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Research paper

Physiological and behavioral responses in offspring mice following maternal exposure to sulfamonomethoxine during pregnancy

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HIGHLIGHTS

- Pregnant SMM exposure enhanced blood glucose level in offspring mice.
- Pregnant SMM exposure induced anxiety in mice offspring late in life.
- SMM exposure impaired the spatial memory more seriously in male offspring.
- Prgnant SMM exposure reduced BH4 and BDNF levels in mice offspring early in life.

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ABSTRACT

Sulfamonomethoxine (SMM), a veterinary antibiotic, is widely used in China. However, the impacts of maternal SMM exposure on neurobehavioral development in early life remain little known. In this study, we investigated the effects of maternal SMM exposure during pregnancy on behavioral and physiological responses in offspring mice. Pregnant mice were randomly divided into three SMM-treated groups, namely low-(10 mg/kg/day), medium-(50 mg/kg/day), and high-dose (200 mg/kg/day), and a control group. The pregnant mice in the SMM-treated groups received SMM by gavage daily from gestational day 1–18, whereas those in the control received normal saline. On postnatal day (PND) 50, spatial memory was assessed using the Morris water maze test, and anxiety was measured using the elevated plus-maze and open field tests. The results showed significantly increased blood glucose in pups whose mothers received a high SMM dose. In addition, maternal SMM exposure increased anxiety-related activities among the offspring; spatial learning and memory were impaired more severely in the male offspring. The contents of tetrahydrobiopterin (BH_4) and brain-derived neurotrophic factors (BDNF) on PND 22 were significantly reduced in the male offspring of the high-dose group compared with the controls. These findings indicate that SMM may be identified as a risk factor for cognitive and behavioral development on the basis of gender and that it may be associated with diminished BH_4 and BDNF levels early in life.

1. Introduction

Sulfonamides (SAs) are widely used in animal husbandry, frequently excreted in the urine and feces of treated animals as parent compounds or metabolites that are easily transferable from contaminated sites to surrounding water. Therefore, SAs are frequently found in waste water, surface water, and drinking water. In addition, SAs are also found in foods such as pork, chicken, beef, eggs, and cheese [1–3]. The rapidly expanding animal food industry is projected to result in a substantial increase in the annual amount of consumed SAs while producing more pollution..

Sulfamonomethoxine (SMM) has the highest antimicrobial activity among various SAs and has been the most widely used antibiotic for therapeutic or prophylactic proposes for diseases in food-producing animals because of its economic advantage gained

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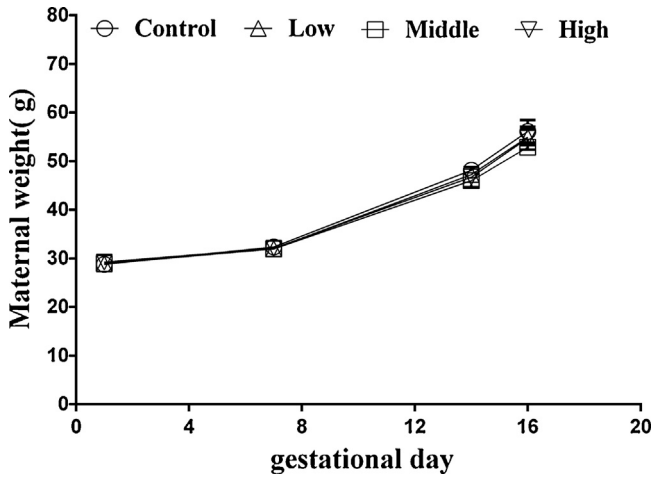

Fig 1. Effects of SMM on maternal weight (n = 16). Data were expressed as mean ± SEM (n = 16).

from its application. It has also been detected in the environment and in food. Despite the extensive use of SMM in some fields and its wide contamination of the environment, information on the neurotoxicity of early-life SMM exposure is insufficient.

Exposing zebrafish embryos to a low concentration of SAs caused obvious toxic effects on spontaneous movements, resulting in characteristic malformations including pericardial edema, yolk-sac edema, hemagglutination, tail deformation, and swimming bladder defects [4]. SMM has been shown to have potentially adverse effects on aquatic organisms, including harm to microalgae [5]. However, these studies have been performed on aquatic organisms and not on mammals in vivo.

In population studies, the most common adverse effects of SAs in humans included nausea and cutaneous hypersensitivity reactions; they also caused urinary tract infections and hemopoietic disorders [6]. In addition, exposure to sulfa drugs during pregnancy may lead to miscarriage [7] and birth defects [8]. The risk for developing acute psychosis appeared to increase with the daily dosage of trimethoprim/sulfamethoxazole in HIV-infected patients [9]. However, research on the neurotoxicity of sulfa drugs is scant, particularly research on the influences of maternal SMM exposure during pregnancy on the anxiety-like behavior and memory of offspring.

