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Mini Review Article

N-Acetylcysteine amide and central nervous system: human studies and animal models

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ABSTRACT

Brain structure is always the first bulwark against the drug delivery tools in the treatment settings of neurologic disorders. Oxidative stress is a critical condition in the pathogenesis of neurologic disorders. N-acetylcysteine amide (NACA), a more lipophilic derives of N-acetylcysteine (NAC), has the potential for treatment of oxidative based disorder especially in the brain. We reviewed 83 papers bearing the acronym NACA in their title. All the papers indicated NACA had a protective effect on toxins-drug toxicity. Most of the papers also reported that NACA was a great therapeutic option for cataracts and eye disorders. Some studies used NACA for treatment of hematologic problems and kidney related disorders. Then, we focused on the neurological application of NACA. It is well-documented that the bio effects of NACA is mediated by antioxidant properties via the –SH group. NACA is more bioavailable and potent than NAC. The lipophilic structure provides a promising result for NACA when this antioxidant molecule is used to treat the brain disorders ranging from trauma to toxins and neurotransmitter toxicity.

ان استیل سیتئین آمید و سیستم عصبی مرکزی: مطالعات انسانی و مدل های حیوانی

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چکیده

ساختار مغز اولین سد در برابر داورسانی موثر در درمان اختلالات عصبی است .استرس اکسیداتیو یک شرایط مهم در آسیب زایی اختلالات عصبی است. N-استیل سیستئین آمید (NACA) ، یک مشتق چربی دوست تر– Nاستیل سیستئین (NAC) که قابلیت زیادی برای درمان اختلال مبتنی بر اکسیداتیو به ویژه در مغز نشان داده است. در این مطالعه، ۸۳ مقاله مورد ارزیابی قرار گرفت که در عنوان آنها کلید واژه"– N استیل سیستئین آمید" وجود داشت. مرور مقالات نشان داد NACA دارای اثر محافظتی در برابر سمیت سموم و داروها است. بیشتر مقالات گزارش کردند که NACA یک گزینه درمانی عالی برای آب مروارید و اختلالات چشمی است. مشکل هماتولوژیک و اختلالات مرتبط با کلیه هدف NACA است. سپس، ما بر روی کاربرد NACA در سیستم عصبی تمرکز کردیم. به خوبی مستند شده است که اثرات زیستی NACA توسط خواص آنتی اکسیدانی به واسطه گروه SH- وساطت می شود. زیست دسترسی و قدرت عمل NACA به طور قابل توجهی بالاتر از NAC است .ساختار لیپوفیلیک سبب ایجاد نتایج امیدوارکننده NACA در درمان اختلالات مغزی شامل تروما، سموم و سمیت انتقال دهنده های عصبی شده است.

واژه های کلیدی: ان استیل سیتئین آمید، استرس اکسیداتیو، مغز، سمیت

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INTRODUCTION

NACA, is a lipophilic derivative of NAC that has a great antioxidant property [1]. The structure of NAC and NACA is depicted in the Figure 1. The hydroxyl group in the carboxyl functional group of the NAC is replaced by amide in the NACA [2]. This thiol-based antioxidant exerts its properties via restoring of glutathione. The reviewed papers (N= 83) investigated the mechanism of action, pharmacokinetics and toxicology of the NACA. Mechanisms and kinetics evaluation indicated that scavenging activity of NACA in aqueous solution is mediated by hydrogen atom transfer from the –SH site. However, the source of hydrogen could be both -SH and CH_2 in the non-polar environment [3]. Pharmacokinetic properties of NACA were analyzed by He et al. They reported that the bioavailability and glutathione replenishing capacity of NACA was four time higher than NAC[4]. Most of the papers evaluated the protective effect of NANA in the eye diseases, especially cataracts, where the eye disorders have been induced by chemical agents. [2, 5, 6]. Nephroprotection, hematological application, protection against drug toxicity, radiation and heavy metals were reported for NACA (Figure 2) [7-11]. Due to the lipophilic properties, the brain disorder treatment by NACA was investigated. In this review, we focused on the application of NACA in the neurology field. We reviewed the effect of NACA on brain and spinal trauma. Some reports supported the effectiveness of NACA on blood brain barrier disruption. NACA protects the brain against methamphetamine neurotoxicity. NACA also affects the glutamate in the brain as a neurotransmitter. Some cellular models revealed the mechanism of NACA in the CNS.

BRAIN AND SPINAL TRAUMA

In 2014, Pandya et al. evaluated the effect of NACA on traumatic brain injury and found that a 15-day post-injury treatment improved the cognitive function and cortical tissue sparing. They also found that NACA administration reduced the brain oxidative damage (after 7 days). Maintaining the mitochondrial glutathione, proposed as an underlying mechanism of action [12]. In a similar study, Zhou et al. showed that NACA could help the treatment of traumatic brain by reducing the oxidative stress. However, the effects were observed less than 3 days and nuclear factor erythroid 2-related factor 2 was represented as the mediating pathway [13]. In another study, administration of 300 mg/kg NACA reduced a post trauma neuronal degeneration and apoptosis that mediated by increasing of the manganese superoxide dismutase [14]. Patel et al. evaluated the effect of short and long term NACA administration on spinal trauma. They found that the effective dose of NACA is 300 mg/kg in short term. In addition, continuous NACA (150 or 300 mg/kg/day) treatment starting at 15 min post-injury for one week increased the tissue sparing at the injury site [15].

