective alertness using a visual analog rating scale (Bond and Lader, 1974). In total, the questionnaire consists of 16 items, 9 of which comprise the subjective alertness subscale. During the 24-h measurement, participants completed the questionnaire again to assess their well-being. In addition, self-reported adverse events were then scored using the Medical Dictionary for Regulatory Activities (MedDRA, version 16.1). Individuals were asked to rate the adverse effects as absent, mild, moderate, or severe.

2.6. Statistical analyses

The primary outcome measure was defined as VLT outcome scores, captured as number of recalled items both in the immediate and in the 2 delayed tests (45 minutes and 24 hours). The variables of the SMT, the Stroop task, and the Bond and Lader scale were secondary outcome measures. Statistical analyses were performed using SPSS. General Linear Model for repeated measures was applied with dose as a within-subject factor. Post hoc analyses (Sidak) were performed to examine dose effects in more detail. In the Bond and Lader scale, treatment effects were analyzed per individual items. A Bonferroni correction was applied to correct for multiple comparisons for all measures of the Bond and Lader. Although one participant was excluded from the behavioral analysis (see Results), the data of all participants were used for the plasma analysis.

3. Results

3.1. Participants

An overview of the demographic characteristics of the population is shown in Table 1. One participant was excluded because this participant did not comply with the protocol instructions.

3.2. Verbal learning task

Over the first 3 trials, the number of recalled words increased [$F(2,114) = 145.26$, $p < 0.001$; see Fig. 1]. Treatment with roflumilast did not have an effect on this immediate recall performance (treatment and treatment*trials: F's > 1.26, n.s.). The delayed recall performance (45 minutes delay) was improved by roflumilast [$F(3,57) = 3.16$, $p < 0.016$]. Post hoc analysis revealed that only treatment with the 100 μg dose increased the number of recalled words with 1.9 words (contrast with placebo: 95% CI 0.36–3.54, $p < 0.011$). The associated effect size was 0.69 (Cohen's d). No effects of

Table 1
Demographic data of the old participants with normal memory performance

	Participants
Age	69.7, 63–78 (0.93)
Sex	15 male/5 female
Smoking	3 (out of 20)
BMI	24.5 (0.65)
Education	2.38 (0.13)

Data represent means, range (SEM). Educational level was score as 1 (low), 2 (middle), and 3 (high).
Key: BMI, body mass index.

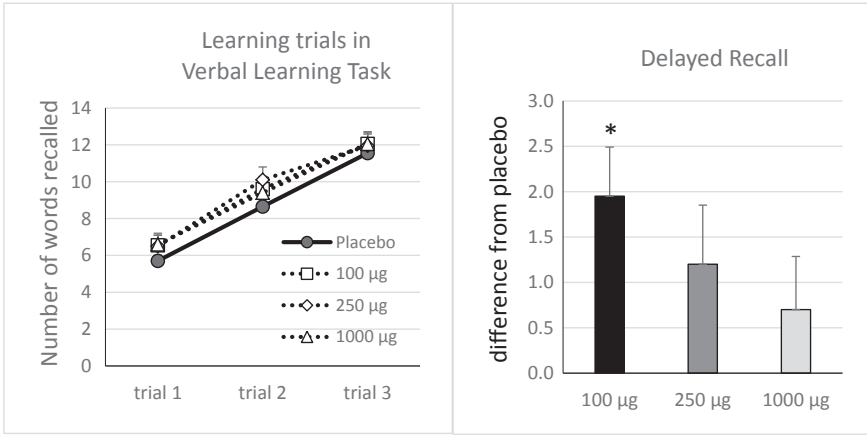

Fig. 1. Performance in the verbal word learning task after treatment with roflumilast. In the left panel, the immediate recall performance on the first 3 trials is presented. In the right panel, the difference scores (different from the placebo condition) for the delayed recall were calculated for the difference doses. All data represent mean (+SEM); *, $p < 0.011$.

roflumilast were found at the 24-hour delay recall scores (data not shown).

