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Research report

Deletion of fibroblast growth factor 22 (FGF22) causes a depression-like phenotype in adult mice

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HIGHLIGHTS

- Mice lacking fibroblast growth factor 22 (FGF22KO) have depressive-like behaviors.
- FGF22KO mice have normal motor, exploratory, and social behaviors.
- Fibroblast growth factor 22 plays specific roles in affective behaviors.

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ABSTRACT

Specific growth factors induce formation and differentiation of excitatory and inhibitory synapses, and are essential for brain development and function. Fibroblast growth factor 22 (FGF22) is important for specifying excitatory synapses during development, including in the hippocampus. Mice with a genetic deletion of FGF22 (FGF22KO) during development subsequently have fewer hippocampal excitatory synapses in adulthood. As a result, FGF22KO mice are resistant to epileptic seizure induction. In addition to playing a key role in learning, the hippocampus is known to mediate mood and anxiety. Here, we explored whether loss of FGF22 alters affective, anxiety or social cognitive behaviors in mice. We found that relative to control mice, FGF22KO mice display longer duration of floating and decreased latency to float in the forced swim test, increased immobility in the tail suspension test, and decreased preference for sucrose in the sucrose preference test, which are all suggestive of a depressive-like phenotype. No differences were observed between control and FGF22KO mice in other behavioral assays, including motor, anxiety, or social cognitive tests. These results suggest a novel role for FGF22 specifically in affective behaviors.

1. Introduction

Fibroblast growth factors (FGFs) are known to play important roles in synapse formation and maintenance [1–3]. Altered expression of, or mutations in, FGFs and their receptors have been implicated in the pathogenesis of many neuropsychiatric diseases, including depression [4], altered social behavior [5], seizures [6] and intellectual disability [6].

FGF22 is a critical determinant of excitatory synapses in the developing hippocampus [1]. When FGF22 is deleted in mice (FGF22KO mice), excitatory synapses in the hippocampus fail to form during development, and this defect persists into adulthood

Abbreviations: FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FGF22, fibroblast growth factor 22; FGF22KO, fibroblast growth factor 22 knockout; NMJ, neuromuscular junction; PTZ, pentylenetetrazol; WT, wild-type.

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[1]. The deletion of FGF22 renders mice resistant to seizure kindling in a pentylenetetrazol (PTZ) kindling model of epilepsy [1], and FGF22KO mice do not display seizure-induced neuropathology, such as increased hippocampal mossy fiber sprouting and hilar cell death, even when seizures are induced [7]. FGF22 has been implicated in the organization of other excitatory synapses in the brain, including retinogeniculate synapses [8] and mossy fiber-dentate granule cell synapses in the cerebellum [3], as well as the peripheral neuromuscular junction (NMJ) synapse [9].

The hippocampus is implicated in mood, anxiety, and learning and memory [10–12]. Since FGF22 is critical for excitatory synapse formation in the hippocampus, we hypothesized that FGF22KO mice may have abnormal affective, anxiety-like, and social cognitive behaviors. Here we performed a battery of behavioral studies and found that FGF22KO mice exhibit passive stress coping behaviors in affective reactivity tests, including the forced swim test and the tail suspension test, the tests that are often used to screen for antidepressants. The FGF22KO mice also prefer sucrose to a lesser degree than WT littermates, suggestive of anhedonia, the failure to engage in pleasurable activity. These alterations in affective tasks are independent of any changes in anxiety-like behaviors, social cognition, and motor phenotypes. Our results reveal a unique role for FGF22 in affective behaviors and suggest that FGF22KO mice may be an ethologically useful animal model for screening antidepressant compounds.

