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Research report

PDE2 and PDE10, but not PDE5, inhibition affect basic auditory information processing in rats

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H I G H L I G H T S

- The PDE2-I BAY 60-7550 affects auditory information processing in the vertex.
- The PDE10-I PQ-10 affects auditory information processing in the hippocampus.
- The PDE5-I vardenafil does not affect auditory information processing.

A R T I C L E I N F O

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Phosphodiesterase type 2 (PDE2), type 10 (PDE10), and type 5 (PDE5) have been considered as relevant targets for cognition enhancement. Although it is well established that PDE inhibitors (PDE-Is) improve memory functions in animals, the effects on auditory information processing are less clear. The aim of this study was to test the effects of PDE2 (BAY 60-7550), PDE5 (vardenafil) and PDE10 (PQ-10) inhibition on sensory gating in rats. Vehicle or 1 mg/kg of a specific PDE-I was given orally 30 min before testing. EEG was recorded from the hippocampus, striatum and vertex. Sensory gating was found for the N1 in the vertex and hippocampus, as revealed by diminished amplitudes to S2 compared to S1. Administration of PDE-Is did not affect sensory gating. However, PDE2 inhibition increased the P1 peak after presentation of S1 at the vertex and PQ-10 increased the N1 peak in general compared to vehicle treatment at the hippocampus. PDE2 and PDE10 inhibition affect auditory information processing in general, whereas PDE5 inhibition has no effect. These findings suggest that the positive effects of PDE5 inhibition on cognition previously found in animals are possibly the results of an effect on higher cognitive functioning specifically, whereas the cognition enhancing effects of PDE2 and PDE10 inhibition might also be influenced by effects on earlier stages of information processing.

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1. Introduction

Phosphodiesterases (PDEs) are enzymes that selectively hydrolyze the second messengers cyclic guanosine monophosphate (cGMP) and/or cyclic adenosine monophosphate (cAMP) by breaking their phosphodiester bond. It has been shown that compounds that inhibit these PDEs, so-called PDE inhibitors (PDE-Is), improve cognitive functioning in a wide variety of behavioral paradigms (for a review see [1,2]). More specifically, it has been demonstrated in various tasks that cGMP-specific PDE5-Is improve memory and learning in unimpaired rodents,

but also in animals with pharmacologically-induced memory deficits or in mice models of Alzheimer's disease (AD) (e.g. [3–8]). Furthermore, the PDE5-I sildenafil improved executive functioning in cynomolgus macaques [9]. In contrast, PDE5 inhibition failed to improve performance on memory and executive functioning tasks in healthy humans so far [10–12], although an improvement was found in patients suffering from erectile dysfunction [13]. The effects of PDE2-Is and PDE10-Is, which elevate both cGMP and cAMP, on cognition have not been investigated very extensively yet. However, it has been shown that the PDE2-I BAY 60-7550 can improve learning and memory in unimpaired rodents as well as in animals impaired by age or pharmacological intervention (e.g. [14–17]). Additionally, PDE2 inhibition improved memory function in a mouse model of AD [18] and executive functioning in pharmacologically-impaired rats [19]. Finally, PDE10 inhibition improved executive functioning and attention in rhesus monkeys [20] and reversed memory deficits induced by pharmacological

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intervention in rats [21,22], but the results in healthy rodents varied [20,22,23]. These results have led to an increased attention for PDEs as a promising target for cognition enhancement.

Localization studies demonstrated that mRNA expression of PDE2 [24–27], PDE5 [24,25,28] and PDE10 [24,29–31] could all be detected in the cortex and hippocampus of mammals with PDE2 mRNA expression being highest and PDE5 mRNA expression being lowest. In addition, in the striatum predominantly PDE10 and – to a lesser extent – PDE2 mRNA expression was demonstrated as well. Combining the behavioral data in the memory deficit models with these localization data support the notion that these PDE-Is might be a suitable tool to treat memory deficits [1,2,32].

Interestingly, the PDE10-I TP-10 was able to reverse d-amphetamine, an indirect-acting monoaminergic agonist known to disrupt sensory gating in humans and animals, induced deficits in a sensory gating paradigm which assesses basic information processing [33]. A study by Grauer et al. [22] indicated that PDE10 inhibition has a positive effect on prepulse inhibition (PPI), which also addresses information processing, in rats and mice. This implies that the therapeutic use of a PDE-I and in particular a PDE10-I might not be limited to memory dysfunction, but also extend to early stages of (auditory) information processing.

