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Research report

Dietary arginine depletion reduces depressive-like responses in male, but not female, mice

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ABSTRACT

Previous behavioral studies have manipulated nitric oxide (NO) production either by pharmacological inhibition of its synthetic enzyme, nitric oxide synthase (NOS), or by deletion of the genes that code for NOS. However manipulation of dietary intake of the NO precursor, L-arginine, has been understudied in regard to behavioral regulation. L-Arginine is a common amino acid present in many mammalian diets and is essential during development. In the brain L-arginine is converted into NO and citrulline by the enzyme, neuronal NOS (nNOS). In Experiment 1, paired mice were fed a diet comprised either of an L-arginine-depleted, L-arginine-supplemented, or standard level of L-arginine during pregnancy. Offspring were continuously fed the same diets and were tested in adulthood in elevated plus maze, forced swim, and resident-intruder aggression tests. L-Arginine depletion reduced depressive-like responses in male, but not female, mice and failed to significantly alter anxiety-like or aggressive behaviors. Arginine depletion throughout life reduced body mass overall and eliminated the sex difference in body mass. Additionally, arginine depletion significantly increased corticosterone concentrations, which negatively correlated with time spent floating. In Experiment 2, adult mice were fed arginine-defined diets two weeks prior to and during behavioral testing, and again tested in the aforementioned tests. Arginine depletion reduced depressive-like responses in the forced swim test, but did not alter behavior in the elevated plus maze or the resident intruder aggression test. Corticosterone concentrations were not altered by arginine diet manipulation in adulthood. These results indicate that arginine depletion throughout development, as well as during a discrete period during adulthood ameliorates depressive-like responses. These results may yield new insights into the etiology and sex differences of depression.

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1. Introduction

L-Arginine is an essential amino acid during development [1,2] and 'conditionally essential' in adulthood [3], meaning that *de novo* synthesis is generally regarded as sufficient for healthy adults not undergoing trauma or pregnancy. Lacking arginine early in life leads to numerous somatic disruptions: e.g., dietary arginine is important for normal growth [4,5] and immune function [6]. Preterm infants, for example, are at high risk for L-arginine deficiency due to underdevelopment of the gastrointestinal tract [2]. Deficiency of arginine may lead to an excess of ammonia as it is critical for ammonia detoxification [7]. In adults, arginine supplementation can increase exercise tolerance, may slow the progression of atherosclerosis (due to the relaxing effect of nitric oxide (NO) on the endothelium), and may reduce hypertension [8]. Additionally, for pregnant women with preeclampsia or chronic hypertension without protein in the urine, arginine supplementation may reduce the likelihood of preterm birth and low birth weight [9]. Little is known, however, about the behavioral changes that manifest after developmental arginine deficiency or supplementation.

Arginine exists in many foods including beef, poultry, nuts, dairy, and eggs and arginine is a precursor for not only nitric oxide (NO), but also ornithine, urea, polyamines, proline, creatine, agmatine, glutamate, and protein. Arginine can also stimulate the release of specific hormones (e.g., insulin, growth hormone, glucagon, and prolactin) which could potentially alter behavior [10]. NO is of particular interest as disruption of its synthetic enzyme potently

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increases aggressive and sexual behaviors [11]. NO is synthesized from L-arginine by nitric oxide synthase (NOS), a process which also produces the byproduct L-citrulline. Many studies involving NO manipulation use mice lacking the nNOS gene [11–14], whereas others manipulate NO levels pharmacologically with NOS inhibitors [14–16,12]. However, behavioral studies of mice using deletion of specific genes suffer the criticism that the gene product is not only missing from the testing period, but also missing throughout development when critical compensatory mechanisms may be activated [17]. Furthermore, behavioral studies using pharmacological means to manipulate biochemical pathways either require surgery or daily injections that run the risk of injuring the animal, or inducing physiological inflammatory or stress responses that can alter behavior. Manipulating dietary intake of nutrients and amino acids circumvents these problems while retaining the ability to influence physiology and behavior. Manipulation of NO by dietary intake of L-arginine has not been extensively studied despite the presence of arginine in many foods.

NO is an atypical neurotransmitter that has multiple functions including neuromodulation in the central and peripheral nervous systems, mediating vascular tone essential for blood pressure regulation, and regulation of some immune functions [18]. In the brain, NO is rapidly synthesized and acts as a gaseous neurotransmitter with a short half-life of 2–5 s. Three distinct NOS isoforms have been described: (1) endothelial NOS (eNOS or NOS-3) in the tissue of blood vessels, (2) inducible NOS (iNOS or NOS-2) found in macrophages, and (3) nNOS (or NOS-1) found in neurons [18]. NO regulates social and affective behaviors. In male mice, selective depletion of the nNOS gene (nNOS−/−) results in hyperaggressiveness. Mice that lack the gene to express nNOS continue attacks towards an intruder mouse despite obvious signs of submission and persist in mounting anestrous females despite vocal and behavioral protests [11]. These behavioral patterns persist despite postural and vocal protests and may reflect deficits in key areas of the brain important for processing social information and for responding accordingly.

Intake of vitamins, amino acids, and other nutrients (especially those that serve as precursors for neurotransmitters) influence affective and behavioral functioning and may provide therapeutic treatment options for some psychological disorders. For instance, eliminating intake of preservatives and artificial food coloring in children with attention deficit hyperactivity disorder (ADHD) increases response rate in retention tests [19,20]. Additionally, a tryptophan-depleted diet improves psychotic symptoms in schizophrenic patients, although minimally [21,22], and also precipitates depressive episodes in vulnerable individuals [23]. Choline supplementation during prenatal development in rats reduces errors in the radial arm maze and alters neuron morphology in the hippocampus [24]. Recent evidence suggests differing concentrations of dietary arginine can affect specific behaviors. Pigs fed a diet fortified with L-lysine and L-arginine reduces stress responses during transportation [25]. Ornithine transcarbamylase-deficient mice fed an L-arginine-depleted diet have impaired cognitive performance compared with mice fed an L-arginine rich diet [26].

