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A working model for the assessment of disruptions in social behavior among aged rats: The role of sex differences, social recognition, and sensorimotor processes

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ABSTRACT

Aging results in a natural decline in social behavior, yet little is known about the processes underlying these changes. Engaging in positive social interaction is associated with many health benefits, including reduced stress reactivity, and may serve as a potential buffer against adverse consequences of aging. The goal of these studies was to establish a tractable model for the assessment of social behavior deficits associated with late aging. Thus, in Exp. 1, 1.5-, 3-, and 18-month-old male Fischer 344 (F344) rats were assessed for object investigation, and social interaction with a same-aged partner (novel/familiar), or a different-aged partner, thereby establishing working parameters for studies that followed. Results revealed that 18-month-old males exhibited reductions in social investigation and social contact behavior, with this age-related decline not influenced by familiarity or age of the social partner. Subsequently, Exp. 2 extended assessment of social behavior to both male and female F344 rats at multiple ages (3, 9, 18, and 24 months), after which a series of sensorimotor performance tests were conducted. In this study, both males and females exhibited late aging-related reductions in social interactions, but these changes were more pronounced in females. Additionally, sensorimotor performance was shown to be impaired in 24-month-olds, but not 18-month-olds, with this deficit more evident in males. Finally, Exp. 3 examined whether aging-related inflammation could account for declines in social behavior during late aging by administering naproxen (0, 7, 14, and 28 mg/kg; s.c.)—a non-steroidal anti-inflammatory drug—to 18-month-old females. Results from this study revealed that social behavior was unaffected by acute or repeated (6 days) naproxen, suggesting that aging-related social deficits in females may not be a consequence of a general aging-related inflammation and/or malaise. Together, these findings demonstrate that aging-related declines in social behavior are (i) specific to social stimuli and (ii) not indicative of a general state of aging-related debilitation. Thus, these findings establish working parameters for a highly tractable model in which the neural and hormonal mechanisms underlying aging-related declines in social behavior can be examined.

1. Introduction

Social interaction is a dynamic process that can be influenced by a number of factors, including motivation to engage in social behavior, familiarity of the testing situation, as well as key features of would-be social partners (e.g. familiarity, presence of social bonds, health status) (Arakawa et al., 2009; Carstensen, 1992). One natural, yet unsettling, consequence of aging in humans is an overall reduction in social interaction that occurs across the lifespan (Carstensen, 1992). This is potentially detrimental to older individuals, because engaging in positive social interaction (relative to social deprivation) produces significant health benefits evidenced by reduced stress reactivity (Carter, 2007, 1998; Nomura and Okuma, 1999), enhanced resilience (Charuvastra and Cloitre, 2008), and faster recovery from neurological deficits induced by stroke (DeVries et al., 2007). Interestingly, prior studies have shown that elderly people gradually narrow the number of people with whom they interact; yet interactions with these individuals deepens across time (Amore, 2005; Lang, 2001; Schiffman, 1997). Indeed, elderly people seem to show a distinct preference for interacting with highly familiar individuals relative to establishment of new social

Abbreviations: AC, Acclimation; CMC, Carboxymethylcellulose; COX, Cyclooxygenase; F344, Fischer 344; FAS, Forepaw Adjusting Steps; NIA, National Institute on Aging; NSAID, Non-steroidal anti-inflammatory drug; PE, Pre-Exposure; SI, Social interaction phase; VEFP, Vibrissae-Evoked Forelimb Placing.

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relationships. While this trend is not problematic in and of itself, the narrowing of social interests becomes a significant threat to overall well-being as aging-associated debilitation (i.e., reduced ability to travel and/or communicate with social partners) and bereavement (death of social partners) compromises the depth and quantity of social engagement (Caruso et al., 2004; Lang, 2001). When combined with other findings showing that the intensity and breadth of positive social interactions are primary indicators of overall happiness and life satisfaction, it is clear that preservation of a broad repertoire of social partners could play a key role in maintaining and/or improving quality of life for aging populations. It is therefore crucial to develop and validate strong preclinical models that can be utilized to better understand the neural mechanisms underlying changes in social behavior that occur across the lifespan.

