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Research report

Sulforaphane produces antidepressant- and anxiolytic-like effects in adult mice

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HIGHLIGHTS

- Sulforaphane exerts antidepressant- and anxiolytic-like activities in mice.
- Sulforaphane exerts anxiolytic-like activities in stress-induced depressed mice.
- Sulforaphane inhibits HPA axis activity in stress-induced depressed mice.
- Sulforaphane inhibits inflammatory response in stress-induced depressed mice.

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ABSTRACT

Increasing evidence suggests that depression is accompanied by dysregulation of neuroimmune system. Sulforaphane (SFN) is a natural compound with antioxidative, anti-inflammatory and neuroprotective activities. The present study aims to investigate the effects of SFN on depressive- and anxiety-like behaviors as well as potential neuroimmune mechanisms in mice. Repeated SFN administration (10 mg/kg, i.p.) significantly decreased the immobility time in the forced swimming test (FST), tail suspension test (TST), and latency time to feeding in the novelty suppressed feeding test (NSF), and increased the time in the central zone in the open field test (OPT). Using the chronic mild stress (CMS) paradigm, we confirmed that repeated SFN (10 mg/kg, i.p.) administration significantly increased sucrose preference in the sucrose preference test (SPT), and immobility time in the FST and TST of mice subjected to CMS. Also, SFN treatment significantly reversed anxiety-like behaviors (assessed by the OPT and NSF) of chronically stressed mice. Finally, ELISA analysis showed that SFN administration blocked the increase in the serum levels of corticosterone (CORT), adrenocorticotropic hormone (ACTH), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) in chronically stressed mice. In summary, these findings demonstrated that SFN has antidepressant- and anxiolytic-like activities in stressed mice model of depression, which likely occurs by inhibiting the hypothalamic-pituitary-adrenal (HPA) axis and inflammatory response to stress. These data support further exploration for developing SFN as a novel agent to treat depression and anxiety disorders.

Abbreviations: ACTH, adrenocorticotropic hormone; CMS, chronic mild stress; CNS, central nervous system; CORT, corticosterone; ELISA, enzyme-linked immunosorbent assay; FST, forced swimming test; GR, glucocorticoid receptor; HPA axis, hypothalamic-pituitary-adrenal axis; IL-1β, interleukin-1β; IL-6, interleukin-6; LAT, locomotor activity test; LPS, lipopolysaccharide; Nrf2, nuclear factor E2-related factor 2; NSF, novelty suppressed feeding test; OPT, open field test; SFN, Sulforaphane; SPT, sucrose preference test; TNF-α, tumor necrosis factor-α; TST, tail suspension test.

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1. Introduction

Major depression, one of the most devastating mental illnesses affects 17% of individuals worldwide [1]. It is estimated that depression causes approximately 1 million people to commit suicide annually, imposing a major burden on the society. Although antidepressants have been clinically available for several decades, only 33% of depressed patients are sensitive to the first antidepressant medication [2]. In addition, the current antidepressants are associated with serious adverse effects. Therefore, natural products have attracted increasing attention for preventing and treating neurodegenerative and psychiatric disorders, including depression. Many types of natural products have comparable efficiency to prescription medications with no or reduced side effects [3–6].

Extensive evidence has shown that stress, especially chronic stress, is one of the most important factors responsible for depressive disorders [7–9]. Maladaptive response to stress causes hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis by stimulating adrenocorticotropic hormone (ACTH) release and subsequent peripheral release of steroids/cortisol from the adrenal grand, while antidepressants could reverse depressive-like behaviors and inhibit the activation of the HPA axis in animal models and patients with depression [10–12]. Depression-related disruptions in a neuroimmune axis control depressive-like behaviors by interfering the immune system and the CNS. It has been found that circulating cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6(IL-6), increased in the patients with depression [13,14]. A recent study showed that peripheral inflammation predates the occurrence of depression [15]. Children with higher circulating levels of IL-6 at age 9 are at a 10% greater risk for developing MDD by age 18 than the general population or children with low levels of IL-6 [15]. Collectively, these studies suggest that aberrant periphery immune responses to stress can lead to exaggerated risks for developing disorders in CNS via amplifying the initial inflammatory signal that can directly or indirectly act on neuronal plasticity, which is contributed to stress susceptibility and depression-like behavioral phenotypes [16,17].