In the present study, we examined the influence of both developmental and adult effects of dietary L-arginine manipulation on social behaviors and affective responses. We hypothesized that a diet depleted of arginine would result in hyper-aggressive behaviors illustrated by persistent attacks on an intruder mouse in the resident-intruder aggression test. We also hypothesized that an arginine-deficient diet would evoke persistent swimming in the Porsolt forced-swim test consistent with the results of previous studies [27,28]. Additionally, we hypothesized that arginine depletion would increase anxiety-like responses consistent with previous results investigating nNOS deletion and inhibition [12].

2. Methods

2.1. Experiment 1

2.1.1. Animals

Adult C57BL6/J mice (11 males, 11 females) were purchased from Jackson Laboratory (Bar Harbor, ME; Stock number: 000664) and were placed on a standard diet (Harlan Teklad Rodent Diet 8640) for 7 days to habituate to housing conditions. All mice were singly housed in polycarbonate cages (32 cm × 18 cm × 14 cm), had *ad libitum* access to food and filtered tap water and were housed in temperature- and humidity-controlled rooms (21 ± 2 °C and 50 ± 10%, respectively). Throughout the study, the light cycle was 16L:8D with the dark phase beginning at 1500 h Eastern Standard Time (EST). After 7 days of acclimation, mice were paired with an opposite-sex conspecific and placed on an arginine-defined diet, with 3 different concentrations of L-arginine (depleted: 0% arginine [$n = 4$], control: 1.5% arginine [$n = 3$], and enriched: 5% arginine [$n = 3$]; Harlan Teklad Custom Research Diets; Madison WI; TD.04139, TD.07826, and TD.07827, respectively). During this time mice were also given ad lib access to food and water. Offspring were weaned at 30 d (±3) and individually housed in cages as described previously. Offspring mice were fed their original diet throughout the course of the study. A total of 54 offspring were used in Experiment 1 and were randomly assigned to the following experimental groups: arginine-depleted males ($n = 10$); arginine-depleted females ($n = 7$); control males ($n = 8$); control females ($n = 12$); arginine-rich males ($n = 9$); arginine-rich females ($n = 14$). Mice were then tested in a battery of behavioral tests designed to assess affective and social behaviors (elevated plus, forced swim, and resident-intruder aggression tests). All procedures were approved by The Ohio State Institutional Animal Care and Use Committee prior to the study and meet guidelines published in the National Institutes of Health (1986) Guide for the Care and Use of Laboratory Animals.

2.1.2. Behavioral testing

Behavioral testing was conducted in adulthood (~90 d of age). Before each test, mice were allowed 15–30 min to acclimate to the testing rooms and all behavioral testing was conducted during the dark phase.

2.1.2.1. Elevated plus maze performance. The maze was ~1 m above the floor and consisted of two open arms bisected by two arms enclosed with dark-tinted acrylic. Mice were placed in the center of the maze, facing a closed arm and were recorded from a camera suspended from the ceiling for 5 min. The maze was cleaned with 70% ethanol between tests. An arm entry was scored when two forepaws entered an open arm. Latency to enter an open arm, total time spent in the open arms, and % of open arm entries were scored and analyzed using Observer software (Noldus Corp., Leesburg, VA).

2.1.2.2. Forced swim test. Mice were placed into a cylindrical tank filled with ~17 cm of water within an opaque, cylindrical tank (24 cm diameter, 53 cm height) with a temperature ranging from 23 °C to 28 °C, for a 5 min testing period. Testing was recorded and scored based on (1) duration of floating, (2) latency to float, and (3) total number of float bouts. Water was changed after each test. Floating was operationally defined as complete immobility or movement only necessary to keep the head afloat for at least 1 s [29].

2.1.2.3. Resident-intruder test. Each mouse remained in his home cage for 2 weeks prior to the test. Subsequently, male test mice were confronted by an unfamiliar, sexually naïve male for a 10 min period in their home cages. Intruder mice were marked on their tail for identification. No wounds were observed in any test. Aggressive behaviors were scored as following: tail rattling, biting, and boxing [11]. Boxing was previously defined as fighting with the forepaws while standing on the hind paws [30].

2.2. Experiment 2

2.2.1. Animals

Thirty adult mice were obtained from Jackson Laboratory (Bar Harbor, ME; Stock number: 000664). Mice were 1 month old upon arrival and placed on a standard diet (Harlan Teklad Rodent Diet) for 5 days to allow for habituation to housing conditions. All mice were singly housed in polypropylene cages (dimensions: 27.8 cm × 17.5 cm × 13 cm) and had *ad libitum* access to food (Harlan Teklad Rodent Diet 8640) and tap water. The light cycle was 16L:8D with the dark phase beginning at 1500 h EST. After 5 days mice were placed on an L-arginine-defined diet containing either 0%, 1.5%, or 5% L-arginine (Harlan; TD.04139, TD.07826, and TD.07827, respectively).

2.2.2. Behavioral testing

Behavioral testing began 14 days after diets were implemented. This is sufficient time to yield stable nitrate concentrations in urine [25]. Before each test, mice were again allowed 15–30 min to acclimate to the testing rooms and all behavioral testing was conducted during the dark phase. Behavioral tests were conducted as previously

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