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Rapid Communication

Mind the gap: Delayed manifestation of long-term object memory improvement by phosphodiesterase inhibitors

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ABSTRACT

We examined the temporal profile of pharmacologically enhanced episodic memory, using the object recognition task. Male Wistar rats were tested at different retention intervals ranging from 1 h to 24 h. The object discrimination performance of all groups (untreated, placebo, drug treatment) gradually decreased up to an interval (8 h). Interestingly, only after this 8 h interval the memory improving effects of vardenafil and rolipram started to emerge. This time-dependent memory performance shows similarities with the Kamin effect. The delayed manifestation of drug-enhanced memory suggests that two separate memory mechanisms are at play, a quick transient form of memory and a more stable memory form that requires several hours to develop. It is important to take this into account when testing treatments intended for long-term memory enhancement.

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1. Introduction

The object recognition tasks (ORT) is a widely used one-trial memory task, allowing the assessment of the effects of interventions on the different stages of memory (Abel & Lattal, 2001; Ennaceur, 2010; Prickaerts, Sik, van der Staay, de Vente, & Blokland, 2005). We have shown that, under our standard test conditions, rats have good object memory after a 1 h inter-trial delay and that the rats do not discriminate between the familiar and novel object after 24 h, i.e. no memory (Akkerman, Blokland, et al., 2012; Rutten, Prickaerts, & Blokland, 2006). This time-dependent forgetting after 24 h can be prevented by treatment with selective phosphodiesterase (PDE) inhibitors which inhibit the degradation of the second messengers cGMP and/or cAMP. The cGMP-specific PDE5 inhibitors (PDE5-I) are effective when injected shortly before learning or immediately after learning. cAMP-specific PDE4 inhibitors (PDE4-I) also improve memory performance but only when given 3 h after learning (Bernabeu et al., 1997; Prickaerts, de Vente, Honig, Steinbusch, & Blokland, 2002; Devan et al., 2004; Rutten et al., 2006; Rutten et al., 2007; Levallet, Hotte, Boulouard, & Dauphin, 2009; Bruno et al., 2011; Reneerkens et al., 2012). It has been proposed that PDE5 and PDE4 inhibition lead to improvement of early- and late consolidation processes, respectively. However, it has not yet been investigated how memory enhanced by PDE inhibition is expressed at intermediate intervals between 1 h and 24 h.

To evaluate the stability of the memory trace during the different stages of memory consolidation we tested rats in the ORT on 6 different retention intervals; 1 h, 4 h, 8 h, 10 h, 12 h and 24 h. First, untreated and vehicle treated animals were used to investigate the temporal profile of normal forgetting in the ORT. Subsequently, the effects of vardenafil (PDE5-I) or rolipram (PDE4-I) were tested at the different inter-trial intervals.

2. Materials and methods

2.1. Animals

Two cohorts of twenty-four 3-months-old male Wistar rats (Charles River, Sulzfeld, Germany) were used. The animals were housed individually in standard Makrolon™ Type III cages on sawdust bedding in an air-conditioned room (about 20 °C). They were kept under a reversed 11/13-h light/dark cycle (lights on from 6 PM to 7 AM). Food and water were provided ad libitum. Animals were housed and tested in the same room while a radio provided background noise 24 h a day.

2.2. Drugs

Four different treatments were tested, vehicle, rolipram, vardenafil and no treatment. Test compounds were freshly dissolved on

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every experimental day. Vehicle composition was similar for rolipram and vardenafil and consisted of a 1% methylcellulose solution and tween 80, proportions were 98% and 2% respectively. Rolipram (i.p., 0.03 mg/kg, in 1 ml/kg) was administered intra peritoneally, 3 h after T1. Vardenafil (p.o., 1 mg/kg in 1 ml/kg) was given orally 4 min after the sample trial (T1). Dose, vehicle and administration time/route were determined based on earlier studies where these drugs showed clear memory-enhancing effects in the same ORT set-up (Rutten et al., 2006, 2007).

2.3. Behavioral testing

We used the ORT as described previously (Prickaerts et al., 2002). Animals were tested in a circular arena (diameter 83 cm) in which 2 objects were presented to them. A test session consisted of two 3 min trials, separated by a retention interval. In the learning trial (T1) 2 similar objects were presented to the animals and in the test trial (T2) these 2 objects were replaced by one identical (familiar) copy and a different (novel) object. We tested each different treatment on a variety of retention intervals, 1 h, 4 h, 8 h, 10 h, 12 h and 24 h. Four different sets of 3 identical objects were used, a set of glass 1 L bottles, a set of iron cubes, a set of grey cones made of polyvinyl chloride (PVC) and a set of bullet-shaped aluminum blocks. Animals were unable to move the objects (for more details about the objects and ORT procedure see Akkerman, Blokland, et al., 2012).

