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Nutrition

Selenium induced anticonvulsant effect: A potential role of prostaglandin E_1 receptor activation linked mechanism

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ABSTRACT

Project: Selenium deficiency has been associated with enhanced propensity of seizures in man and laboratory animals. Therefore, the present study has been designed to investigate the anti-convulsant effect of sodium selenite and seleno-DL-methionine on pentylenetetrazole induced seizures in mice and the role of prostaglandin receptor activation in the proposed anticonvulsant effect of sodium selenite.
Procedure: Sodium selenite (1, 3 and 10 mg kg^{-1}, i.p.) and seleno-DL-methionine (0.3, 1 and 3 mg kg^{-1}, i.p.) was used to evaluate the potential effect on pentylenetetrazole induced seizures in mice. Pentylenetetrazole induced seizures were assessed in terms of onset time of straub's tail phenomenon, jerky movements of the whole body and convulsions. Additionally, an isobolographic study design was used to examine the interaction between sodium selenite and celecoxib (a cyclooxygenase-2 inhibitor). Sodium selenite and seleno-DL-methionine significantly attenuated pentylenetetrazole induced seizures in mice.
Results: Prior administration of misoprostol (a selective agonist of prostaglandin E_1 receptors) markedly attenuated the anticonvulsant effect of sodium selenite as well as seleno-DL-methionine in mice. However, the administration of misoprostol per se did not produce any behavioral changes. Further, sodium selenite was observed to exert a synergistic interaction with celecoxib.
Conclusions: Selenium induced reduction in seizure like behavior might be ascribed to the activation of a prostaglandin E_1 receptor activation linked mechanism. It is further proposed that sodium selenite exerts a synergistic anti-convulsant effect with celecoxib indicating the therapeutic usefulness of combining the two agents to treat epilepsy.

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Introduction

Selenium is a chemical element with the atomic number 34, represented by the chemical symbol Se, having an atomic mass of 78.96. It is a nonmetal, chemically related to sulfur and tellurium. It rarely occurs in its elemental state in nature. Selenium salts are noted to be toxic when ingested in large amounts. However trace amounts of the element are necessary for cellular function in animals, having a virtue of forming the active center of the enzymes glutathione peroxidase and thioredoxin reductase (which indirectly reduce certain oxidized molecules in the living cells) and three known deiodinase enzymes (which convert one thyroid hormone to another). Selenium is noted to regulate the expression and activity of selenoenzymes and thus provides protection from oxidative stress induced cell damage, which otherwise would lead to neuropsychiatric diseases and disorders like cerebrovascular disease, Alzheimer's disease, Parkinson's disease, obsessive compulsive disorders, stroke and epilepsy [1,2]. Selenium linked protection has been ascribed to the involvement of selenoenzymes like glutathione peroxidase (GPx) activity and phospholipid hydroperoxide GPx (GPx4). GPx is a family capable of eliminating peroxides in the neurons by reducing them to H_2O or alcohols, with GSH as reducing substrate [3]. Moreover, GPx is also involved in physiological events such as differentiation, signal transduction and regulation of proinflammotory cytokine production [4]. Thus, in the form of GPx selenoenzymes, Se is involved in the protection of neuronal cells in a diverse manner [5].

Also, selenium is principally used as a dietary supplement as well as in certain pharmaceutical products due to its potent antioxidant activity. Biochemical analysis has shown that selenium in tissues exists mainly in a protein bound form [6]. Moreover, the ion exerts its biological effects predominantly after incorporation into the selenoproteins [7]. Further, certain clinical reports have demonstrated a direct link between blood selenium levels and the neurological condition of intractable seizures in infants, which was observed to be treated by selenium supplementation [8,9]. Furthermore, workers have shown that Se exerts a beneficial effect on iron-induced epilepsy in rats [10,11]. A number of

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studies reported an increased sensitivity of rodents to drug-induced nigrostriatal degeneration when fed a low-selenium diet [12,13]. Se supplementation based prevention of neuronal degeneration has been ascribed to a reduction in lipid peroxidation [14–16]. In addition, an increased hippocampal cell death and more pronounced seizures were observed in kainic acid treated rats when fed a low-Se diet [17]. Thus, selenium may be hypothesized to exert an anti-convulsant activity in consonance with the endogenous selenoproteins. However, this potential anti-convulsant effect of selenium has evaded a systematic experimental study using animal models. Therefore, the present study has been designed to experimentally validate the potential anticonvulsant effect of sodium selenite and seleno-DL-methionine.

It is noted that selenium modulates endogenous antioxidant enzyme systems in quenching reactive oxygen species in the neuronal cells [14–16]. Moreover, cyclo-oxygenase mediated synthesis of arachidonic acid metabolites and their pathways have been shown to work in tandem with the activity of oxygen free radicals to cause seizures [18–22]. Additionally, cyclo-oxygenase inhibition has been shown to attenuate seizures in laboratory animals [19,20]. Therefore, it may be proposed that selenium induced anticonvulsant effect may be mediated by its inhibitory influence over the cyclo-oxygenase and prostaglandin receptors. Misoprostol is a selective agonist of prostaglandin E_1 receptors [23]. Therefore, the present study further explored a potential effect of prior administration of misoprostol, a selective agonist of prostaglandin E_1 receptors, and celecoxib, a cyclooxygenase-2 inhibitor [24], on the anti-convulsant potential of sodium selenite.