2. Materials and methods

2.1. Animals

The generation of FGF22KO mice has been described previously [1]. FGF22KO mice were backcrossed with C57BL/6J mice for at least 20 generations. All mice were bred within our colony, and all wild-type (WT) animals were FGF22KO littermates. Studies were conducted using adult mice (8–30 weeks old). All mice were housed by sex in groups of two to five. Mice were maintained in cages with a 14-h/10-h light/dark cycle for a minimum of one week prior to behavioral experiments. The average ambient temperature was 22 °C and mice were provided with food and water *ad libitum*. All experiments were conducted during the animals' light cycle. Air purifiers (Honeywell, Southborough, MA) were used during all experiments to mask ambient noise. For all experiments, examiner was blinded to mouse genotype. We used several cohorts of mice and used them in multiple tasks. Being mindful of potential order of testing effects [13,14], we tested the mice using the least stressful tasks first and the most stressful tasks last, in the following order: rotarod, open field, light-dark box, elevated zero maze, social recognition, forced swim test, and tail suspension test. Mixed cohorts of males and females were used in each genotype group in all tests except rotarod, open field, and tail suspension, where groups were male (precise numbers of animals for each task can be found in Supplementary Table S1 in the online version at DOI: 10.1016/j.bbr.2016.03.047). Although the rotarod and open field groups were entirely male, in the social recognition task females and males (both WT and FGF22KO) displayed similar exploration (Supplementary Fig. S1 in the online version at DOI: 10.1016/j.bbr.2016.03.047), suggesting that motor exploratory behaviors are similar between males and females in our cohorts. Sucrose preference test was performed on experiment-naïve animals in their home cages without masking of ambient noise. All experiments were conducted according to the National Institute of Health guidelines for animal care and were approved by the University Committee on the Use and Care of Animals of the University of Michigan (PRO00003549 and PRO00004242) and the Institutional Animal Care and Use Committees at Boston Children's Hospital (13-11-2528).

2.2. Behavioral procedures

2.2.1. Open field (OF)

Animals were permitted to explore a transparent acrylic arena for 5 min under white room lights at 33 lx as previously described [15]. Total distance traveled and percent time in periphery of arena were calculated by Limelight automated software via a video camera mounted above the arena (Actimetrics, Wilmette, IL).

2.2.2. Rotarod

Animals were trained to run on rubber-coated rod which accelerated from 4 rpm to 40 rpm (Ugo Basile, Comerio, Italy) over a 5-minute testing period as previously described [15]. Animals underwent one training session per day for 5 consecutive days. Time to passively rotate on the rod or fall off the rod was recorded for each trial.

2.2.3. Elevated zero maze (EZM)

Elevated zero maze was performed as previously described [16] with some modifications, detailed below. The maze is a 6-cm-wide ring (outer diameter 70 cm), divided into 4 quadrants with alternating walled (closed) and unwalled (open) areas, elevated on 70 cm legs. Testing was performed under low light conditions (3 lx). Mice were placed into an open area to start, and allowed to explore for 5 min. Mice were considered to be in an open area if their nose and more than 50% of their body was in the open area. Total time spent in open and closed compartments was calculated by Limelight automated software via a video camera mounted above the box (Actimetrics, Wilmette, IL).

2.2.4. Light-dark box (LDB)

Light-dark box test was performed as previously described [17]. Mice were placed into the lit compartment of a 46-cm-long box divided into a lit opaque white acrylic area (2/3 of surface area) and a lidded dark compartment made of black acrylic (1/3 of surface area). Animals were allowed to freely explore both areas of the acrylic box for 5 min, and total time spent in each compartment was calculated by Limelight automated software via a video camera mounted above the box (Actimetrics, Wilmette, IL).

2.2.5. Social recognition (SR)

Social recognition testing was performed as previously described [18] with some modifications. Testing was performed in a 3-chambered transparent acrylic arena with overhead light set at 6 lx. Mice were habituated for 10 min in the middle chamber of the arena, and then allowed to explore all 3 chambers for 10 min. During the sociability stage of the task (hereafter called the "object phase"), an empty wire cup was placed in one outer chamber, and a novel C57BL/6J mouse (same sex as test mouse) was placed under an identical wire cup in the opposite outer chamber; the test mouse was allowed to explore all chambers for 10 min and movement was recorded with Limelight software via a video camera mounted above the test area. After the object phase, social novelty preference (hereafter called the "social phase") was assessed by placing a second novel C57BL/6J mouse under the first wire cup (which had previously been empty) and the test mouse was allowed to explore all chambers for 10 min. The time between each phase of the task was approximately 1 min. Videos were scored manually for exploration of objects and mice by a trained observer blinded to genotype.

2.2.6. Forced swim test

Animals were placed into a 4L beaker of tepid water (~25 °C) for 5 min, and their behavior was recorded using a video camera mounted on the same level as the base of the beaker. Video recordings were reviewed and scored by a trained observer blinded to