In the present study we therefore specifically investigated the effects of PDE inhibition on information processing, in particular sensory gating in rats. Sensory gating is an adaptive mechanism that helps to prevent overstimulation of higher cortical areas with sensory information (for review see e.g. [34]). This mechanism can be assessed by using a paradigm in which two identical, auditory stimuli are presented with an inter stimulus interval (ISI) of 500 ms and an inter trial interval (ITI) of at least 6 s. Normally, the response to the first auditory stimulus (S1) is significantly larger than the response to the second stimulus (S2) reflecting sensory gating. However, this mechanism can be disrupted by e.g. pharmacological intervention with d-amphetamine [33,35] or clinical disorders such as Alzheimer's disease or schizophrenia [36–38].

In human subjects, the P50 (also known as P1) component of the event-related potential (ERP) is regarded to be the main component in the sensory gating paradigm, although the N100 (N1) and P200 (P2) seem to be involved as well (e.g. [39–42]). There is still a debate about which ERP component in rats is possibly the functional equivalent of the P50 in humans. It has been suggested that the P13 (P1), N40 (N1) or even P60 (P2) might be the functional equivalent of the P50 in humans, while it has also been suggested that the entire P1–N1–P2 complex is the most suitable candidate (e.g. [43–47]).

We previously demonstrated that PDE5 inhibition with vardenafil does not affect sensory gating in rats at doses which are normally able to improve memory [6,48]. This led us to conclude that the positive effects of PDE5 inhibition on cognition are most likely mediated by higher cognitive processes and not by more early stages of (basic) information processing. Since it is difficult to assess the effects of a compound on information processing separately in cognitive tasks such as the object recognition tasks, it is of utmost importance to also test its effects in paradigms assessing information processing, such as sensory gating. Especially to gain further insight into the underlying mechanisms of the cognition enhancing properties of a compound, since improved processing of task relevant information could also account for positive effect on cognition without affecting higher cognitive processing per se. In the current study we investigated the effects of a PDE2-I (BAY 60-7550) and PDE10-I (PQ-10) at the dosage that was previously found to improve memory function as well (e.g. [21,49]). For the EEG measurements we included the vertex, hippocampus and striatum as electrode locations. These three locations were included because of their involvement in sensory gating (e.g. [34,50,51]). We expected that the cGMP-specific PDE5-I vardenafil would not affect sensory

gating as demonstrated previously [48]. Contrarily, the dual substrate PDE-Is BAY 60-7550 and PQ-10 were expected to have an effect on sensory gating, since it was shown that PDE10 inhibition was able to reverse an amphetamine induced sensory gating impairment [33].

2. Methods

2.1. Animals

All experimental procedures were approved by the local ethical committee for animal experiments of Maastricht University and met governmental guidelines. Fourteen 3-month-old male Wistar rats (Harlan, The Netherlands) were used with average body weights of 386 g (± 11.66). The animals were housed individually in standard Makrolon cages on sawdust bedding in an air-conditioned room (about 20 °C). They were kept on a 12/12-h reversed light/dark cycle (lights on from 19.00 h to 7.00 h) and had free access to food and water. The rats were housed in the same room as where they were tested. A radio, which was playing softly, provided background noise in the room. All testing was done between 9.00 h and 18.00 h in a shielded Skinnerbox.

2.2. Surgery and EEG recordings

The animals received 0.1 ml/kg Temgesic (Schering-Plough B.V., Utrecht, The Netherlands) subcutaneously 30 min before surgery as analgesia. Forene isoflurane (Abbott B.V., Hoofddorp, The Netherlands) was used as a general inhalation anesthetic. After the animal was placed into the stereotactic apparatus and an incision was made to expose the skull, lidocaine was applied as additional local anesthesia. Next, bregma was identified and the electrodes were unilaterally placed in the striatum (AP 0.48, ML-3.0, DV-5.0), dorsal hippocampus (AP-2.8, ML-1.8, DV-2.6) and at the vertex (AP-3.5, ML-1.0, DV-1.0) [52]. The reference and ground electrodes were both placed on the cerebellum. The electrodes and the connector were fixed to the skull by using three screws and Paladur denture acrylic (Heraeus Kulzer, Hanau, Germany). The animals were given at least two weeks to recover from the surgery.

