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Emotional behavior in middle-aged rats: Implications for geriatric psychopathologies

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ABSTRACT

Clinical findings reveal that middle-aged patients are more susceptible to suffer from psychiatric disorders than older ones. However, little is known about the emotional behavior of aging rodents. This study aimed to investigate behavioral alterations in male middle-aged Wistar rats in the open-field (OF) test (at illuminated and dimly light conditions), elevated plus maze (EPM), forced swimming (FST) and inhibitory avoidance task (IA). In the EPM, middle-aged rats displayed reduced percentages of the time spent in and entries into open arms. The ambulatory activity measured in the OF under dimly light conditions was identical among groups. However, under illuminated conditions, a reduction in the number of crossings was detected in older rats, reinforcing that aged animals display a genuine anxiogenic-like phenotype. Additionally, aged rats showed an increase in the immobility time in the FST, and a reduction in the latency to step down the platform in the IA. A negative correlation was found between the immobility time and latency to step down the platform, suggesting a relationship between depressive-behavior and cognitive impairment in old rats. Altogether, male middle-aged rats are more anxious, depressed, and display aversive memory impairments. These observations contribute to investigate biological mechanisms and therapeutic interventions for geriatric anxiety and depression.

1. Introduction

Mental health is one of the most relevant factors related to quality of life among the elderly [1]. Some decades ago, neurodegenerative disorders and dementia were on the top of the most prevalent and devastating diseases in older adults, while epidemiological studies were pointing to anxiety, and also depression, as psychiatric disorders less common among this population [2,3].

In the last decade, many studies have been focused on diagnosis and treatment of anxiety and depression in late-life. Indeed, an epidemiological study using 2575 participants from the community with 55 years and older showed that the prevalence rates of DSM-IV mood and anxiety disorders in late-life tend to decline with age, and middle-aged humans display higher rates compared to older people [4]. Authors have postulated that anxiety and depression are subestimated in old individuals, especially because these psychopathologies are qualitatively different from that experienced by younger persons, and, the symptoms experienced by elders are commonly superposing disabilities generated by senescence, i.e. apathy, cognitive impairments, and sleep disorders [for a review see: 2,3]. However, because of its devastating consequences, late-life depression is an important public health problem. It is associated with increased risk of morbidity and suicide, decreased physical, cognitive, and social functioning, and greater self-neglect, all of which are in turn associated with increased mortality [5].

It should be mentioned that subjective complaints of poor memory and concentration are also common among depressed older adults. Slower cognitive processing speed and executive dysfunction are frequent findings from objective testing [6]. In fact, literature supports that geriatric depression is more frequently associated with cognitive deficits and somatic complaints than depression in younger age [for a review see: 7], consequently, depressive symptoms in the elderly are often misinterpreted and not treated adequately.

Few studies are available in the literature reporting the behavioral alterations of middle-aged male rats. Generally, the available data regarding the effects of aging on animal's behavior were obtained from old rodent. Very recently, an interesting study reported that there was an age-related decline in the performance of male Fisher-344 rats in the inhibitory avoidance, water maze, defensive freezing,

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and forced swim tasks [8]. The authors reported that middle-aged and aged rats display spatial and aversive memory decline, and depressant-like behavior compared to younger animals. Additionally, authors reported that aging is associated with a decrease in 3alpha-androstanediol production, and the administration of this hormone reinstates cognitive and affective performance of aged male rats [8]. The cognitive impairment evoked by aging in rodents is a consensus between distinct authors (for a review see: [9]), however the effects of senescence on emotional behavior are quite a puzzle. Some studies reinforce the view that aged rodents display a depressant-like behavior when assessed in behavioral despair test and olfactory bulbectomy [10–12]. In contrast, Kaschow et al. [13] observed no differences between adult, and middle-aged F344/Brown–Norway rats when subjected to the forced swimming test. Regarding anxiety-related behaviors experienced by aged rodents, literature data showed that animals could display increase or decrease of anxiety experienced, depending on animal's species, strain, or animal model used [12,14–19].

Altogether, clinical findings reveal that middle-aged adults are susceptible to suffer from psychiatric disorders, such as major depression, and anxiety, in addition to the cognitive impairments well described to late-life. As commented above, epidemiological studies point to these problems in humans, however, little information is still available on the literature concerning the emotional behavior of middle-aged rodents. This information is very relevant, since based on animals' observations neuroscientists will be able to understand the pathophysiology of these psychiatric disorders in the elderly and, therefore, to investigate new therapies and pharmacological targets to treat them. It should be noted that a study has showed an age-related decline in locomotor activity and explorative behavior in rats [20]. Thus considering that animal models for investigating memory, anxiety-, and depression-like behavior in rodents are dependent on locomotor activity and explorative behavior, middle-aged rats could provide a more ideal condition for testing the effects of aging on animal behavior compared to aged animals (20-month-old rats or older). Therefore, the aim of the present study was to investigate the behavioral alterations observed in naïve male Wistar rats at 12 months old regarding their performance on animal models of anxiety, behavioral despair and aversive memory.

