CREM mutations and ADHD symptoms

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SUMMARY

CREM mutant mice have behaviors similar to symptoms seen in ADHD such as the increased level of physical activity as well as altered emotional and stress responses. Our results demonstrate that all the four participants with ADHD had elevated levels of nocturnal melatonin in urine samples before starting the methylphenidate treatment. We hypothesize that abnormalities in CREM protein functions or mutations in the CREM gene may be underlying at least some of the symptoms in patients with ADHD.

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Introduction

Recent studies have demonstrated that the cyclic adenosine monophosphate responsive element modulator (CREM) gene of the mouse and its encoded protein isoforms may have essential role for the function of the hypothalamus-pituitary axis and for the rhythmic production of melatonin [1]. Several hypothalamus-pituitary axis hormones are involved in behavioral responses including emotional state and stress [2,3]. Thus, malfunction of the hypothalamus-pituitary axis may lead to conditions such as chronic stress and circadian rhythm disturbances.

CREM mutant mice have behaviors similar to symptoms often seen in attention deficit hyperactivity disorder (ADHD) [1]. This finding led us to hypothesize that patients with ADHD may have deficits in CREM expression. There are interesting similarities between ADHD patients and CREM mutant mice. For example, both ADHD patients and CREM mutants show increased locomotor activities as well as altered emotional and stress responses.

ADHD and methylphenidate treatment

ADHD is considered as a neurodevelopmental disorder which mainly is caused by mutations in genes that encode the dopamine transporters and dopamine receptors [4]. ADHD patients tend to have mutations in genes encoding serotonin and adrenergic receptors as well [4]. These mutations lead to dysfunction in both dopaminergic and noradrenergic transmission circuits, resulting in the symptoms of ADHD. The key symptoms are hyperactivity or impulsivity, and inattention. Co-morbid disorders of ADHD include specific learning problems, anxiety disorder and substance abuse. At least 30% of ADHD patients experience also chronic sleep problems such as delayed sleep phase and restless sleep plus have daytime sleepiness. ADHD patients sleep worse, show higher nocturnal motor activity and have more parasomnias [5] than their healthy controls [6]. The prevalence rates of ADHD range from 2% to 18% globally [7].

The primary treatments of ADHD are psychosocial operations such as peer group therapy, ADHD coaches and pedagogical actions in school system. Severe ADHD symptoms are treated with medication. The drug of choice has been the stimulant methylphenidate. Methylphenidate has shown to be effective mainly on the hyperactive and impulsive symptoms, and also to some extent on the inattentive symptoms. Insomnia is known to be one of the side effects of stimulant treatments. However, clinical experience suggests that ADHD patients with circadian rhythm and sleep disorders in fact sleep better when they are treated with methylphenidate. It appears that methylphenidate treatment normalizes the sleep of patients with ADHD [8] making it more stable and refreshing.

CREM null mice

Maldonado et al. pointed out that CREM null mice show a drastic increase in locomotion along the circadian cycle compared to normal mice although the anatomy of the suprachiasmatic nucleus is normal in CREM null mice [1]. CREM null mice do not show the characteristic day-night change in locomotion unlike the normal mice which show increased activity during the dark period only. Thus, CREM null mice resemble ADHD patients who express higher levels of nocturnal motor activity than their controls. Moreover, the production of melatonin from the pineal gland seems to be altered in CREM mutants. Interestingly, CREM mutants have significant increases in explorative activity during behavioral tests. Increased exploration and experimentation are features of ADHD and thought to give explanation to the drug-seeking behavior of ADHD patients.
Melatonin hypersecretion and stress

Many features of chronic stress are found both in ADHD and in CREM null mice. CREM null mice show significant changes in the corticosterone levels [9], and symptoms of psychological distress are often evident in ADHD. ADHD patients seem to suffer from melatonin hypersecretion which coincides with chronic stress [10,11]. Altered melatonin secretion is seen in CREM null mice as well [1]. Furthermore, the daytime sleepiness is common symptom of both ADHD and chronic stress. It is possible that the melatonin hypersecretion explain at least partly the sleepiness in stress and in ADHD. We have also noticed that our ADHD patients often suffer from bruxism, which is known to be linked to chronic stress. In addition, there is a single-nucleotide polymorphism in dopamine receptor D_{4} that is associated with both stress and ADHD [12].

It might be that ADHD patients and CREM mutant mice suffer from chronic stress because of the continuous over-activation. Thus, it would be important to measure stress hormone levels among ADHD-patients and analyze whether these levels are elevated as they are in CREM null mice.

Methylphenidate treatment and melatonin levels of adult ADHD patients

In our recent research, we noticed that the methylphenidate treatment changed the melatonin levels of adult ADHD patients. We measured the melatonin levels of adult ADHD patients from the whole-night urine samples, collected in the hospital. The whole-night urine samples comprised all urine from the measurements (from 10 pm to 7 am). At the baseline, each patient had a careful physical examination including laboratory tests and urine screen. Assigned subjects were recently diagnosed patients with no medication prior to study. Concomitant psychotropic medication was not allowed during the study period. The urine samples were gathered before the patients started methylphenidate treatment and after two weeks of medication. Methylphenidate dosage was flexible. The starting daily dose was one capsule, equal to 18 mg in the morning, and the daily dose could increase up to three capsules at the maximum, equal to 54 mg in the morning. ADHD diagnosis was made according to DSM-IV using Conners’ Adult ADHD Diagnostic Interview for DSM-IV using multiple sources of information. A comprehensive neuropsychological test battery is also included in the diagnostic process.

The nocturnal melatonin secretion is different between individuals but similar from one day to another in same individual. Previous studies have shown that the nocturnal melatonin secretion vary between 11 and 28 pmol/h in healthy adults [13]. The melatonin samples of our recent study were analyzed by using radioimmunoassay [13]. Our results show that all four participants had highly elevated levels of nocturnal melatonin (from 34 to 64 pmol/h) in their urine samples before starting the methylphenidate treatment. After the medication, the levels of nocturnal melatonin decreased significantly in two participants being in normal level (from 16 to 22 pmol/h) at the end of the study. The nocturnal melatonin secretion decreased also in the third participant after the medication had started (from 64 to 53 pmol/h) but did not reach the normal levels at least during the study period. The nocturnal melatonin level was increased after the medication in the fourth participant (from 48 to 65 pmol/h). Because the melatonin levels decreased in all but one participant, we suggest that there is a link between melatonin secretion and methylphenidate treatment.

Hypothesis

Given the associations above, we speculate that CREM mutations may be involved in ADHD in a similar way to mutations in dopamine transporters and receptors. CREM mutations may be underlying at least some of the symptoms in patients with ADHD.

Testing the hypothesis

A well-designed study protocol could provide evidence for the role of melatonin and CREM mutations in ADHD, and elucidate the disease mechanisms of action. It would be important to clarify how common the hypersecretion of the melatonin is among ADHD patients. Melatonin or its metabolite levels can be measured easily from blood or urine samples. If prospective studies were to show that there is hypersecretion of melatonin in ADHD, new diagnostic methods could be developed and the treatment of ADHD improved. In addition, the function of the hypothalamus–pituitary–adrenal axis can be assessed with a dexamethasone suppression test and CREM mutations among ADHD patients could be explored with genetic analyses and proteomics.

Conclusions

We hypothesize that at least some symptoms or traits of ADHD might be linked to CREM mutations or abnormalities in the regulation of CREM. In animals, CREM mutations lead to increased locomotion, altered stress reactions and changes in melatonin levels which are similar to symptoms often seen in ADHD.

References