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BRAIN RESEARCH

Research Report

Enhancement of reference memory in aged rats by specific activation of 5-HT$_4$ receptors using an olfactory associative discrimination task

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ABSTRACT

In normal aging, or pathological brain diseases in humans, implicit memory (or procedural memory in rats) is spared while explicit memory (or reference memory in rats) is deeply impaired. Selective activation of 5-HT$_4$ receptors by a partial 5-HT$_4$ receptor agonist (SL65.0155) improved memory performance in an olfactory associative discrimination task in aged rats. Detailed analysis of subcategories of long-term memory using a hippocampal-dependent olfactory associative discrimination task revealed a substantial benefit on reference memory. This agent could be used to treat early mnesic deficits observed in normal aging or in neurodegenerative disorders like Alzheimer disease.

1. Introduction

One of the most troubling aspects associated with of normal aging for many individuals is the impairment of learning and memory. Like aged humans, aged rodents exhibit memory impairments (Barnes and McNaughton, 1980; Gallagher and Burwell, 1989; Roman et al., 1996).

Among the numerous 5-hydroxytryptamine (5-HT) receptors, there is evidence that the 5-HT$_4$ receptor subtype plays an important role in long-term memory (Marchetti et al., 2000, 2004; Marchetti-Gauthier et al., 1997; Segu et al., 2010), and more recently, the activation of 5-HT$_4$ receptors by the selective partial 5-HT$_4$ agonist SL65.0155 led to a promnesic effect on several learning and memory tests in normal and experimentally induced amnesic adult rodents (in both rats and mice: Marchetti et al., 2008; Micale et al., 2006; Moser et al., 2002). Moreover, recent reports indicate that the administration of this agonist prior to training both enhances simultaneous olfactory discrimination performance and potentiates learning-induced dendritic spine growth in the mouse hippocampus (Restivo et al., 2008). The present study was designed to further investigate the eventual involvement of 5-HT$_4$ receptors in memory of aged rats through the use of a hippocampal-dependent olfactory associative discrimination task allowing to assess potential effects of SL65.0155 on different subcategories of long-term memory.

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2. Results

2.1. Phase 1

Training of the adult and aged groups, assessed by the percentage of correct responses (Fig. 1A), showed that only the adult group improved their overall performance across the five sessions (MANOVA, Group × Session interaction: $F(4,120) = 16.44$, $p < 0.001$). Subsequent ANOVAs revealed that a clear-cut difference between the two groups emerged from the fourth session: ($F(1,30) \geq 7.57$, $p \leq 0.01$).

Training performance analyzed in terms of S+ and S– latencies (Fig. 1B) showed a substantial learning impairment in the aged group. Indeed, inversely to the adult, the aged group was unable to make correct associations on S+ and S– stimuli. The adult group made significant correct associations from the third session onward (ANOVAs, $F(1,30) \geq 16.54$; $p \leq 0.001$). The aged animals' group showed a slight gradual decrease in the time taken to respond to both stimuli. The adult group showed a continuous, significant decrease in latencies of response to S+ stimuli throughout the training session, while for S– stimuli a decrease was observed during sessions 1 and 2, before animals began to withhold their responses (and therefore, started to exhibit correct behavior) in session 3. Consequently, a significant difference between the groups was observed on both S+ and S– stimulus response latencies throughout the sessions (MANOVAs: $F(4,120) \geq 3.13$; $p \leq 0.05$). Detailed analysis by block of 10 trials of the latencies (Fig. 2) revealed precisely that adult rats started to make correct associations firstly during the fifth block of the second session (S2) (ANOVA, $F(1,30) = 20.34$; $p < 0.001$), secondly during the third block onward on session 3 (S3) (ANOVAs, $F(1,30) \geq 4.85$; $p \leq 0.05$) and finally throughout the sessions 4 and 5 (S4; S5) (ANOVAs, $F(1,30) \geq 12.34$; $p \leq 0.001$). Adult rats responded faster to the S+ stimuli than the aged rats in phase 1 excepted during the first session (ANOVAs, $F(1,30) \geq 39.36$; $p \leq 0.001$) and to the S– stimuli on sessions 2 and 3 (ANOVAs, $F(1,30) \geq 6.02$; $p \leq 0.05$).