The purpose of this study was to determine the effects of maternal SMM exposure during pregnancy on the neurobehavioral development of mice offspring. Based on the results obtained, the underlying mechanism of SMM-induced neurotoxicity might be attributed to the diminished tetrahydrobiopterin (BH_4) and brain-derived neurotrophic factor (BDNF) levels early in life.

2. Materials and methods

2.1. Animals and treatment

ICR (Institute of Cancer Research) mice (8 weeks old) were purchased from the Beijing Vital River Laboratory Animal Center (Beijing, China), whose foundation colonies were all introduced from the Charles River Laboratories (Boston, MA, USA). They were fed under normal condition. All animal experiments were performed according to the guidelines for humane treatment established by the Association of Laboratory Animal Sciences and the Center for Laboratory Animal Sciences at Anhui Medical University.

Following a 1-week acclimation to the colony room, the male and female mice were paired (a pair with a male and 2 females) in breeders. The existence of a vaginal plug was designated as gestational day (GD) 1. All pregnant mice (at least n = 64) were randomly divided into three SMM-treated groups, namely low-(10 mg/kg/day), medium-(50 mg/kg/day), and high-dose (200 mg/kg/day) groups, and a control group. The pregnant mice in the control group received normal saline, whereas those in the SMM-treated groups received SMM sodium with a purity of 99% (CAS: 38006-08-5; Anhui Hua Ao Biotechnology Co., Ltd.) by gavage daily from GD 1–18. Within 24 h after birth, excess pups (more than 10 pups per litter) were removed so that 10 pups (5 males, 5 females) were kept with the dam (1 litter) until they were weaned at postnatal day (PND) 21. Notably, the pups from the culled 8 litters in each group were randomly weighed during lactation.

On PND 22, all the pups were randomly divided into an experimental group again. And then the pups in the 8 litters of each group were used for analysis of physiological responses early in life; the other 8 litters of each group were housed until adulthood (PND 50), used for the behavioral tests. The body weights of the dams and pups (litter base) were measured weekly during the experimental period.

2.2. Analysis of physiological responses

On PND 22, the pups from the 8 litters in each group, fasted for 12 h and then anesthetized with 10% chloral hydrate. The serum was collected for measuring thyroxin (T_4), triiodothyronine

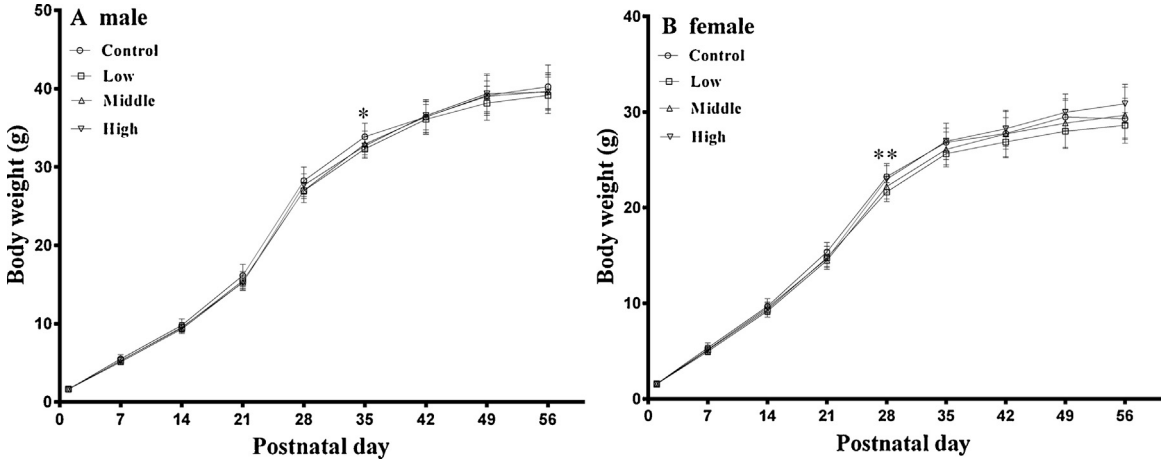

Fig. 2. Effects of SMM on body weight in mice. The body weight of male (A, n = 8) and female (B, n = 8) were examined at PND 1, 7, 14, 21, 28, 35, 42, 49, 56. Data were expressed as mean ± SEM. *p < 0.05, **p < 0.01 as compared with controls.