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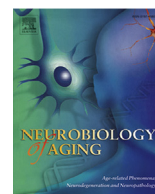

Impaired thermoregulation and beneficial effects of thermoneutrality in the 3×Tg-AD model of Alzheimer's disease

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A B S T R A C T

The sharp rise in the incidence of Alzheimer's disease (AD) at an old age coincides with a reduction in energy metabolism and core body temperature. We found that the triple-transgenic mouse model of AD (3×Tg-AD) spontaneously develops a lower basal body temperature and is more vulnerable to a cold environment compared with age-matched controls. This was despite higher nonshivering thermogenic activity, as evidenced by brown adipose tissue norepinephrine content and uncoupling protein 1 expression. A 24-hour exposure to cold (4 °C) aggravated key neuropathologic markers of AD such as: tau phosphorylation, soluble amyloid beta concentrations, and synaptic protein loss in the cortex of 3×Tg-AD mice. Strikingly, raising the body temperature of aged 3×Tg-AD mice via exposure to a thermoneutral environment improved memory function and reduced amyloid and synaptic pathologies within a week. Our results suggest the presence of a vicious cycle between impaired thermoregulation and AD-like neuropathology, and it is proposed that correcting thermoregulatory deficits might be therapeutic in AD.
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1. Introduction

The main risk factor for Alzheimer's disease (AD) is unquestionably aging. The incidence of sporadic AD is extremely low before 65 years of age; it then doubles every 5–6 years to surpass 3 cases per 100 person/year after 80 and 8 cases per 100 person/year after 85 (Rocca et al., 2011; Ziegler-Graham et al., 2008). According to the Alzheimer's Association USA *Facts and Figures* report, more than 81% of patients suffering from AD in the United States are 75 years of age or older (Alzheimer Association, 2014). Even the most penetrant AD-causing gene mutations on amyloid-β (Aβ) precursor protein (APP) or presenilins (PS1 and PS2) require aging factors to translate into the full clinical expression of the disease (Goate et al., 1991; Levy-Lahad et al., 1995; Ridge et al., 2013; Sherrington et al., 1995). Such an influence of age on AD risk strongly suggests that aging-related processes culminating at very old ages are central to the pathogenesis of the disease.

The human aging process includes a variety of changes linked to energy metabolism, which becomes particularly noticeable after 85 (Fox et al., 1973; Frisard et al., 2007; Rizzo et al., 2005; Touitou et al., 1986). Several reports suggest that old age is associated with lower brain glucose metabolism, which becomes more striking in AD patients (Cunnane et al., 2011). Old age is also associated with a dramatic decrease in body temperature, which is a likely consequence of a deficit in thermoregulation and, more particularly, thermogenesis (Fox et al., 1973; Gomolin et al., 2005; Weinert, 2010; Whittington et al., 2013). Furthermore, AD pathologic markers are found in brain regions implicated in the regulation of body temperature, such as the hypothalamus (Simpson et al., 1988; van de Nes et al., 2006). Interestingly, the amplitude of rhythmic oscillations in body temperature was found to be of a greater magnitude in demented patients (Okawa et al., 1991), and AD patients display a pronounced phase delay in the circadian cycling of

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body temperature (Satlin et al., 1995). Although little is known about the underlying mechanisms, multiple experimental paradigms used to lower body temperature have been associated with a rise in the phosphorylation of tau (Holtzman and Simon, 2000; Korneyev, 1998; Korneyev et al., 1995; Planel et al., 2004, 2007, 2009; Whittington et al., 2013).

Since the development of metabolic defects and hypothermia in the elderly coincides with a sharp rise in the incidence of AD, we hypothesized that old age leads to deficits in thermoregulation, which consequently accelerate AD pathogenesis. In parallel, AD progression could contribute to thermoregulation defects, thereby leading to a self-amplifying loop.

