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(Review Article)

Management of Claustrophobia: An Overview

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Abstract

Claustrophobia, the well-known fear of being trapped in narrow/closed spaces, is often considered a conditioned response to traumatic experience. Surprisingly, we found that mutations affecting a single gene, encoding a stress-regulated neuronal protein, can cause claustrophobia. Gpm6a-deficient mice develop normally and lack obvious behavioral abnormalities. However, when mildly stressed by single-housing, these mice develop a striking claustrophobia-like phenotype, which is not inducible in wild-type controls, even by severe stress. The human GPM6A gene is located on chromosome 4q32-q34, a region linked to panic disorder. Sequence analysis of 115 claustrophobic and non-claustrophobic subjects identified nine variants in the noncoding region of the gene that are more frequent in affected individuals (P=0.028). One variant in the 3′untranslated region was linked to claustrophobia in two small pedigrees. This mutant mRNA is functional but cannot be silenced by neuronal miR124 derived itself from a stress-regulated transcript. We suggest that losing dynamic regulation of neuronal GPM6A expression poses a genetic risk for claustrophobia.

Keywords: Chromosome 4, GPM6A, Human Pedigree, Mir124, Mouse Mutant, Panic Disorder

INTRODUCTION

The neuronal tetra span membrane glycoprotein Gpm6a has been implicated in neurite outgrowth and dendritic spine formation, but the lack of a mouse mutant has prevented any in vivo analysis of Gpm6a function. Specifically, the observation that Gpm6a expression in rodent brain is downregulated by cortisol or following physical restraint stress has been puzzling. As stress is a key factor for triggering mental disorders, we investigated the behavioural consequences of resident-intruder stress in mice lacking the Gpm6a gene. We report here the unexpected finding that the neuronal gene Gpm6a constitutes a genetic cause of a highly unusual ‘claustrophobia-like' phenotype in null mutant mice, which otherwise develop completely normally. In fact, only Gpm6a mouse mutants that have experienced a mild ‘social stress' exhibit this ‘claustrophobia-like' behaviour. Moreover, we translate this finding to human individuals, where we find rare sequence variants in the GPM6A gene associated with claustrophobia. Mechanistic insight is provided by the demonstration of a human variant-specific loss of GPM6A reliability. We conclude that reliability of the GPM6A gene under stress is required to avoid claustrophobia, which emerges as an unusual stress response.

Claustrophobia is a form of anxiety disorder, in which an irrational fear of having no escape or being closed-in can lead to a panic attack. For behavioural testing, mice were housed in groups of three to five in standard plastic cages, food and water ad libitum. The temperature in the colony room was maintained at 20–22 °C, with a 12-h light/dark cycle (light on at 0700 hours). Behavioural experiments were conducted by an investigator, blinded to the genotype, during the light phase of the day (between 0800 hours and 1700 hours). For behavioural experiments, eight different cohorts of mice were used. The order of testing in the first cohort was as follows: elevated plus maze (EPM), open field, hole board, rota rod, pre-pulse inhibition, fear-conditioning, visual cliff. In further cohorts, EPM release in closed arms, EPM in the dark, mouse light/dark box test, mouse wide/narrow box test, EPM retesting (‘exposure treatment') and hearing were performed. For electroretinogram, olfaction testing and corticosterone determination upon metabolic cage exposure, separate cohorts were used. The age of mice at the beginning of testing was 19 weeks. The inter-test interval varied depending on the degree of ‘test invasiveness' but was at least 1 day. During all tests, the investigator was ‘blinded', that is, unaware of mouse genotypes. For comprehensive test description of basic tests, that is, EPM, open field, hole board, rotarod, visual cliff test (vision), buried food finding test (olfaction), sucrose preference test (motivation), pre-pulse inhibition, cued and contextual fear-conditioning, and ultrasound vocalization analysis, please see El-Kordia et al. Described in the following are additional, modified or specifically designed tests.

EPM with release in closed arms

In this modified version, mice were placed in the closed arms in the same plus-maze described above.

This test was done to address potential motor factors influencing the time spent in arms. The test was otherwise conducted in the same manner as the classical EPM.

EPM in darkness

This test was again performed like the classical EPM, just in full darkness to address potential visual/perceptual factors affecting behavior in open/closed space. The behavior of mice was monitored via infrared camera.