In the first week after recovery, the animals were handled daily and adapted to the procedure, i.e. they were connected to the EEG set-up and allowed to explore the Skinnerbox in which the recording would take place. In addition the rats were adapted to p.o. administration procedures by saline injections (2 ml/kg). Next, the control condition was tested, i.e. animals were treated with vehicle; this was tested twice and averaged for the statistical analysis. Subsequently three doses of the PDE5-I vardenafil were randomly tested (0.3, 1, 3 mg/kg, p.o.). The results of this experiment were recently published [48] including only the animals whose dataset was complete and electrode localization was validated for the vehicle treatment and all PDE5-I conditions. Additionally, we randomly tested the PDE2-I BAY 60-7550 and the PDE10-I PQ-10 (both 1 mg/kg p.o.). The sensory gating paradigm consisted of 70 pairs of auditory stimuli which were presented with stimulus duration of 10 ms, inter-stimulus interval of 500 ms and inter-trial interval 6–10 s. The EEG signal was sampled at 1000 Hz, filtered between 1 Hz and 133.5 Hz and stored on a personal computer. The stimuli were 2500 Hz clicks with a sound intensity of 80 dB and duration of 10 ms. After the study was finished, the animals were killed by decapitation and the brains were taken out. The brains were stored in 4% formaldehyde at 4–6 °C until electrode localization took place, which was done as described previously [48].

2.3. Treatment

BAY 60-7550, vardenafil, and PQ-10 were first dissolved in 1.5 ml ethanol with 2% Tween 80. After extraction of ethanol via vaporization under N₂ gas, the compounds were dissolved in 0.5% methylcellulose. It was chosen to test the previously found most effective dose (1 mg/kg, p.o.) of each PDE-I in improving memory in an object recognition task. All compounds were administered by oral gavage (2 ml/kg) 30 min before testing. BAY 60-7550 and vardenafil were a gift from BAYER (Wuppertal, Germany); PQ-10 was kindly donated by Johnson & Johnson (Beerse, Belgium). All animals were treated with each condition once, except for the control condition (vehicle), which was tested twice as part of the training.

2.4. Statistical analysis

Segments between 100 ms before until 500 ms after stimulus onset were made for each stimulus type (S1 and S2) separately, using the last 100 ms before onset as baseline. High pass (1 Hz) and low pass (30 Hz) filters were applied. The segments were visually checked and removed from the data set if a movement artifact occurred within 500 ms after stimulus presentation. Both the grand average (all animals) and the individual data (single animal) were used to determine the auditory evoked potential (AEP) components. In general, P1 was defined as the most positive value between 20 ms and 55 ms after stimulus onset, N1 as the most negative value between 35 ms and 75 ms, P2 as the most positive value between 55 ms and 100 ms.

General linear models (GLM) repeated measures were used to analyze the amplitudes of the components. First, the responses to the S1 and S2 were compared for the vehicle condition to see whether sensory gating occurred. Next, the responses

Fig. 1. Effects of vehicle on grand average ERPs after the presentation of S1 and S2. $N_{\text{vertex}} = 13$; $N_{\text{hippocampus}} = 14$; $N_{\text{striatum}} = 12$. Effects on gating are depicted with asterisks in the saline condition (* $P < 0.05$).

to the PDE-Is conditions were compared to placebo condition for each stimulus (treatment: vehicle and PDE-I) separately as well as for both stimuli together (treatment $\times$ stimulus). One animal was excluded from the vertex and two animals from the striatum electrodes because of no reliable EEG signal at the corresponding electrode.

3. Results

3.1. Effects of vehicle on sensory gating

The effects of vehicle treatment on sensory gating are depicted in Fig. 1. GLM repeated measures showed that the N1 peak was less negative after S2 than S1 in the vehicle condition ($F_{1,12} = 6.12$, $P < 0.05$) at the vertex and hippocampus ($F_{1,13} = 6.20$, $P < 0.05$). In the striatum, no effects were found. Thus, sensory gating was generally found in the hippocampus and the vertex.