Experimental conditions were semi-randomly assigned to experimental days which were separated by a wash-out period of at least a 24 h to prevent drug/dose interactions. 48 rats were divided into 2 cohorts of 24 animals. Within the cohorts a maximum of 3 different conditions could be tested on each experimental day, because 8 animals are required per condition in order to rule out side- and object biases (for details see Akkerman, Blokland, et al., 2012). The first cohort of 24 animals performed each retention interval without receiving any treatment (untreated condition) and was subsequently tested in combination with vardenafil treatment (vardenafil condition). The second cohort performed each retention interval with vehicle treatment (vehicle condition) and also with rolipram treatment (rolipram condition). All treatment conditions are schematically presented in Table 1. As vehicle treated animals were part of the rolipram cohort, vehicle (1 ml/kg) was administered i.p., 3 h after T1. Hence, no vehicle injection was given to these animals in the 1 h retention interval and the treatment was in fact the same as that of the 1 h untreated condition in the vardenafil cohort. However, this retention interval was designated as the 1 h vehicle condition to include it in the overall analysis. Of note, the untreated and vehicle treated animals had similar memory performance on every retention interval (see Section 3).

Table 1
Experimental conditions.

Animals	Cohort	Treatments	ORT retention intervals					
48	1 (n = 24)	Untreated	1 h	4 h	8 h	10 h	12 h	24 h
		Vardenafil	1 h	4 h	8 h	10 h	12 h	24 h
	2 (n = 24)	Vehicle	1 h[a]	4 h	8 h	10 h	12 h	24 h
		Rolipram	x	4 h	8 h	10 h	12 h	24 h

This table gives an overview of the experimental conditions. All animals were fully habituated to the ORT procedures before the start of the experiment. 48 Animals were divided over 2 cohorts. Each cohort received 2 different treatments which were tested in 6 separate retention intervals. In the untreated condition rats did not receive any injections. Vardenafil was administrated p.o., 4 min after T1. Rolipram was administered i.p. 3 h after T1, therefore no 1 h interval was tested with rolipram. Vardenafil and rolipram were dissolved in the same vehicle. For the vehicle condition i.p. injections were given 3 h after T1.

[a] Therefore, no vehicle was administered in the 1 h retention interval.

The times rats spent exploring each object was measured. Time spent exploring the sample/familiar and the novel objects will be represented by 'a' and 'b', respectively. The following variables were calculated; $e1 = a_1 + a_2$, $e2 = a_3 + b$, the relative discrimination index, $d2 = (b - a_3)/e2$.

2.4. Statistical analysis

The effects of vehicle treatment were compared to the untreated condition using a repeated measures ANOVA (Interval (6) × Treatment (2)). Subsequently, the effects of vardenafil and rolipram treatments were analyzed using an Interval (6) × Treatment (4) ANOVA. Differences between treatment conditions on $e1$, $e2$ and $d2$ measures were analyzed for every separate retention interval using one-way ANOVA. LSD t-tests ($p < 0.05$) were used to compare conditions per time point. Furthermore, one-sample t-statistics were performed on the $d2$ measure to assess whether there was a difference from zero, which indicates recollection of the sample object (for more details see Akkerman, Prickaerts, Steinbusch, & Blokland, 2012).

3. Results

3.1. Time dependent forgetting

When comparing vehicle and untreated test conditions, no significant interaction effects were found on the exploration and discrimination measures (F's$_{(5,275)} < 1.16$, p's > 0.33). There was a significant main effect of interval on $e1$ ($F_{(5,275)} = 3.72$, $p < 0.003$). Post hoc analysis of the intervals showed that $e1$ was increased at the 12 h interval compared to all other intervals. There was also a main effect of treatment on $e1$ ($F_{(1,275)} = 109.20$, $p < 0.001$) and $e2$ ($F_{(1,275)} = 101.50$, $p < 0.001$). Post hoc comparison of the treatments revealed that both $e1$ and $e2$ of the vehicle treated animals were significantly higher compared to untreated animals. This appears to be a general difference between the two cohorts.

Regarding the $d2$ measure, which is depicted in Fig. 1, a significant main effect was found for Interval ($F_{(5,275)} = 16.21$, $p < 0.001$) but not for Treatment ($F_{(1,275)} = 0.013$, n.s), which shows that vehicle administration had no effect on memory performance. Post hoc analysis showed that the $d2$ measure of both treatment conditions significantly decreased from the 1 h to the 8 h interval and remained at the same level after longer intervals. The $d2$ of untreated animals (data not shown) as well as vehicle treated animals was significantly higher than zero after the 1 h and 4 h retention interval (t's > 4.26, p's < 0.002). When the retention delay was 8 h or longer the $d2$ index was equal to zero, i.e. chance level, in both experimental conditions, indicating no recognition of the familiar object in T2. Taken together these findings indicate that natural memory extinguished between 4 and 8 h and vehicle treatment had no effect on forgetting.

3.2. Time dependent effects of PDE-Is on memory

Main effects of Interval ($F_{(5,526)} = 5.56$, $p < 0.001$) and Treatment ($F_{(3,526)} = 60.57$, $p < 0.001$) were found for $e1$. An interaction effect between Interval and Treatment was present for $e2$ ($F_{(14,526)} = 2.60$ $p = 0.001$). One way ANOVA's on each separate interval showed no differences in $e1$ and $e2$ between the untreated and vardenafil treatment condition or between the vehicle and rolipram treated condition (data not shown). This again reflects the general difference in exploration levels between both cohorts. The average exploration difference between both cohorts over all intervals was: 10.66 s in T1 and 10.50 s in T2. Despite this difference both cohorts

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