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Brief communication

Stress-induced corticosterone secretion covaries with working memory in aging

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ABSTRACT

A substantial literature details the relationship between age-related changes to the hypothalamic-pituitary-adrenal axis and deterioration of mnemonic functions that depend on the hippocampus. The relationship between adrenocortical status and other forms of memory that depend on the prefrontal cortex is less well understood in the context of advanced age. Here, we characterized performance of young adult and aged F344 rats on a prefrontal cortex–dependent working memory task and subsequently measured corticosterone (CORT) levels over the diurnal cycle and during exposure to an acute stressor. Our analyses revealed that aged rats with better working memory mounted a greater CORT response during acute stress exposure than either young adults or age-matched rats with impaired working memory. We also observed that age-related elevation of basal CORT levels is not associated with working memory performance. Jointly, these data reveal that the hypothalamic-pituitary-adrenal axis–mediated response to acute stress is positively associated with working memory in aging.

1. Introduction

Secretion of glucocorticoids mediated by the hypothalamic-pituitary-adrenal (HPA) axis is an essential physiological process that balances cellular energy requirements over the circadian cycle and also in response to stressful experiences (de Kloet et al., 2005; Herman et al., 2003; Keller-Wood and Dallman, 1984). Lower expression of glucocorticoid receptors (GRs) in the aging hippocampus associates with dysregulated release of glucocorticoids and impaired spatial memory (Bizon et al., 2001; Issa et al., 1990; Montaron et al., 2006; Yau et al., 1995). GRs in the prefrontal cortex (PFC) also regulate HPA axis activity (Diorio et al., 1993; Radley et al., 2006a), but few studies have investigated the relationship between modulation of glucocorticoid secretion and age-related decline of PFC-dependent memory. Specifically, working memory, which involves the temporary maintenance of information used to guide current and future action, critically depends on PFC (Funahashi et al., 1993; McQuail et al., 2016; Sloan et al., 2006) and deteriorates with age across species (Bachevalier et al., 1991; Beas et al., 2013; Hernandez et al., 2017; Lamar and Resnick, 2004; Oscar-Berman and Bonner, 1985; Rapp and Amaral, 1989). In this study, we examined differences in circadian- and stress-associated glucocorticoid secretion between young and aged rats in relation to performance on a PFC-dependent working memory task.

2. Materials and methods

2.1. Subjects

Male, Fischer 344 (F344) rats were acquired at ages of 4 months (young adults, n = 11) or 20 months (aged, n = 16) from the Aging Rodent Colony maintained by Charles River Laboratories for the National Institute on Aging. All rats were housed in an AAALAC-accredited vivarium in the McKnight Brain Institute Building at the University of Florida in accordance with the rules and

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regulations of the University of Florida Institutional Animal Care and Use Committee and NIH guidelines. The facility was maintained at a consistent 25 °C with a 12-hour light/dark cycle (lights on at 0600 hours) with free access to food and water except as noted below.

2.2. Delayed response testing

All rats were restricted to 85% of ad libitum fed weight and shaped to perform a delayed response test of working memory (Fig. 1A). This task requires intact function of medial PFC (McQuail et al., 2016; Sloan et al., 2006), the rodent homolog of the primate dorsolateral PFC. Behavioral testing was conducted in operant testing chambers (Coulbourn Instruments, Whitehall, PA, USA) using shaping procedures identical to those described previously (Beas et al., 2013; McQuail et al., 2016). In the testing phase of the task, each trial was comprised of 3 phases. In the "sample" phase, a single response lever (left or right, randomly counterbalanced within pairs of trials) was extended into the chamber. A lever press resulted in retraction of the lever and initiated a delay of 0, 2, 4, 8, 12, 18, or 24 seconds (presented in a randomized order in each block of 7 trials). During this "delay" phase, rats were required to nose-poke into the central food trough. The "choice" phase was initiated by the first such nose-poke emitted after the delay period expired. In the "choice" phase, both left and right levers were extended, and a press on the same lever presented during the sample phase (a correct response) resulted in retraction of both levers and delivery of a single food pellet. A press on the opposite lever (an incorrect response) resulted in the retraction of both levers and initiation of a 5 seconds "timeout" during which the house light was extinguished. Rats were tested in one 40-minute session per day until achieving stable performance over 5 consecutive days. Stability was defined as <10% variation in performance at 18 and 24 seconds delays while completing no fewer than 70 trials per day.