Studies have demonstrated that aged rodents exhibit alterations in a number of behavioral domains, including impaired cognitive function (Barrientos et al., 2012; Foster, 2012; Gallagher and Rapp, 1997; Nomura and Okuma, 1999; Rosenzweig and Barnes, 2003), increased anxiety-like (Boguszewski and Zagrodzka, 2002; Darwish et al., 2001; Frussa-Filho et al., 1991; Hunt et al., 2011; Imhof et al., 1993; Miyagawa et al., 1998) and depressive-like behaviors (Kiss et al., 2012; Moretti et al., 2011), decreased locomotor activity (Gage et al., 1984; Godbout et al., 2008; Hunt et al., 2011), and importantly, impaired social interaction (Andersen et al., 1999; Hunt et al., 2011; Markel et al., 1995; Mencio-Wszalek et al., 1992; Salchner et al., 2004; Shoji and Mizoguchi, 2011; Soffié and Bronchart, 1988). Aged male rats (14–30-months-old) have been reported to exhibit reduced play behavior (Soffié and Bronchart, 1988), fewer social interactions (Markel et al., 1995; Salchner et al., 2004), less social investigation (Andersen et al., 1999), and to engage in less contact with conspecifics (Hunt et al., 2011) relative to adolescent or young adult rats (1.5–6-months-old). Importantly, these aging-related social deficits are ubiquitous across many rat strains, including the Wistar (Andersen et al., 1999; Hunt et al., 2011; Markel et al., 1995; Soffié and Bronchart, 1988), Sprague–Dawley (Salchner et al., 2004), and Fischer 344/Brown Norway-cross strain (Shoji and Mizoguchi, 2011), yet to our knowledge, only one study has examined potential sex differences in social behavior in aged animals. Hunt et al. (2011) found that aged male and female Wistar rats (22–30 months) exhibited similar reductions in interaction with a novel age- and sex-matched social partner. Furthermore, age-related alterations in social interaction have not been assessed in the F344 rat strain. Although adult F344 rats have been shown to differ in frequency and duration of social interaction, from other strains (Berton et al., 1997; Ramos et al., 1997; Rex et al., 1999), none of these studies examined social interaction in aged F344 rats. Given that F344 rats have an 80–90% survival rate at the desired ages (Turturro et al., 1999), and have been under-represented in previous studies of aging-related declines in social behavior (particularly with respect to potential sex differences in social behavior), this strain of rat was selected for the current series of experiments. F344 rats are also a commonly used strain in aging studies, evidenced by the fact that F344 is one of only a few select rat lines maintained by the National Institute on Aging (NIA) for use in NIA-funded projects.

When examining reduced social interaction in aged animals, some studies have reported concomitant reductions in locomotor activity (Hunt et al., 2011), whereas others showed no such hypoactivity (Andersen et al., 1999; Salchner et al., 2004; Shoji and Mizoguchi, 2011). Furthermore, few studies have manipulated features of the dyadic interaction [i.e., familiarity and age of social partner (Yates et al., 2013)], and to our knowledge, no studies have manipulated these features in aged animals to determine what aspect(s) of social behavior are impacted in aging. Since social interaction is a dynamic process that can be influenced by a number of factors, more detailed assessments of social behavior are required to disentangle other, off-target processes that may influence social functioning. For instance, reduced social interaction in aged rats might result from aging-related inflammation that may be associated with a general state of achiness or malaise, reduced motivation to engage in social behavior (Varlinskaya et al., 1999), the inability to detect, remember, and/or recognize conspecifics (Mencio-Wszalek et al., 1992; Guan and Dluzen, 1994; Prediger et al., 2006, 2005; Terranova et al., 1994), or aging-related increases in anxiety that may suppress social interaction (Darwish et al., 2001; File, 1990; Hunt et al., 2011; Miyagawa et al., 1998).

This report presents our initial working model of aging-associated alterations in social behavior. Overall, we considered 4 key variables that might influence social behavior assessments: (i) general exploratory activity, (ii) sensorimotor function, (iii) familiarity of the social partner, and (iv) age of the social partner. In Exp. 1, aging-related alterations in object exploration and social interaction were assessed in male rats. Exp. 2 then evaluated social interaction across the lifespan in males and females, while also conducting detailed assessments of sensorimotor function. Lastly, Exp. 3 tested whether administration of naproxen, a non-steroidal anti-inflammatory drug (NSAID), would attenuate the aging-related decline in social interaction, with the idea that NSAID treatment might alleviate aging-related inflammation and temper any general achiness and/or malaise that could account for declines in social behavior during late aging in females. Naproxen—a non-selective cyclooxygenase (COX) inhibitor—was selected as an initial pharmacological approach because it has been classically used to reduce fever, pain, and inflammation (Clarke et al., 1994), and more recently to alleviate illness-related changes in social behavior in guinea pigs (Hennessy et al., 2015). Together, these experiments represent our development of a tractable working model to assess mechanisms underlying late-aging associated social deficits.

2. Materials & methods

2.1. Subjects

F344 rats were used in all experiments, with the vendor and source of the animals explained for each experiment below. Animals were provided *ad libitum* access to both food and water throughout all experiments. At all times, animals were maintained and treated in accordance with the guidelines set forth by the Institute of Laboratory Animal Resources (1996), and in accordance with the protocol approved by the IACUC at Binghamton University.

2.1.1. Experiment 1

Male F344 rats (n = 6–9/group) of different ages (1.5, 3, and 18 months) were obtained from the NIA colonies at Taconic. All rats were given at least 1 week to acclimate to the colony conditions before the onset of experimentation. Colony conditions were maintained at 22 ± 1 °C with a 14:10 light:dark cycle (lights on 0600). Rats remained pair-housed except during the brief (30–40 min) sessions during which behavioral testing occurred.

2.1.2. Experiment 2

Male and female F344 rats (n = 6–10/group) of different ages (3, 9, 18, and 24 months) were obtained from the NIA colony at Charles River Laboratories. Due to federal restrictions on the number of animals that can be obtained from the NIA colony, a separate group of 3-month-old F344 rats (males and females) was purchased from Charles River to serve as social partners. This approach had the added advantage of ensuring that social partners were truly unfamiliar to the test subjects. All rats were given at least 1 week to acclimate to the colony conditions (22 ± 1 °C; 12:12 light:dark cycle with lights on at 0700) before the onset of experimentation. On the day prior to the start of behavioral testing, rats were handled for 3 min. Additionally, in this study, experimental subjects and social partners were single-housed for five days prior to the onset of behavioral testing, and remained individually housed throughout the experiment, as previous research has demonstrated that brief periods of social deprivation increase the motivation