Moreover, a seleno-DL-methionine treatment arm was added in the study to affirm the efficacy of the complex in the short time window like sodium selenite.

Materials and methods

Animals

Male inbred Swiss albino mice weighing 25 ± 2 g maintained on standard laboratory diet (Supplier: Kisan Feeds Ltd., Mumbai, India: Rat Feed/Mice Feed Composition vide Certificate of Analysis Report of International Testing Centre {A Government of India Approved Test House} is (% by mass): moisture – 6.81%; ash insoluble – 0.72%; total ash – 0.53%; crude protein – (N × 6.25) – 21.76%; crude fat – 7.82%; crude fiber – 5.83%; calcium – 1.67%) having free access to tap water were employed in the present study. They were housed in the departmental animal house and were exposed to 12 h cycle of light and dark. The experiments were conducted in a semi-sound proof laboratory. The experimental protocol was approved by institutional animal ethics committee and care of the animals was carried out as per the guidelines of committee for the purpose of control and supervision of experiments on animals (CPCSEA), Ministry of Environment and Forest, Government of India (Chitkara College of Pharmacy Animal Facility Registration Number: 1181/ab/08/CPCSEA).

Drugs and chemicals

Sodium selenite (Central Drugs House, Lucknow, India), seleno-DL-methionine (Sigma Aldrich Chemicals Pvt. Ltd., New Delhi, India), pentylenetetrazole (Sigma Aldrich Chemicals Pvt. Ltd., New Delhi, India), misoprostol (Cipla Pharmaceuticals Private Limited, Baddi, India) and celecoxib (Zydus-Cadila Pvt. Ltd., New Delhi, India) were dissolved in dimethylsulfoxide (DMSO). All drug solutions were freshly prepared before use.

Assessment of pentylenetetrazole induced seizure intensity

An injection of pentylenetetrazole (80 mg kg^{-1}, i.p.) was given to elicit seizure like activity in mice. Time of appearance of straub's tail phenomenon [tail in a state of catatonic rigidity during dorsiflexion] was used as a preliminary indicator of the stimulated state of the brain just prior to a seizure. Further, onset time of jerky movements of the whole body and convulsions [a series of typical cycles of generalized clonic as well as tonic phase of a seizure] were recorded as quantitative measure of the seizure activity elicited by pentylenetetrazole administration [25–27]. The animals that did not demonstrate any of the behavioral criteria for a period of 10 min were awarded an arbitrary time latency score of 600 s. An observer blind to the dosage regimen made the behavioral assessments. Percentage mortality in mice after pentylenetetrazole administration in various treatment groups was recorded. The selection of the doses of sodium selenite, seleno-DL-methionine, misoprostol and celecoxib employed in the present study were based on pilot studies.

Assessment of the effect of sodium selenite, seleno-DL-methionine, misoprostol and celecoxib on pentylenetetrazole induced seizures

A prior injection of sodium selenite/seleno-DL-methionine was followed by vehicle/misoprostol or vehicle/celecoxib treatment(s) at various dose levels as detailed in the protocol. After an additional period of 15 min pentylenetetrazole induced seizure activity was elicited in mice. Appearance of straub's tail phenomenon, onset of jerky movements of the whole body, convulsions and death associated with tonic flexion confirmed the seizure activity in mice [25]. An observer, blind to the dosage regimen, made the behavioral assessment. Percentage mortality in mice after the treatments in various treatment groups was recorded.

Experimental protocol

In the present study a total of twenty groups were employed and each group comprised of 8–10 animals (Fig. 1).

Selenium efficacy assessment protocol

Group I (Vehicle control group). Vehicle (DMSO, 1 mL/kg, i.p.) for misoprostol/celecoxib was administered 15 min before the injection of vehicle (DMSO, 1 mL/kg, i.p.) for sodium selenite. After additional time duration of 15 min, vehicle (saline, 10 mL/kg, i.p.) for pentylenetetrazole was injected and the observation procedure was initiated immediately.

Group II (Pentylenetetrazole control group). Vehicle (DMSO, 1 mL/kg, i.p.) for misoprostol was administered 15 min before the injection of vehicle (DMSO, 1 mL/kg, i.p.) for sodium selenite/celecoxib. After additional time duration of 15 min, pentylenetetrazole (80 mg kg^{-1}, i.p.) was injected and the observation procedure was initiated immediately.

Group III (Sodium selenite control group). Vehicle (DMSO, 1 mL/kg, i.p.) for misoprostol was administered 15 min before the injection of sodium selenite (10 mg kg^{-1}, i.p.). After additional time duration of 15 min, vehicle (Saline, 10 mL/kg, i.p.) for pentylenetetrazole was injected and the observation procedure was initiated immediately.

Group IV–VI (Sodium selenite + pentylenetetrazole treatment groups). Vehicle (DMSO, 1 mL/kg, i.p.) for misoprostol was administered 15 min before the injection of sodium selenite (at dose levels of 1, 3 and 10 mg kg^{-1}, i.p. for groups IV, V and VI respectively). After additional time duration of 15 min, pentylenetetrazole (80 mg kg^{-1}, i.p.) was injected and the observation procedure was initiated immediately.

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