Hot plate test

The hot plate test is used as a measure of pain sensitivity. Mice were placed on a metal plate (Ugo Basile, Comerio, Italy), preheated up to 55 °C. The latency of hind paw licking or jumping was recorded. Mice were removed from the platform immediately after showing the response. A 40-s cutoff time was supposed to prevent wounds, although none of the tested mice reached it.

Assessment of hearing by the acoustic startle response

Individual mice were placed in small metal cages (90 × 40 × 40 mm3) to restrict major movements and exploratory behavior. The cages were equipped with a movable platform floor attached to a sensor that records vertical movements of the floor. The cages were placed in four sound-attenuating isolation cabinets (TSE GmbH, Bad Homburg, Germany). Startle reflexes were evoked by acoustic stimuli delivered from a loudspeaker that was suspended above the cage and connected to an acoustic generator. The startle reaction to an acoustic stimulus (pulse), which evokes a movement of the platform and a transient force resulting from this movement of the platform, was recorded with a computer during a recording window of 100 ms and stored for further evaluation. The recording window was defined from the onset of the acoustic stimulus. An experimental session consisted of a 2-min habituation to 65 dB background white noise (continuous throughout the session), followed by a baseline recording for 1 min at background noise. After baseline recording, stimuli of different intensity and fixed 40 ms duration were presented. Stimulus intensity varied between 65 and 120 dB, such that 19 intensities from this range were used with 3 dB step. Stimuli of each intensity were presented 10 times in a pseudorandom order with an interval ranging from 8 to 22 s. The amplitude of the startle response (expressed in arbitrary units) was defined as the difference between the maximum force detected during a recording window and the force measured immediately before the stimulus onset. Amplitudes of responses for each stimulus intensity were averaged for individual animals. Mean values for each experimental group were plotted on the graph to provide the stimulus–response curves.

Mouse light/dark box test

The apparatus (36 × 20.5 × 19 cm3) consisted of two equal acrylic compartments, one roofed, dark and one white, with a 300-lx light intensity in the white compartment and separated by a divider with an opening (size: 5.7 × 5 cm2) connecting both compartments. Each mouse was tested by placing it in the black/dark area, facing the white one, and was allowed to explore the novel environment for 5 min. The roof of the dark compartment was closed after releasing the mouse. The number of transfers from one compartment to the other and the time spent on the illuminated side were measured. This test exploited the natural conflict between the animal's drive to explore a new environment and its tendency to rather stay in a closed, dark and protected environment and to avoid bright light.

Mouse wide/narrow box test

This in-house-made box (test arena: length 60 cm, width 60 cm and height 30 cm) consisted of two equal (each 30 cm length) gray plastic compartments. One compartment was wide and open, the other one narrow (consisting of 30 × 5 × 30 cm3 corridor). Mice were placed in the wide compartment, facing the narrow corridor. Light intensity in the wide compartment was 300 lx, in the corridor 150 l ×. Time to enter the corridor was recorded by a stopwatch. The behavior was recorded throughout the 10 min testing period by a PC-linked overhead video camera. 'Viewer 2' software was used to calculate velocity, distance travelled, number of visits of and time spent in both compartments.

Before the experiments, animals were dark adapted for at least 12 h and all preparations were carried out under dim red light. Mice were anaesthetized by intraperitoneal injection of ketamine (0.125 mg g−1) and xylazine (2.5 µg g−1). Supplemental doses of 1/4 the initial dose was administered when changes in the constantly monitored electrocardiogram or movements indicated that the animals were waking up. Mice were placed on a heated mat (Hugo Sachs Elektronik–Harvard Apparatus, March, Germany) that kept the body temperature constant at 37 °C under the control of a rectal thermometer. The head of the mouse was placed inside a custom-designed Ganzfeld bowl illuminated by a ring of 20 white light-emitting diode. The pupil of the left eye was dilated with 1% atropine sulfate and a silver wire ring electrode was coupled to the corneal surface using electrode gel. The eye and electrode were kept moist by a drop of 0.9% saline applied every 30 min. Subcutaneous needle electrodes were inserted between the eyes (reference) and near the tail (ground). Electrical potentials were amplified 1000 times, filtered between 0.1 and 8 kHz and notch-filtered at 50 Hz using custom-designed hardware. The Tucker Davis System III hardware and BioSig software (Tucker-Davis Technology, Alachua, FL, USA) were used for stimulus control and recordings. Scotopic responses to 10 white light flashes were averaged for each stimulus condition. Interstimulus intervals were 5 s for light intensities below 1 cds m−2 and 17 s for light intensities above 1 cds m−2. The amplitude growth functions and latencies of the A-waves, B-waves and oscillatory potentials in response to 0.1, 1 and 5 ms long-light

flashes ranging between 0.0003 and 10 cds m−2 was analyzed using custom-written mat lab (MathWorks, Natick, MA, USA) software

