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Early onset of cognitive impairment is associated with altered synaptic plasticity and enhanced hippocampal GluA1 expression in a mouse model of depression

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ABSTRACT

Memory deficit is a common manifestation of age-related cognitive impairment, of which depression is a frequently occurring comorbidity. Previously, we developed a submissive (Sub) mouse line, validated as a model of depressive-like behavior. Using learning paradigms testing hippocampus-dependent spatial and nonspatial memory, we demonstrate here that Sub mice developed cognitive impairments at earlier age (3 months), compared with wild-type mice. Furthermore, acute hippocampal slices from Sub animals failed to display paired-pulse facilitation, whereas primed burst stimulation elicited significantly enhanced long-term potentiation in region CA1, relative to control mice. Changes in synaptic plasticity were accompanied by markedly reduced hippocampal messenger RNA expression of insulin-like growth factor and brain-derived neurotrophic factor. Finally, we identified markedly elevated protein levels of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor subunit GluA1 in the hippocampi of Sub mice, which was exacerbated with age. Taken together, the results point to a linkage between depressive-like behavior and the susceptibility to develop age-related cognitive impairment, potentially by hippocampal α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor–mediated glutamatergic signaling.

1. Introduction

Extension of the human life expectancy introduced myriad health care and social problems, particularly significantly increased occurrence of neurodegenerative disease (Bear et al., 2007). Specifically, deterioration of memory integrity may occur with differential severity during aging. Although most people will not have dementia, but will instead undergo “normal” aging, a significant part of the population will experience aging-related cognitive impairment associated with decline of episodic memory and intellectual ability (Backman et al., 2001). These signs are also the earliest marks of emerging Alzheimer’s disease (AD) at the preclinical stage (Castellani et al., 2006). Cognitive impairment and depression are 2 common age-related syndromes, each of which presents in approximately a quarter of the elderly population (Bennett and Thomas, 2014; Enache et al., 2011; Marazziti et al., 2010; Potter and Steffens, 2007). Although exclusion criteria render problematic the estimation of the comorbidity of depression and cognitive impairment (Huang et al., 2011; Korczyn and Halperin, 2009; Weisenbach et al., 2012), several studies have established depression as a risk factor for cognitive impairment and the development of dementia with age (Gabryelewicz et al., 2007; Katon et al., 2010; Panza et al., 2010). Moreover, the most recent studies convincingly demonstrated objectively measurable deficits in key cognitive functions in a large proportion of patients in the midst of a major depressive episode (Papakostas, 2014; Trivedi and Greer, 2014); for review, see Marazziti et al. (2010). Thus, depressed mood may possess a causal role in the Submissive (Sub) mice’s subsequent development of cognitive impairment with age.

Alterations in the hippocampal expression of neurotrophic factors (Duman and Monteggia, 2006; Martinowich et al., 2007) and the associated changes in synaptic plasticity observed in depression (Marsden, 2013) are associated with the development of cognitive decline (Pittenger and Duman, 2007; Wuwongse et al., 2010).

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Furthermore, age-related changes in hippocampal synaptic plasticity have been shown to correlate with altered patterns of glutamate neurotransmission (Barnes, 1979; Barnes and McNaughton, 1980; Barnes et al., 2000; Gleichmann et al., 2011). Changes in expression of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) subunit GluA1 associated with aging were suggested to lead to changes in synaptic plasticity (Kim et al., 2005) and may be associated with age-dependent cognitive impairment (Pagliusi et al., 1994). In addition, the implication of AMPAR current in age-related changes in memory formation was supported by the recovery of age-related cognitive decline in rats via treatment with an AMPAR modulator (Bloss et al., 2008). Furthermore, altered patterns of synaptic plasticity in the hippocampus seen previously in animal models of depression (Alfarez et al., 2003; Pavlides et al., 2002) were reversed by treatment with clinical antidepressants (Holderbach et al., 2007; Matsumoto et al., 2005). Thus, accumulating evidence hints that behavioral disturbances accompanying neurodegenerative and affective disorders may share common molecular mechanisms (Bertram and Tanzi, 2005; Rodriguez and Verkhratsky, 2011).

Among the behaviors expressed in affective disorders are dominance and submissiveness (Johnson and Carver, 2012; Pearson et al., 2010; Price and Sloman, 1984). It was suggested that mechanisms responsible for the expression of dominance and submissiveness contribute to the pathogenesis of affective disorders such as anxiety, bipolar mood disorder, and major depressive disorders (Moussaieff et al., 2012; Nesher et al., 2013; Pinhasov et al., 2005a). We investigated the link between affective disorders and cognitive decline using mice displaying robust characteristics of dominance and submissiveness (Feder et al., 2010; Malatynska and Knapp, 2005; Malatynska et al., 2005, 2007). These animals were developed using selective breeding according to their behavioral traits (Feder et al., 2010; Nesher et al., 2013). Sub mice were previously validated as a preclinical model of depression using a range of behavioral and pharmacological approaches (Malatynska et al., 2007; Nesher et al., 2013; Pinhasov et al., 2005a). In this study, we clearly demonstrate that the Sub mouse model of depressive behavior exhibits significant cognitive deterioration, which appears at early age (3 months) with altered hippocampal expression of the AMPAR subunit GluA1 and significant changes in synaptic plasticity.