3.3. Spatial memory task

Roflumilast did not improve the memory parameters in the spatial memory test. Some incidental effects were found (see Table 2).

3.4. Stroop test

Roflumilast did not have an effect on the behavioral measures in the Stroop test.

3.5. Physical and subjective complaints

The number, percentage, and severity of the complaints reported by the participants are shown in Table 3. Adverse events were scored as mild, moderate, or severe. Only mild complaints were experienced. None of the participants reported any adverse effects that were moderate or severe in intensity.

Analyses of Bond and Lader subscale items did not show effects of roflumilast treatment were found.

3.6. Pharmacokinetics

The plasma concentrations of roflumilast and roflumilast N-oxide are shown in Table 4. The pharmacokinetic data would fit historical data in healthy participants and participants with COPD published in the literature (Lahu et al., 2010).

4. Discussion

The aim of the present study was to examine whether the PDE4 inhibitor roflumilast could improve memory performance in healthy old participants with a normal verbal learning memory performance (within 0.5 standard deviation of the norm). Roflumilast improved the delayed recall memory performance in a VLT. The performance was improved by 1.9 words, which is an increase of about 30%. This improvement was associated with a large effect size (Cohen's d 0.69). This is a first study showing that a PDE4 inhibitor (roflumilast) can improve delayed recall performance in old human individuals.

In a previous study, we found that roflumilast improved the immediate recall performance, but not delayed recall performance, in young healthy volunteers (Van Duinen et al., 2018). It is interesting to note that the present study with elderly showed an improved memory at a dose of 100 µg, which is the same dose at which we found a positive effect on verbal memory in young healthy participants (Van Duinen et al., 2018). However, it should be noted that in our previous study, roflumilast improved the immediate third recall but not the delayed recall. These differences may be related to the differences in baseline performance in young and old individuals and age-related differences in forgetting. On the one hand, the young participants had high baseline performances, which could have obscured an effect on delayed recall (ceiling effect, see Van Duinen et al., 2018). On the other hand, old participants improved their immediate recall scores much slower than the young participants did. In addition, the forgetting after 45 minutes was more pronounced in old participants, which offers more room for improving recall performance. Of note, from a clinical perspective, it is more relevant that the older participants showed a better delayed recall performance after 45 minutes as actually this performance has most predictive value regarding the progression of dementia toward the onset of Alzheimer's disease (Hamel et al., 2015). Finally, it could be argued that the cAMP tone in the 2 different ages may differ (Ramos et al., 2003) and that this may lead to a differential effect on the delayed memory performance in both age groups.

Table 2
Effects of acute roflumilast treatment (100, 250, and 1000 µg) on the secondary outcome measures in the spatial memory task

Spatial memory test	Difference	95% confidence interval
Immediate recall (number correct)	–	
Immediate recall (reaction time)	1000 µg: 169 ms (slower)	18–321 ms ($p < 0.03$)
Delayed recall (Number correct)	–	
Delayed recall (reaction time)	–	
24-h Recognition (incorrect new)	250 µg: 3.4 items (more)	0.94–5.87 items ($p < 0.008$)

Statistical reliable differences were analyzed using the placebo condition as contrast for the different variables.

Table 3
A summary of the most frequently reported adverse events

Adverse event	Number of participants			
	Placebo, n = 20	Roflumilast 100 μg, n = 20	Roflumilast 250 μg, n = 20	Roflumilast 1000 μg, n = 20
Headache	4	3	4	7
Dizziness	-	-	1	4
Fatigue	3	1	-	1
Insomnia	-	-	1	4
Nausea	-	1	-	1
Diarrhea	-	-	1	2
Other[a]	2	-	2	4

All entries are reports of mild events. No moderate or severe adverse events were reported.
[a] Includes muscle strain, stomach acid, cramps, back pain, or transpiration.