3.2. Effects of PDE inhibition on information processing

3.2.1. Vertex

The PDE2-I BAY 60-7550 did not have an effect on the ERP components of the S2 or sensory gating. However, GLM repeated measures showed that the P1 peak of the S1 was more positive after BAY 60-7550 than vehicle treatment ($F_{1,10} = 7.59$, $P < 0.05$) (see Fig. 2). No other effects of PDE2 inhibition were found. In addition, treatment with the PDE5-I vardenafil or the PDE10-I PQ-10 did not affect S1, S2 or sensory gating (data not shown).

3.2.2. Hippocampus

No effects of PDE2 or PDE5 inhibition on the ERP components of the S1, S2 or sensory gating were found (data not shown). The PDE10-I PQ-10 did not affect S1 or S2 separately either. Yet, the GLM repeated measures with treatment as well as stimulus as a within subject variable showed that PQ-10 treatment increased the overall N1 compared to vehicle treatment ($F_{1,13} = 4.71$, $P < 0.05$). This is

also illustrated in Fig. 3 showing the effects of all PDE-Is on their hippocampal N1 peaks that showed sensory gating in the placebo condition (see Fig. 1).

3.2.3. Striatum

GLM repeated measures demonstrated no effects of PDE2 ($n = 11$), PDE5 ($n = 11$) or PDE10 ($n = 12$) inhibition on the ERP components of S1, S2 or sensory gating (data not shown).

4. Discussion

The present study showed that after treatment with vehicle the N1 in the vertex and hippocampus was less negative after S2 than after S1 indicating sensory gating in both electrode locations. However, in the striatum, no sensory gating was found. None of the PDE-Is affected sensory gating directly as no stimulus $\times$ treatment interaction was found. Yet, it was demonstrated that the PDE2-I BAY 60-7550 increased the P1 peak after S1 compared to vehicle in the vertex. In addition, the PDE10-I PQ-10 affected the N1 in general, with this peak being more negative after PQ-10 than vehicle treatment in the hippocampus.

Administration of the PDE5-I vardenafil did not have an effect on sensory gating as we already recently showed in rats and humans [48]. Although the effect of PDE5 inhibition on learning and memory has been widely investigated (for review see e.g. [2,3]), little is known about the effects on ERPs. A study by Schultheiss et al. [12] investigated the effects of PDE5 inhibition on ERPs in humans. They showed that sildenafil (100 mg p.o., 1 h before testing) reduced N150/250 and increased P300 activity related to the improvement in attention in healthy human adults. Additionally, to our knowledge only one study has thus far examined the effects of PDE5 inhibition on ERPs and information processing in animals [48]. Our results indicate that the effects of PDE5 inhibition during memory tasks using the same dosage range [6,8,53–56] are predominantly

Fig. 2. Effects of treatment with a PDE2-I (BAY 60-7550), PDE5-I (vardenafil) or PDE10-I (PQ-10) on the mean amplitude ($\pm$ SEM) of the P1 in the vertex after the presentation of S1 and S2. $N_{\text{PDE2}} = 11$; $N_{\text{PDE5}} = 11$; $N_{\text{PDE10}} = 12$.

mediated by effects on higher cognitive processes and not on early stages of information processing, since the early ERP components were not affected by PDE5 inhibition.