2. Materials and methods

2.1. Animals

The dominant (Dom) and Sub animals used in this study were derived from the Sabra line, selectively bred for 22 generations on the basis of their behavior in the dominant-submissive relationship test (Feder et al., 2010), as well as randomly bred, wild-type (wt) outbred Sabra mice (Harlan Laboratories, Jerusalem, Israel) used as controls. Sub mice have served as an animal model of depression in the testing of novel antidepressants (Gross et al., 2013; Malatynska et al., 2007; Moussaieff et al., 2012), whereas Dom mice represent a population exhibiting exaggerated, even paradoxical response to common psychotrophic agents (Nesher et al., 2013). After weaning at postnatal day 25, male mice were housed in groups of 5 per cage. Separate animal populations were used at the ages of 3 and 9 months, respectively, for behavioral testing, followed by culling and brain tissue harvesting for molecular, biochemical, and ex vivo electrophysiological analysis. All mice in the present study also underwent a reference memory paradigm of the Morris water maze (data not shown) as part of the behavioral testing regimen, under standard conditions (Hirst et al., 2006; Glazner et al., 2010). Animals were given standard laboratory chow and water ad libitum, with the exception of the 5 days preceding the radial arm maze (RAM), during which time animals were denied access to food for 12 hours daily, with free access to water, inducing a reduction in body weight of not more than 15%. Animals were housed in a colony room maintained on a 12-hour light-dark cycle (lights on from 7 AM to 7 PM). The experiments were conducted in compliance with the National Institute of Health/United States Department of Agriculture (NIH/USDA) guidelines, under the approval of the Ariel and Tel Aviv Universities' Animal Care and Use Committee.

2.2. Behavioral paradigms

2.2.1. The radial 8-arm maze

2.2.1.1. Test description. The RAM test (Brady et al., 2012; Cheng et al., 2013) was conducted using a Plexiglass maze whose 8 arms (35 cm × 8 cm × 8 cm) are connected by removable guillotine doors to a circular central chamber (21 cm diameter). At the end of each arm was a 3-cm dish in which bait (semisoft cheese, 15% fat) was placed as needed. Four of the 8 arms were marked with spatial cues for navigation purposes. Animals underwent 5 days of food deprivation (12 hours daily without access to food, water accessible ad libitum) preceding the test, inducing a reduction in body weight of not more than 15%. RAM habituation began with a 3-day training period, during which each animal was placed in the maze for 8 minutes daily, with free access to 5 g of bait located at the end of each arm. After the habituation period, the animals were left for 2 additional days without training. Subsequently, animals' learning ability was assessed daily during a 5-day testing period, in which 3 randomly chosen arms were baited. The baited arms differed from mouse to mouse but remained constant for each individual mouse during the 5-day learning period. In the beginning of the trial session, the mouse was placed in the center of the maze, with doors closed. Then, the doors were opened, allowing the animals to freely enter arms. Each mouse remained in the maze for 8 minutes or until all the bait was consumed. Each animal performed the task once per day, and the apparatus was thoroughly washed with ethanol and dried with tissue paper between subjects. Animals' navigation of the maze was recorded by EthoVision video tracking system (version 7.1; Noldus Information Technology) and analyzed according to the following parameters: (1) correct entries: entries to baited arms as a portion of total arm entries; (2) incomplete entries: entries to baited arms without consuming bait, as a portion of total entries to baited arms; (3) latency, a time from the trial start point to complete bait consumption; (4) re-entries to formerly baited arms; (5) distance traveled (cm); and (6) velocity (cm/s). The mice were deemed to have entered an arm when its center point was located in the arm. Animals' learning was assessed as gradual elimination of randomness in animals' navigation of the maze, reducing bait consumption time, re-entry, and incorrect entries. Furthermore, learning ability of the animals was validated using factor analysis.

2.2.1.2. Data analysis. To facilitate comparison and comprehensive visual estimation of the animal groups' performance, raw data values were standardized by conversion into Z scores using the standard score calculation equation: $Z = (x - \bar{x})/s$, where x is a raw data measurement, $\bar{x}$ is the raw data array average, and s is the standard deviation. Z scores (± standard error of mean) of latency to enter baited arms were calculated from the distribution and standard deviation and averaged from absolute values observed from each animal. The rate of entries into the baited arms, as a portion of total arm entries, was similarly expressed as Z scores calculated from averaged absolute values. In the case of narrow versus wide ranges of change in the rate of entries into the baited arms between animal groups (as in Fig. 1B, inset), Z scores were replaced by range-standardized scores (z), calculated with the equation: $z = (x - x_{\min})/(x_{\max} - x_{\min})$. This transformation enabled more