BLOOD BRAIN BARRIER

The blood brain barrier is an essential factor for the central nervous system, and any disruption in its integrity is associated with diseases. Kawoos et al. disrupted a blood brain barrier in rats and evaluated the barrier function with Dextran and imaging technique. They found NACA treatment at a single dose protected the BBB breakdown [16]. Administration of HIV proteins including gp120 and Tat with methamphetamine could impair the blood brain barrier via oxidative stress. The report showed that pretreatment with NACA restored the oxidative balance and protected the

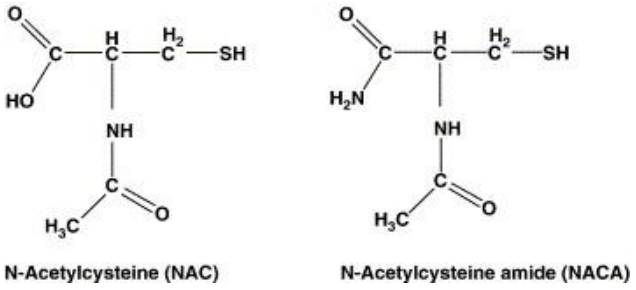

Figure 1. The structure of NAC and NACA

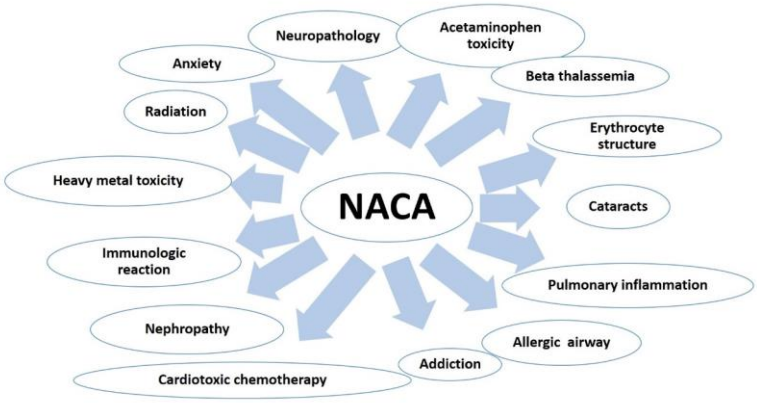

Figure 2. Current knowledge finds NACA as an effective option for a plethora of disorders

brain from toxins and inflammation [17]. The protective role of NACA against HIV-1 -Tat and methamphetamine was reported by Zeng et al. However, besides the antioxidative role, the mTOR signaling was reported as themediator affected by NACA [18]. Price et al. showed that dHIV-1 viral proteins gp120 and Tat induce BBB impairment by increases oxidative stress of brain endothelial cells, which NACA could reduce the deteriorating effect [19].

METHAMPHETAMINE NEUROTOXICITY

Methamphetamine also induces oxidative stress and neurotoxicity in human brain endothelial cells that is reversed by NACA [20]. Methamphetamine administration increases the oxidative stress per se and damages the liver, kidney and brain, which is antagonized by NACA, 250 mg/kg body weight. The authors concluded that oxidative stress was the underlying mechanism in this situation [21]. More recently, Koriem et al. proposed that besides oxidative stress, the protective effect of NACA against methamphetamine was mediated by DNA and other genetic factors such as proteins disappearance [22]. Protein's disappearance occurred in post treatment protein electrophoresis analysis.

GLUTAMATE

Glutamate, a neurotransmitter, can induce neuron cell death after hyperglycemia, ischemia, and hypoxia via increasing the lipid peroxidation and oxidative stress. Penugonda et al. indicated that NACA protected PC12 neuronal cell line against the glutamate cytotoxicity that was mediated by restoring glutathione levels [23]. Glutamate and lead co administration induces the PC12 cell death via simultaneous oxidative stress and ATP

depletion. NACA mitigates glutamate and lead cotoxicity [24]. On the other hand, maintaining the glutamate levels in the synaptic space reduces the craving in cocaine addicts during starvation. In this term, NACA increases the glutamate and helps the addict person to avoid drug. The increased glutamate levels are mediated via cysteine-glutamate antiporters [25]. Behavioral study, biochemical and histological analysis revealed that the protective effect of NACA against paraquat-induced neurotoxicity in a rat model. The paraquat toxicity is dependent on oxidative stress; the protective effect of NACA is mediated by antioxidant properties. Not only total glutathione but also antioxidant enzymes including superoxide dismutase, glutathione peroxidase and catalase are targeted [26].

OTHER MODELS AND MECHANISMS

The protective effect of NACA is confirmed in the microphysiological neurology model [27]. Differentiation of stem cells to the dopaminergic neurons which harboring a mitochondrial dysfunction provides a model that mimics mitochondrial diseases. In this model, NACA was considered as a promising potential therapy for neurological-mitochondrial diseases [28]. Perinatal asphyxia damages the brain by oxidative stress and inflammation [29]. Animal study showed that NACA exerts neuroprotective effects by reducing inflammatory markers such aIL-1β and TNFα and the transcription factor NF-Kb [30]. In another study, they found that the protective effects of NACA against perinatal asphyxia are mediated by inhibiting proteolytic activity [28]. In addition, the behavioral study in zebrafish showed that NACA had anxiolytic effects which was more effective than NAC [31].

CONCLUSION

In conclusion, the bio effects of NACA is based on its antioxidant properties that is not different from NAC in mechanism of action. However, the bioavailability and potency of NACA is significantly higher than NAC. Due to the lipophilic structure of NACA and observed experiments, this drug exerts promising effect on brain disorders ranging from trauma to toxins.

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ETHICS

Approved.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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