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Comparison of behavioral and biochemical deficits in rats with hereditary defined or D-galactose-induced accelerated senescence: Evaluating the protective effects of diosgenin

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ABSTRACT

One of the important factors in aging is oxidative stress and aging-related disturbances are believed be ameliorated by antioxidants. Diosgenin is a bio-active ingredient of dioscorea that is widely used in Chinese medicine, shows anti-oxidant activity and improves some aging-related deficits in senescent and menopausal animals.
We compared alterations in behavior, biochemical parameters (plasma levels of the uric acid, creatinine, calcium, phosphate, total cholesterol, low-density lipoprotein cholesterol and triglycerides, and the plasma activity of aminotransferases AST and ALT), and sperm motility in two models of accelerated senescence (D-galactose-induced (150 mg/kg/day, i.p., 57 days) aging in Wistar rats vs. genetically defined in OXYS rats) and examined the protective effects of diosgenin (10 or 50 mg/kg/day, p.o., 57 days). Both models had augmented levels of ALT activity indicating hepatopathology. Compared to D-galactose-treated animals, OXYS rats demonstrated profound biochemical alterations (hypocalcemia, hypophosphatemia, and hypocholesterolemia) and behavioral deficits (impaired object recognition, decreased sexual motivation and locomotor activity, retarded learning) that confirmed the difference in the mechanisms of accelerated senescence in these models. We first showed diminished sperm motility in males of both models of accelerated senescence studied.
Chronic diosgenin treatment failed to improve biochemical and behavioral disturbances and had some undesirable side effects on body weight and working memory in OXYS rats. However, diosgenin restored moderately decreased sperm motility in D-galactose-treated Wistar males and might be recommended for treatment of mild age-related reproductive dysfunctions.

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1. Introduction

One of the important factors in aging and the aging-related neurodegeneration and cognitive decline is considered to be the oxidative stress caused by the imbalance of the reactive oxygen species (ROS) generation and their removal by antioxidant system. This may originate from an overproduction of ROS or from a reduction in antioxidant defense and a breakdown of reactive species by reducing agents and enzymes, known as antioxidants (Olanow, 1993; Valko et al., 2007). Oxidative stress has been also associated with decreased male fertility due to accumulating seminiferous tubule damage with increasing age and reduced motility of spermatozoa (Chen et al., 2013). Thus, a promising avenue for the prevention and reversal of aging-related deficits is the dietary antioxidants.

Among the natural antioxidants, dioscorea (wild yam) is worthy of note. Dioscorea, a common food and Chinese medicine (Liu et al., 1995) that contains phytosteroids, such as diosgenin and steroidal saponins (Hidaka et al., 2004) has long been used to treat menopausal syndrome and has anti-osteoporotic activity (Chen et al., 2008; Yin et al., 2003). It also decreases anxiety levels and inflammatory cytokine levels in the brain of menopausal rats (Ho et al., 2007). Diosgenin, the main steroidal saponin in dioscorea, has a similar chemical structure to steroid hormones and is used as a precursor in the manufacture of estrogen, progesterone, testosterone, and cortisol (Djerassi, 1992; Rosenkranz et al., 1951). In addition, diosgenin has antioxidant and free radical scavenging activity in rats (Son et al., 2007), prevents H_2O_2-induced apoptosis in human vein endothelium cells (Gong et al., 2010), shows anti-aging effects in human chronic

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myelogenous leukemia K562 cells (Liu et al., 2005), and improves epidermal functions in aging mice (Tada et al., 2009).

We suggested that diosgenin might have beneficial effects on mental and sexual functions of aging animals as well. To prove this suggestion in the present study we used two animal models of accelerated senescence. One was a widely used pharmacological model according to which natural aging is induced by chronic administration of D-galactose (Wei et al., 2005) in Wistar male rats. D-galactose, a reducing sugar, stimulates the production of free radicals, causes accumulation of ROS (Zhang X.L. et al., 2007) and decreases the activity of antioxidant enzymes in vivo (Wei et al., 2005) resulting in oxidative stress and aging-related changes (Zhang et al., 2005).

Another model used in the study was inbred rat strain of hereditary defined accelerated senescence — OXYS rats. OXYS strain was produced in the Institute of Cytology and Genetics SB RAS (Novosibirsk, Russia) with selective breeding of Wistar rats that were highly sensitive to cataractogenic effect of D-galactose. Selective breeding of the rats resulted not only in the early spontaneous cataract in OXYS rats but also in the early development of the complex of degenerative features which are regarded as a syndrome of accelerated senescence (Kolosova et al., 2009). OXYS rats are known for shortened lifespan and an early development of age-related pathological phenotypes similar to geriatric disorders observed in humans, including cataract, retinopathy similar to age-related macular degeneration (Markovets et al., 2010; Zhdankina et al., 2008), high blood pressure (Bobko et al., 2005), and accelerated involution of the thymus (Obukhova et al., 2009).