2. Material and methods

2.1. Animals

Adult (3 months old) and middle-aged (12 months old) male Wistar rats were employed in the present study. These rats were obtained from our breeding colony (UNESC). Animals were housed in cages sizing 41×34×16 cm, five to cage up to 6 months old, in which they were re-housed three to cage, with food and water freely available and were maintained on a 12-h light/dark cycle (lights on at 7:00 a.m.) in a temperature of 23±1 °C. Behavioral procedures were conducted between 8:00 and 12:00 a.m. All experimental procedures were performed in accordance with the NIH Guide for the Care and Use of Laboratory Animals and the recommendations of the Brazilian Society for Science on Animals of Laboratory (SBCAL) for animal care. All behavioral data were conducted in a calm room; the observer was in the room where experiments were performed, and was blind to the animal condition. All rats were weighed one week before starting behavioral tests.

2.2. Behavioral tests

One group of 15 adult rats and 12 middle-aged rats was tested only once at the paradigms described bellow in the following order: elevated plus-maze and open-field test (under illuminated room). Another group of 10 adult and 8 middle-aged rats was tested in all three paradigms in the following order: open-field test (under dimly light room), inhibitory avoidance task and forced swimming test. The sequence of behavioral tests was adapted from previously published reports, showing that this study design would not affect behavioral test performance [21,22]. A 3-day inter-test interval was adopted in the present study.

2.3. Elevated plus-maze test

The rats were tested for 5 min in the elevated plus-maze, a behavioral model of anxiety, as previously described by Pellow et al. [23]. The maze consisted of the two open arms, 50×10 cm, and two closed arms, 50×10×40 cm without roof, arranged such that the two arms of each type were opposite each other. The maze was elevated to a height of 50 cm of floor. The experiment was leading in a dark room with red light under 50 cm from the center of the plus-maze. At the beginning, the rat was placed into the center of the maze facing a closed arm and any subsequent visit to one of the 4 arms was recorded when rat had entered with 4 paws. The number of entries and the time spent into open and closed arms were registered during 5 min of trial. The ratios 'time spent in the open arms/time spent in all (i.e. open and closed) arms' and 'frequency of entries into open arms/total entries into all arms' were calculated and multiplied by 100, to yield the percentages of the time spent in and of frequency of entries into open arms, respectively. Both parameters are considered to reflect fear induced inhibition from entering the open arms and can be related to the 'anxiety' level experienced by the animal. Furthermore, the number of entries into closed arms was used as an index of general activity.

2.4. Step-down inhibitory avoidance task

The step-down inhibitory avoidance task was conducted as previously described by Gold [24]. The apparatus consisted of a 50×25×25 cm plastic box with a front glass wall, whose floor had parallel 10-mm bronze bars. The left end of the grid was occupied by a 7-cm wide, 2.5-cm high formica platform. The rats were gently placed on the platform facing the rear wall, and their latency to step down with all four paws on the grid was recorded. In the training session, after stepping down, the animals received a 0.4-mA, 2-s scrambled footshock and were withdrawn immediately from the cage. Twenty-four hours later (test session), the procedure was repeated, but footshock was not given. This session was used as a measure of inhibitory avoidance memory retention. A ceiling of 180 s was imposed on the latency to step down the platform.

2.5. Forced swimming test

The forced swimming test consisted of placing rats, individually, in Plexiglas cylinders (46 cm high, 20 cm in diameter) containing water (24–26 °C, 30 cm deep), for two swimming sessions: an initial 15-min training session, which was followed, 24 h later, by a 5-min test session, as described by Porsolt et al. [25]. At the end of each swimming session, the animal was removed from the cylinder, dried with paper towels, placed in an individual cage to rest and recover for 15 min and then returned to its collective home cage. Three behavioral parameters were scored cumulatively in the second swimming session test only: (i) immobility time (i.e. the time spent floating in the water without struggling, making only those movements necessary to keep the head above the water), (ii) swimming time (i.e. the time spent making active swimming motions to move around in the cylinder) and (iii) climbing time (i.e. the time spent making active movements with its forepaws in and out of the water, directed specifically to the cylinder wall).