Although we observed a memory-enhancing effect in the verbal memory test, we did not observe an effect of roflumilast in the spatial task. Animal studies have shown that PDE4 inhibition can improve spatial memory performance in different models (Peters et al., 2014; Vanmierlo et al., 2016). However, it should be noted that animal studies do not always predict an effect in human models. In addition, the type of spatial information that the participants had to process in the current spatial test is different from the spatial memory in the test used in animals. Maybe other spatial tests have to be considered for testing the effects of PDE4 inhibitors in spatial memory (e.g., Nonaka et al., 2017).

Like in the previous study with young healthy adults (Van Duinen et al., 2017), the plasma levels and the pharmacokinetic data of roflumilast and the roflumilast N-oxide in the old participants were generally consistent with the historical data in healthy participants published in the literature (Lahu et al., 2010). For instance, the highest dose of 1000 μg roflumilast has similar plasma levels of roflumilast and roflumilast N-oxide as known for repeated daily administration of 500 μg roflumilast (Lahu et al., 2010). This indicates that the drug exposure is the same in both the young and elderly populations.

A positron emission tomography study confirmed that the marketed 500 μg dose for COPD has brain penetration in humans (Ji, 2010). Further support of brain penetration comes from a positron emission tomography study in nonhuman primates (Takano et al., 2018) and our previous study with young healthy adults showing an effect on both VLT memory performance and EEG (Van Duinen et al., 2018). Furthermore, a central effect is supported by a recent study showing an effect on sensory gating in young health volunteers (Heckman et al., 2018). Of note, the VLT task and sensory gating were assessed 1 hour after administration, which is at t_{max} for roflumilast (Lahu et al., 2010). Mainly based on pharmacokinetic animal data (see Vanmierlo et al., 2016), it can be extrapolated that the maximal plasma concentrations of the 100 μg dose results in brain concentrations, which are below the PDE4 IC50, that is, 50% enzyme inhibition (see also Van Duinen et al., 2018). This also aligns to the finding that similar plasma levels of roflumilast like those at the t_{max} in our human studies resulted in a low brain PDE4 occupancy of about 5%–10% in the nonhuman primate (Takano et al., 2018). Apparently, more enzyme occupancy and stronger enzyme inhibition is not effective to improve brain function which is in accordance with the animal data (Vanmierlo et al., 2016).

It is important to note that the 1000 μg acutely dose (present study) results in plasma levels corresponding to a chronic daily dose of 500 μg as being prescribed for COPD. This dose has been reported to cause nausea in approximately 5% of the patients with COPD (Rabe et al., 2005), which contributed to the drug being considered safe and approved for treatment. In the present study, nausea was reported likewise in 5% (1 participant) of the participants with similar plasma levels after a single dose of 1000 μg. A lower single dose of 250 μg roflumilast had no case of nausea, although after the lowest dose of 100 μg roflumilast, again one participant reported nausea. Another important side effect to consider is diarrhea. At the memory-enhancing dose of 100 μg, no effects on diarrhea were reported. After administration of 250 μg, the incidence for diarrhea is low (1 participant), yet it increased to 2 participants after administration of 1000 μg. Two other known side effects of roflumilast are dizziness and insomnia. At the 2 lower doses, this is still incidental (5% for each symptom), but is clearly present at the highest dose (20% for each symptom). Considering the occurrence of the memory-enhancing effect at the lowest dose (100 μg) and the occurrence of adverse effects at the higher doses, it can be argued that roflumilast has a very favorable therapeutic window. It should also be noted that the participants only reported mild effects, whereas no moderate or severe effects were reported.