The cumulative time (Fig. 1C) decreased across sessions for the adult group, while for the aged group an increase was observed from the first to the second session before reaching the same performance as control rats. Separate ANOVAs revealed only a significant group difference in session 1 [$F(1,30) = 4.912$, $p < 0.05$]. Detailed analysis by block of 10 trials (Fig. 3) confirmed the difference observed on global performance on session 1, as all the six blocks were statistically different between the adult and aged rats (ANOVAS, $F(1,30) \geq 5.5$; $p \leq 0.05$). In addition, a significant difference was observed again during the three first blocks of the second session (ANOVAs, $F(1,30) \geq 4.67$; $p \leq 0.05$) and during the fourth block of the fifth session (ANOVA, $F(1,30) = 7.62$; $p < 0.01$).

2.2. Phase 2

Both sub-divided adult and aged groups were trained on the new odor pair (Fig. 4). The two adult sub-groups began to exhibit correct associations reaching a correct-response rate of at least 60%. In contrast the two aged sub-groups performed at the chance level. Consequently significant differences on

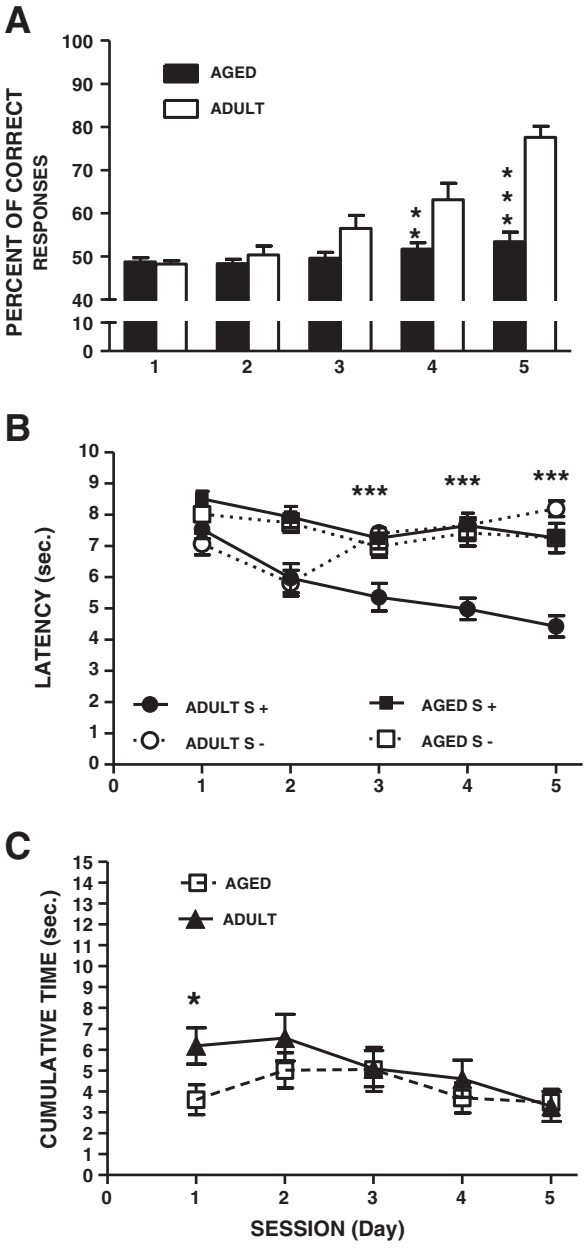

Fig. 1 – Mean performance (±SEM) obtained with the learning and memory of a first odor pair across five sessions (phase 1). (A) Mean percent correct responses. (B) Mean latencies (in s): S+ are latencies for the positive odors, S– for negative odors. (C) Mean cumulative time (in s) added to the fixed inter-trial interval of 15 s when rat's behavior delayed the next trial. ADULT = Adult rat; AGED = Aged rat. ADULT S^+ and ADULT S– = time taken (latencies) by the adult rats to respond to the positive (S+) or negative (S–) odor stimulus, respectively. 10 s is the maximum duration of odor presentation. AGED S^+ and AGED S– = latencies for the aged control group. Comparisons were made between aged ($n = 16$) and adult rats ($n = 16$) rats in A and C. Statistical significance in B was obtained by comparing S+ and S– latencies and only adult rats did significant associations from session 3.