Sulforaphane (SFN: 1-isothiocyanato-4-methylsulfinylbutane) is an organosulfur compound found in broccoli and other cruciferous vegetables (chemical structure is shown in (Fig. 1). As a dietary phytochemical with low toxicity, sulforaphane is widely consumed and has qualified for consideration as food, dietary supplement, or drug, depending on its intended use. Sulforaphane has multiple health benefits, such as anticancer, antioxidant, anti-inflammatory and neuroprotective effects [18–21]. A recent study found that the induction of nuclear factor E2-related factor 2 (Nrf2) by SFN could reverse LPS-induced depressive-like behaviors in mice, indicating the potential antidepressant-like effects of sulforaphane [22].

Therefore, the present study aimed to examine whether repeated SFN administration produces antidepressant-like effects in a validated mouse models of depression. In addition, we assessed the HPA activity and immune response by measuring the serum levels of corticosterone (CORT), ACTH, IL-6 and TNF-α to elucidate the potential mechanism of SFN action.

2. Materials and methods

2.1. Animals

One hundred and twenty male ICR mice (with a 5% attrition rate), weighing 22–24 g, were individually housed at a constant temperature (23 ± 2 °C) with 12 h/12 h light/dark cycles and free access to food and water. All mice were transferred to the experimental room 1 h before behavioral tests, and all drug administration and behavioral tests were performed in the dark phase. All animal procedures were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and they were approved by the Local Animal Use Committee of Hebei Medical University.

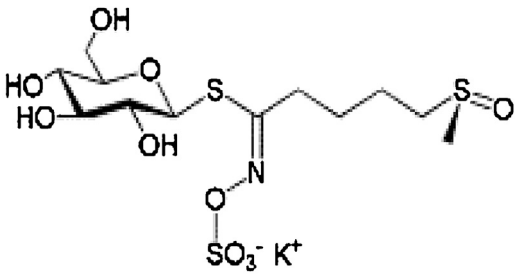

Fig. 1. Chemical structure of sulforaphane.

2.2. Drugs

DL-Sulforaphane (SFN) [Sigma–Aldrich (Shanghai) Trading Co., Ltd.] was dissolved in saline and administered by the intraperitoneal (i.p.) route; SFN was injected once daily for 14 continuous days within the dose range of 1 to 10 mg/kg (i.p.) [23]. Fluoxetine hydrochloride [Sigma–Aldrich (Shanghai) Trading Co., Ltd.], acting as a positive control drug, was dissolved in saline and paralleled injected (10 mg/kg, i.p.) for 14 consecutive days.

2.3. Tail suspension test

The tail suspension test was performed according to previous reports [24,25]. Briefly, mice were suspended 50 cm above the floor by adhesive tape placed approximately 1 cm from the tip of the tail for 6 min. Immobility was defined as the absence of limb or body movements, except for those caused by respiration when the mice hung passively and were completely motionless. During the test, mice were separated from each other to prevent possible visual and acoustical associations. The results were expressed as the time (in s) that animals spent immobile in the last 4 min of the 6 min session.

2.4. Forced swimming test

The forced swimming test was performed as previously described [24,26]. Mice were placed into a 20-cm diameter × 35-cm high plastic cylinder filled to a depth of 20 cm with23–25 °C water for 6 min. This session was videotaped, and the floating time was measured. Immobility was defined as the absence of movement, except for motion that was required to maintain the animal's head above the water. The results were expressed as the time (in seconds) that animals spent immobile in the last 4 min of the 6 min session.

2.5. Open field test

The apparatus consisted of a (40 cm × 40 cm × 35 cm) square arena that was divided into 25 equal squares on the floor of the arena. Mice were individually placed in the center of the cage, and the number that crossed to adjacent squares was counted as horizontal locomotor activity for 5 min. The time in the central zone was recorded to reflect the anxiety-like behaviors of mice [27].

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