DEEP BRAIN STIMULATION IN TREATMENT-RESISTANT DEPRESSION IN MICE

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Introduction

Major depressive disorder (MDD) is a widespread and costly illness that affects roughly 10% of the world’s population. A variety of treatments is available, but a significant proportion of patients do not respond to conventional antidepressants. Indeed, current antidepressants have limited therapeutic efficacy as approximately 30% of patients are treatment-resistant [1]. Deep Brain Stimulation (DBS), which is successfully used in patients with Parkinson’s disease has recently been suggested to represent a possible therapeutic strategy for treatment-resistant depression [1]. It was notably shown that chronic electrical stimulation of the subthalamic nucleus (STN) in the subthalamic nucleus caused a striking and sustained remission of depression [1]. In this study, we used a modified version of the unpredictable chronic mild stress (UCMS) test, a naturalistic model of depression, to validate high-frequency electrical stimulation of the subnigral-cingulate cortex (sNCg), i.e. Bedworth area 29 as a possible treatment of drug-resistant depressive-like state.

Materials and Methods

ALL EXPERIMENTS WERE CONDUCTED IN MALE BALB/c MICE (8-WEEK-OLD), HOUSED INDIVIDUALLY, IN ACCORDANCE WITH THE “GUIDE AND CARE AND USE OF LABORATORY ANIMALS” (NATIONAL INSTITUTE OF HEALTH) AND THE IN-HOUSE ANIMAL ETHICS COMMITTEE.

UNPREDICTABLE CHRONIC MILD STRESS

The protocol consists of the sequential and unpredictable application of a variety of mild stressors during 8 weeks. The stressors include altered bedding (change or removal of successive straw sawdust bedding, cage-filling, cage exchange, mice were placed in the empty cage of another male, altered length and time of light-dark cycle etc. For more details, see [2].

SELECTION OF TREATMENT-RESISTANT MICE

We evaluated on a weekly basis the physical state of the coat, an index of depressive-like state in these animals. The coat state evaluation involved the assessment of eight different body parts: head, neck, dorsal coat, ventral coat, tail, forepaws, hind paws and genital area. For each body area, a score of 0 was assigned for a coat in good condition or a score of 1 for a dirty and damaged coat. The total score was defined as the sum of the scores for each body part. From week 3 until the end of week 5, mice received either a saline injection or were treated with the antidepressant fluoxetine. At the end of week 5, fluoxetine-treated mice were subdivided into two groups based on their coat state score: the most responsive (−2.5) to fluoxetine and the less responsive (≥2.5) to the drug. The latter were considered as “treatment-resistant” and were subsequently used for bilateral DBS at two different parameters. The effectiveness of the procedure was further confirmed by observing the changes in the coat state score of mice treated with the CRF receptor antagonist SSR125543, based on the idea that the blockade of this receptor may represent a possible therapeutic strategy for treatment-resistant patients [3]. Following two weeks of daily 1-Hz DBS or SSR125543 treatment, mice were tested in a variety of behavioral procedures measuring different aspects of depressive-like behaviors in mice (Figure 1).

DEEP BRAIN STIMULATION

Stereotaxic surgery was carried out for bilateral implantation of bipolar stimulating electrodes. The electrodes were made of two parallel insulated platinumiridium electrodes, coated with Teflon. Electrodes were introduced bilaterally into the sNCg as the following coordinates in mm relative to bregma: anterior-posterior: + 1.3 mm, mediolateral: ±1.2 mm, dorso-ventral: −2.6 mm. Stimulation was given at approximately 30% of patients are treatment-resistant. Deep depression. SSR125543 treatment, mice were tested on a weekly basis the physical state of the coat, an index of depressive-like state in these animals. The coat state evaluation involved the assessment of eight different body parts: head, neck, dorsal coat, ventral coat, tail, forepaws, hind paws and genital area. For each body area, a score of 0 was assigned for a coat in good condition or a score of 1 for a dirty and damaged coat. The total score was defined as the sum of the scores for each body part. From week 3 until the end of week 5, mice received either a saline injection or were treated with the antidepressant fluoxetine. At the end of week 5, fluoxetine-treated mice were subdivided into two groups based on their coat state score: the most responsive (−2.5) to fluoxetine and the less responsive (≥2.5) to the drug. The latter were considered as “treatment-resistant” and were subsequently used for bilateral DBS at two different parameters. The effectiveness of the procedure was further confirmed by observing the changes in the coat state score of mice treated with the CRF receptor antagonist SSR125543, based on the idea that the blockade of this receptor may represent a possible therapeutic strategy for treatment-resistant patients [3]. Following two weeks of daily 1-Hz DBS or SSR125543 treatment, mice were tested in a variety of behavioral procedures measuring different aspects of depressive-like behaviors in mice (Figure 1).

Discussion

UCMS led to an alteration of the efficiency in building a nest. Repeated treatment with fluoxetine, SSR125543 and DBS at 120 Hz tended to decrease the ability of stressed mice to build elaborated nests, albeit these effects just failed to reach statistical significance. UCMS significantly decreased the latency to first attack the intruder. Repeated treatment with SSR125543 and DBS at both 80 and 120 Hz significantly increased the latency to first attack in stressed mice.

Conclusion

These findings demonstrate for the first time that bilateral DBS of the sNCg and, to a lesser extent, pharmacological blockade of the CRF, receptor in "treatment-resistant" chronically stressed mice can attenuate several depressive-like behaviors, suggesting that these approaches may represent valid alternatives for the treatment of drug-resistant depressed patients.

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References