It has been shown that behavior of young OXYS rats is similar to the behavior of old Wistar rats. At the age of 3 months, OXYS rats are characterized by significantly reduced locomotor and exploratory activities in the open field test and in the hole-board task, increased anxiety in the elevated plus-maze (Loskutova and Zelenkina, 2002; Markova et al., 2005; Markova et al., 2003; Sergeeva et al., 2006) and impairments of learning in the passive avoidance test, as compared to Wistar rats (Kolosova et al., 2006). OXYS rats also manifest impaired learning abilities in the Morris water maze in comparison with Wistar rats (Stefanova et al., 2010). Behavioral alterations in OXYS rats are accompanied with signs of neurodegeneration in the brain identified using magnetic resonance imaging (MRI) (Agafonova et al., 2011). Recently, some aging-related features of OXYS rats were found to be corrected or improved by anti-oxidant drug treatment (Amstislavskaya et al., 2010; Kolosova et al., 2006; Obukhova et al., 2009; Stefanova et al., 2010). Thus, OXYS rats appear to be especially useful for detecting the effects of potential anti-oxidant drugs.

The present study was aimed 1) to compare alterations in behavior, biochemical parameters, and sperm motility in D-galactose-induced aging Wistar male rats with that in OXYS male rats and 2) to examine the protective effects of the natural-derived antioxidant diosgenin (10 or 50 mg/kg/day, p.o., 57 days) on these aging models.

2. Materials and methods

2.1. Experimental animals

Twelve-week old male Wistar rats weighing 359.2 ± 29.1 g were purchased from the National Laboratory Animal Center, ROC, and were housed in groups of four or five in acrylic cages (35 × 56 × 19 cm) in an animal room with a 12 h light–dark cycle (lights on at 07:00 h) with food and water available *ad libitum*. Each animal was handled for 5 min/day on 3 consecutive days, starting 1 day after arrival. In parallel, OXYS male rats of the same age weighing 266.6 ± 4.6 g from the Institute of Cytology and Genetics, Russian Academy of Sciences, Russia were used. Wistar rats were divided into four experimental groups: control ($n = 12$), D-galactose-treated ($n = 11$), D-galactose + diosgenin (10 mg/kg)-treated ($n = 11$), and D-galactose + diosgenin (50 mg/kg)-treated ($n = 12$) animals. OXYS rats were divided into three experimental groups: control ($n = 13$), diosgenin-treated at a dose of 10 mg/kg ($n = 15$), and diosgenin-treated at a dose of 50 mg/kg ($n = 16$) animals.

Three-month old Wistar female ($n = 40$) and male ($n = 40$) rats were used in the sexual incentive motivation test sexual motivation as a sexually or socially significant stimulus for the experimental males, respectively.

All experimental procedures were performed according to the NIH Guide for the Care and Use of Laboratory Animals and were approved by the Animal Care Committee of Chung Shan Medical University (IACUC approval No.: 1018). All efforts were made to minimize the number of animals used and their suffering.

2.2. General procedure

Starting from the age of 12 weeks (day 0), the Wistar rats received 57 daily intraperitoneal (i.p.) injections of D-galactose (150 mg/kg/day) or saline. Respective groups of D-galactose-treated or OXYS rats received diosgenin treatment (10 or 50 mg/kg daily, p.o.) starting from the age of 12 weeks during 57 days. Rats were weighed weekly during the experiment to correct drug dosages. To assess the effects of experimental factors on body weight gain, the values of body weight measured before the sacrifice of animals were analyzed.

In the last week of treatment, i.e. at the age of 19 weeks, all animals were subjected to a battery of behavioral tests performed as in our previous studies (Sy et al., 2010; Wang et al., 2009): the open field test on the day 49 of the treatment, T-maze test on days 50–52, object recognition test on days 53–55, and sexual incentive motivation test in the evening of days 56–57. All behavioral observations were started at least 2 h after the beginning of the light phase (7:00 h). For behavioral testing, the animals were placed individually in a clean cage (25 × 41 × 19 cm), and transported to a dim observation room (28 lx of the red light) with sound isolation reinforced by a masking white noise of 70 dB. Performance in the behavioral tests was monitored using a video camera positioned above the apparatus and a home-made video image analysis system (VIAS) (Li and Chao, 2008) or the original EthoStudio software (Kulikov et al., 2008). Data were acquired and scored using the VIAS and in-house-developed software. The spatial resolution of the VIAS was set to 0.7 cm and the image processing capability was higher than 14 pictures/s. The test equipment and objects used in this study were cleaned using 20% ethanol and thoroughly dried before each test trial. On day 58 the rats were sacrificed by exposure to CO_2, immediately after sacrifice blood samples were taken for biochemical assays and the vasa deferentia were taken for the assay of sperm motility.

2.3. Drugs and drug administration

D-galactose was purchased from Sigma-Aldrich Co., diluted in saline and injected i.p. daily at 15:00 h during 57 days in a volume of 1 mL/kg. Control Wistar rats received saline injections of the same volume.

Diosgenin was purchased from Sigma-Aldrich Co. Appropriate amount of the drug was mixed with flour and water to produce pellets of 0.8 g each. A pellet was given daily to each rat at 12:00–13:00 h during 57 days. Control rats received pellets without drug. The pellet mixture was prepared for each cage separately taking the body weight of rats in the cage into account. Body weight of the rats was measured weekly and hence the drug amount added to the mixture was corrected.

2.4. Behavioral tests

2.4.1. Locomotor activity

Locomotion of the rats was measured in an acrylic box (40 × 40 × 40 cm) by an automated activity monitoring system (Tru ScanTM, Photobeam Sensor-E63-22; Coulbourn Instruments; USA). One grid of infrared sensor beams was mounted horizontally 3 cm above the floor, and a second tier of beams was mounted 16.5 cm above the

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