Electroretinogram

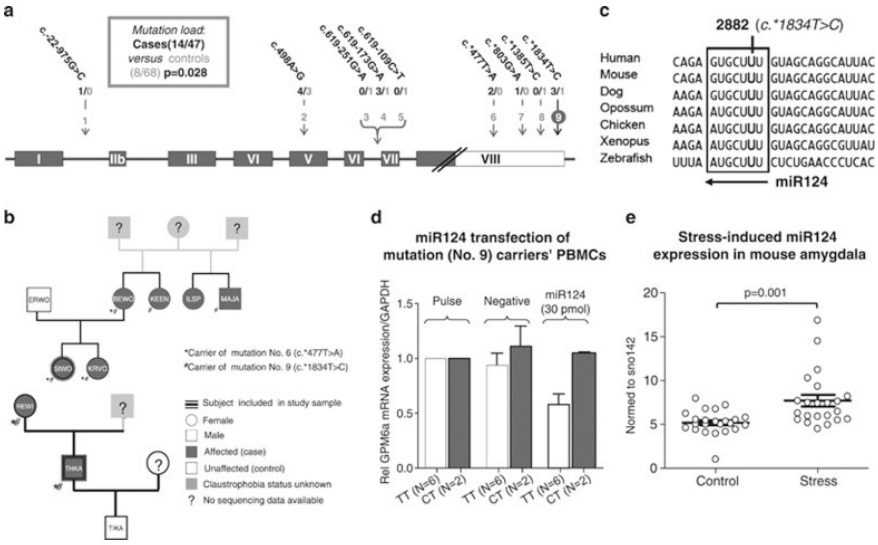

Figure 1: Electroretinogram

Corticosterone excretion: Urine samples were collected using in house-made metabolic cages. Mice were placed in small, narrow metal cages (90 × 40 × 40 mm3) to restrict major movements and exploratory behavior, thus resulting in stress-induced corticosterone release. These cages had a wire-mesh floor enabling urine collection via a funnel. The funnel was fixated on top of a collecting flask. Mice (12 per genotype) were placed in the metabolic cages at 2200 hours for 3 h each. The urine was collected at 0100 hours. Concentrations of corticosterone were measured using a commercially available EIA kit (BIOTREND, Cologne, Germany) according to the manufacturer's protocol. Urine creatinine was determined photometrically (Jaffe method). Sample analysis of WT and knockout (KO) animals was performed blinded and in random order. Values were expressed as nmol per day per g body weight.

Resident-intruder (psychosocial stress) test

The procedure is described in detail elsewhere. Briefly, male mice of both genotypes (28 days old) were randomly assigned to either the 'stress' or 'sham stress' group. As intruders, they were subjected for 21 days (1 h daily, from 0900–1000 hours) to resident male mice (male FVB, 2–3 months old, habituated to resident cages for ⩾10 days). To prevent injuries, direct interaction was immediately terminated at the first attack (usually occurring after a few seconds) by putting a grid cage (140 × 75 × 60 mm3) over the intruder. Afterwards, intruder mice were placed back in their home cage. Mice were confronted with a different resident every day. Sham stress consisted of placing the intruder mouse in an empty novel cage for 1 h.

Mice were kept undisturbed for at least 1 week until a single 6-h restraint stress was performed in a separate room (with mice left in their home cages and put in wire mesh restrainers, secured at the head and tail ends with clips) during the light period of the circadian cycle as described. Control animals were left undisturbed.

Amygdala dissection

Mice were anaesthetized (intraperitoneal sodium pentobarbital 50 mg kg 1) and perfused transcardially (ice-cold PBS). Amygdalae were dissected from a coronal slice −0.58 to −2.3 mm relative to Bregma and stored in RNA later (Qiagen) at 4 °C until processed.