2.3. Blood collection and corticosterone measurement

After behavioral testing was complete, rats were returned to free feeding for a minimum of 2 weeks before blood collection. To evaluate circadian variation in corticosterone (CORT) levels, blood was obtained via tail bleed between 0700 and 0800 hours (lights on at 0600 hours) and between 1900 and 2000 (lights off at 1800 hours; similar to time course used in Sapolsky et al., 1983). One week later, rats were subjected to a 60-minute period of restraint stress. Beginning between 0900 and 0930 hours, rats were placed into Plexiglas restrainers and blood collected at 0, 15, 30, and 60 minutes following the onset of restraint and also at 120 minutes, which was 60 minutes after being released and returned to home cage (similar to time course used in Segar et al., 2009). Plasma CORT was assayed in duplicate using the Immun-Chem Double Antibody CORT ^{125}I RIA Kit for rats and mice (MP Biomedicals, Orangeburg, NY, USA) as previously described (Daubert et al., 2014).

2.4. Statistical analyses

The chief index of delayed response performance was choice accuracy, or the percentage of correct responses after each delay. Choice accuracy was analyzed using a 2-way, mixed factors analysis of variance testing age as a between-subject factor and delay as a repeated, within-subjects factor. Aged rats were classified into cognitive subgroups on the basis of whether choice accuracy of each rat averaged across 18 and 24 seconds delays fell within (aged-unimpaired; [AU]) or below (aged-impaired; [AI]) the range of young adults. CORT concentration ([CORT]; ng/mL) was determined by fitting activity counts of unknown samples to a standard curve comprised of known [CORT] after accounting for nonspecific binding (determined in the absence of primary anti-CORT). To account for non-normal distribution of circadian [CORT], nonparametric Mann-Whitney U or Kruskal-Wallis tests were used to compare [CORT] between ages or cognitive subgroups. To analyze [CORT] during/following restraint, age or cognitive subgroup was tested as a between-subject factor and time point as a repeated, within-subjects factor followed by Bonferroni post hoc comparisons at specific time points. Bivariate correlations were used to test the relationship between [CORT] and working memory in aged rats. All data are reported as the mean ± standard error and $p < 0.05$ was considered significant in all comparisons.

3. Results

Choice accuracy of aged rats was significantly impaired compared to young adults in a delay-dependent manner (effect of age: $F(1,25) = 27.735$, $p < 0.001$; age × delay interaction: $F(6, 150) = 3.350$, $p = 0.010$; Fig. 1B). Using the average of performance at the longest delays (18 and 24 seconds) as an index of individual differences in accuracy, n = 8 aged rats performed within the range

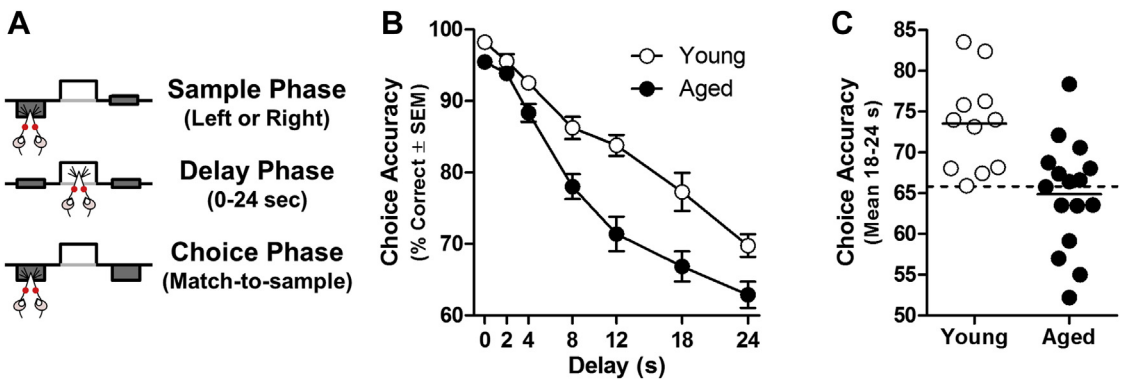

Fig. 1. Age-related decline of working memory. (A) Schematic of a trial in the operant delayed response task used to assess working memory in rats. (B) Delayed response choice accuracy of aged rats (n = 16; black circles) is reduced relative to young (n = 11; white circles), particularly at longer delays (age × delay interaction: $p < 0.05$). Data are mean % correct choices (y-axis) ± SEM plotted as a function of delay (in s; x-axis). (C) Choice accuracy (averaged across 18 and 24 seconds delays) of individual young and aged rats. Within the aged population, some performed within the range of young (n = 8; AU), whereas the remaining aged rats performed below the range of young (n = 8; AI). Solid lines indicate group mean performance and dashed line indicates the lowest level of young performance. Abbreviations: AU, aged-unimpaired; AI, aged-impaired; SEM, standard error of the mean.