Because the clinical potential of PDE inhibitor gained interest, there has been a great effort in developing PDE4 inhibitors for the treatment of cognitive dysfunctions. However, the development was hampered by the emetic side effects of PDE4 inhibitors (e.g., Richter et al., 2013; Robichaud et al., 2002). Roflumilast appears to be an exception because no clear adverse effects were reported, especially not at the dose that improved the memory performance. Recent studies showed that the subfamily PDE4D could be the best target for memory enhancement (Gurney et al., 2015; Richter et al.,

Table 4
Plasma concentrations (ng/mL) of roflumilast and its N-Oxide at different postdose times (h) in the healthy elderly

Time	100 μg			250 μg			1000 μg		
	N	mean	SD	N	mean	SD	N	mean	SD
Roflumilast									
1.17	17	0.83	0.61	20	2.74	1.36	18	7.77	4.56
2.33	17	0.98	0.63	15	3.42	4.06	17	8.37	2.77
24.5	18	0.11	0.06	19	0.32	0.20	19	1.21	0.61
N-Oxide									
1.17	17	0.64	0.52	20	2.22	1.28	18	5.43	3.73
2.33	17	1.21	0.62	15	3.91	2.56	17	10.56	6.04
24.5	18	1.23	0.30	19	3.51	2.12	19	11.75	2.77

Key: SD, standard deviation.

2013; Zhang et al., 2017). First inhibitors of PDE4D have been developed, and one approach to reduce emetic effects is the development of negative allosteric inhibitors, which partially inhibit PDE4D (Burgin et al., 2010; Zhang et al., 2017). Another approach is to develop full PDE4D inhibitors, which seem to have less affinity for the PDE4D isoforms involved in emesis (e.g., Bruno et al., 2011; Ricciarelli et al., 2017). Although roflumilast is not selective for the different PDE4 isoforms, developing selective PDE4D inhibitors appears promising to minimize the adverse side effects.

Some limitations could be linked with the current findings. Although we performed a power analysis to test an appropriate group size, it could be argued that a bigger group size is required to more firmly conclude that roflumilast improves memory. A second possible limitation is related to the mechanism of action by which roflumilast improved the verbal recall performance. Animal studies indicate that acute PDE4 inhibition improves memory function via hippocampal LTP (Bollen et al., 2014). The available data suggest that roflumilast enters the brain, but the exact mechanism of action, also in relation to the level of enzyme inhibition, remains to be demonstrated in humans. Third, although we investigated the effects of roflumilast treatment in young individuals (Van Duinen et al., 2018), we did not compare young and old participants directly in one study. Therefore, we cannot make any direct inferences with respect to age-related effects of roflumilast treatment yet.

In the present study, we examined the effects of treatment by comparing the effects of roflumilast with the placebo condition. This may not reflect the effects of roflumilast treatment as a function of baseline impairment that can be observed in this age group (without any treatment). Finally, the present study applied an acute administration of the drug, whereas it needs to be demonstrated whether long-term use will also have beneficial effects. Thus, it could be argued that the PDE4 enzyme desensitizes or that the enzyme is upregulated, which would limit the effects of a PDE4 inhibitor after long-term treatment. Interestingly, a recent study showed that roflumilast improved verbal word memory in schizophrenic patients after 8 days of treatment (Gilleen et al., 2018). This may suggest that PDE4 inhibitors could be used for long-term treatments.

In summary, we found that acute roflumilast treatment selectively improved episodic verbal memory in old participants. Importantly, long-term treatment with PDE4 inhibitors also improved brain plasticity and memory in rodent models of aging and even Alzheimer's disease (see Heckman et al., 2015). We therefore assume that chronic treatment may have a beneficial effect on brain function and thus may delay memory decline in old age. On basis of the current data, we feel that chronic studies are warranted as they may test the potential of PDE4 inhibitors. In addition, it could be speculated that PDE4 inhibition may also improve memory performance in other neuropsychiatric conditions.

Disclosure

AB, JP, and AS have a proprietary interest in the PDE4 inhibitor roflumilast. MT, GL, and TU are employees of Takeda Development Center Americas.

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Authors' contribution: AB, MvD, AS, TU, and JP were responsible for the design of the study; MvD, AS, and PH conducted the study; MT analyzed the data; GL was responsible for the pharmacokinetics; AB, AS, and JP wrote the article; all authors gave comments on earlier versions of the article.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2019.01.014.

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