The PDE2-I BAY 60-7550 and PDE10-I PQ-10 did not affect sensory gating either. Schmidt et al. [33] previously showed that the PDE10-I TP-10 (3 mg/kg) reversed sensory gating deficits in the hippocampus induced by d-amphetamine. However, this study was performed in anesthetized rats while we used freely moving animals in the present study. In addition, we did not use a deficit model here, which clearly could explain the difference between both studies. Furthermore, based on the IC_{50} values it could be argued that PQ-10 is about 10 times less potent than TP-10 [57], yet we tested PQ-10 at a dose (1 mg/kg) known to improve memory processes [21]. Finally, the routes of administration differed between both studies (intravenously versus orally), which might also have an effect. In contrast to auditory sensory gating, the TP-10 compound did not have an effect on sensorimotor gating in PPI paradigms [33]. However, the PDE10-Is papaverine and MP-10, approximately 5 times less potent and 10 times more potent than PQ-10 respectively [57,58], reversed MK-801, an N-methyl-D-aspartate (NMDA) receptor antagonist that disrupts particularly memory and attention processes, induced PPI deficits in rats and improved PPI-linked sensorimotor gating in healthy mice [22]. This suggests that it would be interesting to test PQ-10 in a PPI paradigm as well. Nevertheless, although we presently did not find a direct effect of PDE10 inhibition with PQ-10 nor of PDE2 inhibition with BAY 60-7550 on auditory sensory gating, PQ-10 as well as BAY 60-7550 showed effects on information processing. Administration of BAY 60-7550 increased the P1 peak after presentation of S1 at the vertex, which might indicate an arousal effect, and PQ-10 increased the N1 peak at the hippocampus in general compared to vehicle treatment, which might point to a general enhancing effect on auditory information processing.

Interestingly, the PDE-Is that have an effect on information processing both affect cGMP and cAMP, whereas PDE5 is cGMP specific (e.g. [59]). The fact that we only found an effect of the

dual substrate PDE-Is suggests that information processing might be influenced by cAMP. This would also be in line with previous findings of Maxwell et al. [60] who demonstrated that the cAMP-specific phosphodiesterase type 4 inhibitor (PDE4-I) rolipram enhanced the amplitude of the P20 (P1) and N40 (N1) peaks after S1 in the hippocampus in non-anesthetized mice in a sensory gating paradigm. In addition, this compound reversed an amphetamine-induced deficit at these peaks after S1. However, no effects on sensory gating were found for the P20 and N40. Another study [35] showed that the PDE4-I Ro-20-1724 increased the response to S1 at the P20 (P1) and N40 (N1) peaks in the hippocampus in mice in a sensory gating paradigm as well. In addition, they found that this PDE4-I reversed a decreased N40 after S1 and a N40 gating deficit induced by d-amphetamine. Interestingly, they did not find an effect of PDE4 inhibition on a d-amphetamine induced PPI deficit in mice. These results imply that dual substrate as well as cAMP specific PDE-Is are able to affect auditory information processing in a sensory gating paradigm, but that the results differ when it comes to other paradigms such as PPI.

Furthermore, the fact that PDE5 inhibition did not affect basic auditory information processing, whereas PDE2 and PDE10 inhibition did have an effect, might also be explained by previous localization data of the corresponding PDEs. PDE2 mRNA expression has been localized in the striatum, hippocampus and cortex, whereas PDE10 is predominantly localized in the striatum and to a lesser extent in the hippocampus and cortex [24–26,29–31]. Given the high expression of PDE2 and PDE10 in the striatum, BAY 60-7550 and/or PQ-10 might be expected to affect information processing in general as in the hippocampus and the vertex. Yet the lack of an effect of PDE inhibition on information processing in the striatum suggests that these types of PDE in the striatum are not implicated in auditory information processing. PDE5 can be detected in the CNS as well, but at a lower level than PDE2 and PDE10 [24]. So it might also be the case that the amount of PDE5 in the CNS is just too low to affect information processing.

Fig. 3. Effects of treatment with a PDE2-I (BAY 60-7550), PDE5-I (vardenafil) or PDE10-I (PQ-10) on the mean amplitude ($\pm$ SEM) of the N1 in the hippocampus after the presentation of S1 and S2. $N_{\text{PDE2}} = 13$; $N_{\text{PDE5}} = 14$; $N_{\text{PDE10}} = 14$.

To summarize, the PDE5-I vardenafil did not have an effect on basic auditory information processing examined in a sensory gating paradigm. This in contrast to administration of the PDE2-I BAY 60-7550 or PDE10-I PQ-10 which affected auditory information processing in general. These results imply that the positive effects of PDE5 inhibition on cognition previously found in animals are possibly the results of an effect on higher cognitive functioning specifically whereas the cognition enhancing effects of PDE2 and PDE10 inhibition might also be influenced by effects on earlier cognitive processes such as information processing. To further elucidate the effects of PDE inhibition on information processing deficit models (e.g. d-amphetamine) and other paradigms (e.g. PPI) could be employed.

Conflict of interest

None declared.

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