Quantitative reverse transcription-PCR from amygdala. Amygdala tissue was homogenized in Quiazol (Qiagen, Hilden, Germany). Total RNA was isolated by using the miRNAs Mini Kit (Qiagen). The first strand cDNA was generated from total RNA using N9 random and Oligo (dT) 18 primers. The relative concentrations of mRNAs of interest in different cDNA samples were measured out of three replicates using the threshold cycle method (delta Ct) for each dilution and were normalized to the normalization factor of Hprt1 and H2afz genes calculated by the geNorm analysis software. Reactions were performed using SYBR green PCR master mix (ABgene, Foster City, CA, USA) according to the protocol of the manufacturer. Cycling was done for 2 min at 50 °C, followed by denaturation at 95 °C for 10 min. The amplification was carried out by 45 cycles of 95 °C for 15 s and 60 °C for 60 s. The specificity of each primer pair was controlled with a melting curve analysis.

First strand cDNA synthesis and reactions were generated from total RNA using the TaqMan MicroRNA RT Kit, TaqMan MicroRNA Assay for hsa-miR124, TaqMan MicroRNA Assay for sno-

RNA142 as a housekeeper and TaqMan 2 × Universal PCR Master Mix (ABgene) according to the manufacturer's protocol. Cycling was done with 10 min denaturation at 95 °C and amplification for 40 cycles at 95 °C for 15 s and 60 °C for 60 s.

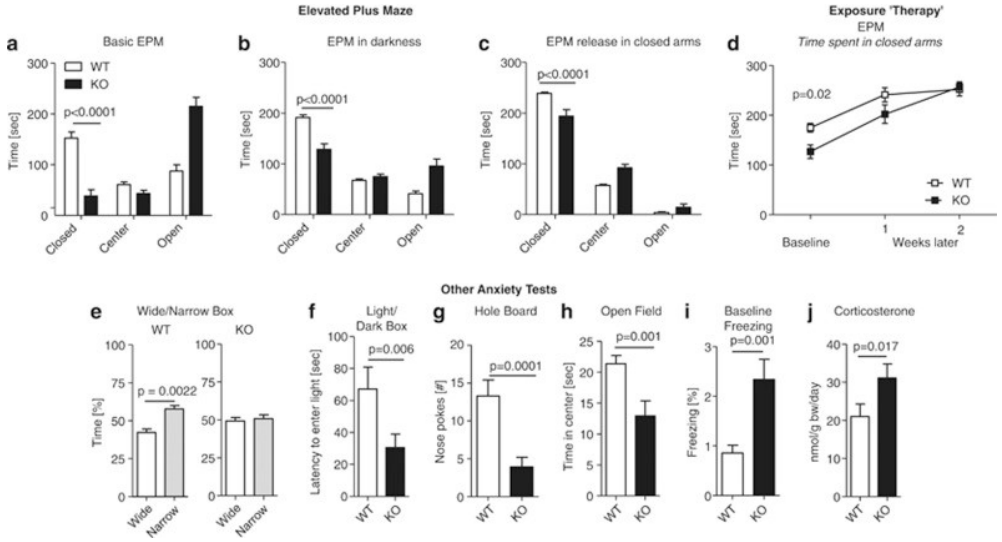

Figure 2: Quantitative reverse transcription-PCR from amygdala

Treatment

Cognitive behavioral therapy and exposure therapy are the standard treatments for claustrophobia. However, virtual reality represents another novel approach on the horizon. In virtual reality exposure therapy (VRET), negative stimulus can be applied for exposure purposes, but in a manner that is less expensive and intimidating than exposure to the real stimulus.

The goal of virtual reality systems is to invoke the presence of the trigger, eliciting an emotional response. In one study of a virtual reality exposure therapy prototype system, the system was effective in creating a sense of presence in triggering environments and showed potential for future use in therapy.

CONCLUSION

As virtual reality exposure therapy gains acceptance and support, it moves naturally from a research topic to a desirable patient application. While many areas of anxiety disorders have not been fully explored, the limited testing has shown promise. As the hardware becomes less and less expensive, budget concerns give way to the ability for greater impact. As the software base expands and becomes more usable, technological trepidation can be replaced by confident care.

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