2. Materials and methods

2.1. Animals and diets

The triple-transgenic mouse model of AD (3×Tg-AD) was used for this study. Homozygous 3×Tg-AD mice (APPswe, PS1M146V, tauP301L) harboring cerebral amyloid and tau pathology and nontransgenic (NonTg) control mice were produced at our animal facility (Oddo et al., 2003). For ethical reasons, all mice had to be anesthetized (100 mg/kg ketamine and 10 mg/kg xylazine), although it is known that anesthesia has an effect per se on body temperature (Lenhardt, 2010). To keep the mice group at their respective housing temperature during anesthesia, their cages were either kept on ice or maintained at room temperature until intracardiac perfusion. In separate experiments, we determined that ketamine-induced decreases in body temperature were not significantly different between NonTg (−1.61 °C ± 0.22 °C, n = 7) and 3×Tg-AD (-1.76 °C ± 0.27 °C, n = 8) mice. In addition, the decrease in body temperature caused by ketamine-induced anesthesia were higher after pre-exposition to 4 °C in NonTg mice (−3.23 °C ± 0.64 °C, n = 7, $p < 0.01$) but not in 3×Tg-AD mice (−2.29 °C ± 0.36 °C, n = 7). Mice were killed by intracardiac perfusion with 0.1 M phosphate buffer saline solution, containing phosphatases (sodium pyrophosphate, 1 mM and sodium fluoride 50 mM) and proteases (SigmaFast protease inhibitor tablets, Sigma-Aldrich, St-Louis, USA) inhibitors. Brain and brown adipose tissue (BAT) of mice were rapidly dissected and kept at −80 °C until processing for Western blot, high-performance liquid chromatography (HPLC), enzyme-linked immunosorbent assay (ELISA), and Real-Time Quantitative Reverse Transcription polymerase chain reaction (qRT-PCR) analysis. All experiments were performed in accordance with the Canadian Council on Animal Care and were approved by the Animal Ethics Committee of the Université Laval.

2.2. Evaluation of body temperature

Body temperature was evaluated using an electronic thermometer equipped with a rectal probe (Traceable, Fisher Scientific, Ottawa, Canada). For temperature measurement in 6, 10, and 14-month-old mice, all rectal temperature were taken between 7 AM and 8 AM and during the diestrus phase of the estrus cycle in females to limit variation because of the estrus cycle phase and the period of the day. Rectal assessment of body temperature was selected because of relative ease of the procedure, and previous observations showing that rectal temperatures follow very closely core body (Padovani et al., 2016). However, measurements of the body temperature using a rectal probe may have some limitations. For example, the handling of the animal can induce a stress response modifying the body temperature (Cabanac and Briese, 1992). Thus, rectal temperature was measured at the end of exposure session to 4 °C or 28 °C (i.e., after the behavioral assessment, just before anesthesia, at their specific ambient temperature) to avoid the confounding effect of stress.

2.3. Indirect calorimetry

Indirect calorimetry was performed in a 28 °C room in NonTg and 3×Tg-AD mice at 11 months of age (Guesdon et al., 2009). Mice were put in metabolic chambers apparatus (Oxymax/Comprehensive Lab Animal Monitoring System, Columbus, OH, USA) with access to food and water ad libitum (Kandasamy et al., 2012). They were acclimated to their environment for 24 hours, and the measures were taken for 2 days. Data from each mouse represent the mean from 48 hours of recording. Oxygen consumption (VO_2), carbon dioxide production (VCO_2), and heat production were measured.

2.4. Cold and heat exposure experiments

Mice were housed individually in a room at 4 °C or 22 °C for 24 hours for cold exposure experiment. For the group of mice at 4 °C, cages were kept on ice after anesthesia until perfusion. The mice at 22 °C were kept at room temperature from anesthesia to the sacrifice. For heat exposure, mice were put in a room at 28 °C (or 22 °C for controls) for one week. Behavioral assessment was done the day before sacrifice in the housing room. Mice were anesthetized and perfused at their respective housing temperature. The control temperature was set at 22 °C, as in most animal facilities (Cannon and Nedergaard, 2004; Karp, 2012), to allow comparison with previously published data on the 3×Tg-AD mouse model.

2.5. Behavioral assessment

To evaluate recognition memory, object recognition was performed. Mice were put in a clear box (29.2 × 19 × 12.7 cm^3) with 2 objects for 5 minutes. One hour later, they were put in the same box with a new and a familiar object for 5 minutes. Recognition index ([Time exploring the new object−time exploring the old object]/time exploring the old object) was used to evaluate mice memory function (Arsenault et al., 2011; Filali et al., 2012; St-Amour et al., 2014). The object recognition task was performed 6 days after the beginning of the external temperature change. Anxiety-like behavior was evaluated using the dark−light emergence test (Latapy et al., 2012; St-Amour et al., 2014) performed in a box divided in 2 compartments (16 × 17 cm^2 each): a dark one and a clear one with an opening between them (4 × 4 cm^2) to allow the mice to pass from one compartment to the other. The mice are placed in the center of the dark compartment. Time spent in each compartment was observed during a 5-minutes session. The dark−light emergence test was performed 5 days after the beginning of the external temperature change. Since mice at 22 °C and 28 °C were housed in different room, to be able to compare them, we reported there results to the behavioral experiments to NonTg mice that were located in the same room.

2.6. Plasma triiodothyronine measurement

Plasma triiodothyronine (T3) concentration was determined with a T3 (total; mouse and/or rat) ELISA Kit (Abnova, Taipei, Taiwan) accordingly to the manufacturer instructions.

2.7. High-performance liquid chromatography

BAT norepinephrine (NE) content was determined by HPLC with electrochemical detection as previously described (Bousquet et al., 2011). BAT was powderized and homogenized in perchloric acid

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