REGULAR ARTICLES

Gold nanoparticles and lipoic acid as a novel anti-inflammatory treatment for autism, a hypothesis

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Abstract

Autism is a neurodevelopment disorder. Its aetiology and pathophysiology are not clearly known. However, mitochondria may play a significant role at least in some cases of autism. There is no therapeutic approach for autism. Moreover, there are only few Food and Drug Administration (FDA)-approved medications for autism. Therefore, providing novel therapeutic approaches are highly required. Oxidative stress is suggested as an important factor in the aetiology of autism. Already some interventions targeting oxidative stress in autism are suggested.

This article reviews evidence about the possible role of gold nanoparticles and lipoic acid (LA) as anti-inflammatory agents. It mentions some evidence about the possible role of oxidative stress. Then, the role of gold nanoparticles and LA for the management of autism is discussed.

According to the above-mentioned evidence, it is hypothesised that gold nanoparticles and LA may reduce neuro-inflammation in autism.

Controlled experimental studies are needed to test whether gold nanoparticles plus LA enhance antioxidative stress system leading to the improvement of autism clinical symptoms.

Introduction

Gold nanoparticles increase cutaneous wound healing in mouse through its anti-inflammatory and antioxidative effects [1]. Moreover, gold implants and the increased expression of metallothionein-I/II are suggested as possible therapeutic approach for autism [2]. According to the following evidence, gold nanoparticles plus lipoic acid (LA) may be a hypothesised treatment for autism symptoms. Other interventional approaches such as gold implants [2], targeting of nuclear factor kappa B (NF-κb) [3], ol esoxime [4], zonisamide [5], ziconotide [6], c-Kit+ cell transplantation [7] and the targeting of glycine site on N-methyl-D-aspartate (NMDA) receptor [8] are also suggested to tackle oxidative stress in autism.
The role of LA in mitochondrial dehydrogenase reactions is crucial. A disulphide bond attaches two sulphur atoms of LA. LA can be oxidised. Dihydrolipoic acid is the reduced form of LA with pharmacological benefits. It is an important cofactor for mitochondrial enzymes of pyruvate dehydrogenase (PDH) and α-ketoglutarate dehydrogenase (KGDH). LA is a possible modulator of redox status in cells [9]. LA reacts with reactive oxygen species (ROS) including superoxide radicals, hydroxyl radicals, peroxyl radicals and singlet oxygen.

LA is suggested for the treatment of oxidative stress-associated problems such as multiple sclerosis [10] and acute optic neuritis in humans [11]. α-LA has an anticonvulsant effect and decreases pilocarpine-induced seizure in animals [12,13]. It inhibits caspase-3-dependent apoptosis through cytochrome c [12]. Moreover, LA scavenges free radicals and is suggested as a reason for lowering seizure susceptibility [13]. In addition, LA removes ROS and increases the level of reduced glutathione [14]. The improvement of Na⁺, K⁺, ATPase activity is also associated with LA [13]. This enzyme plays an important role for maintaining the ionic gradient required for neuronal excitability. Free radicals impair the activity of this enzyme.

α-LA also has anti-inflammatory effects. The neuroprotective effects of α-LA are suggested due to its anti-inflammatory and antioxidant properties [15]. LA reduces the expression of pro-inflammatory proteins such as tumour necrosis factor (TNF) and inducible nitric oxide synthase [14]. Furthermore, the anti-inflammatory effects of α-LA can be through the inhibition of NF-κB activation [16]. Moreover, the anti-inflammatory effects of oral administration of LA can be provoked via cyclic adenosine monophosphate (cAMP) and protein kinase A signalling [17].

In addition, LA increases the superoxide dismutase and catalase activities [18] and glutathione peroxidase in animal models (Fig. 1). LA increases cerebral glutathione (GSH) levels. In addition, LA increases GSH level and glutathione peroxidase (GSH-Px) activity [13]. Both of them have an important role in antioxidant function. The inducing of GSH synthesis enzymes and other antioxidant protective enzymes by LA are reported [19].

Autism is a disorder that its aetiology and neurobiology are not clearly known. Oxidative stress is enhanced in autism [20]. Oxidative stress plays a significant role in the neurobiology of autism [21,22] and the targeting of oxidative stress is suggested as a therapeutic approach [21]. Antioxidant enzymes of superoxide dismutase (SOD) and GSH-Px are lower in autism than the controls [23,24]. In addition, the concentrations of exogenous antioxidants, vitamins E and A, and lycopene in individuals with autism are not sufficient [25].

Impaired mitochondrial energy production has an aetiolog-ical role for autism too [26]. Moreover, brain inflammation is also associated with autism. Inflammation and apoptosis have important causative roles for autism [27]. Meanwhile, anti-apoptotic signalling pathway is compromised in the brain in autism [28]. The expression level of pro-inflammatory cytokines TNF-α and interleukin-6 (IL-6) are increased but B-cell lymphoma (Bcl)2 expression is reduced [27]. The expression
enhanced in autism [29]. The management of inflammation of caspase-3, which is an important executioner of apoptosis, is
42 A. Ghanizadeh
may play a role in the treatment of autism[30,31]. Fig. 1 shows the possible role of LA on them.

Hypothesis

According to the above-mentioned evidence and the anti-inflammatory effect of LA for treatment of neuritis [11], and the effect of gold nanoparticles plus LA through anti-inflammation and antioxidation effects [1], it seems to be reasonable to hypothesise that gold nanoparticles and LA can be a novel treatment for autism too.

Evaluation of hypothesis

Therefore, animal model experimental studies are suggested to test this novel hypothesised treatment. A study with two arms is suggested. One group will receive gold nanoparticles plus LA. The other group will receive placebo. There are two types of outcome measurements. The first one assesses the possible changes in antioxidative stress activity of SOD, GSH-Px and catalase. In addition, the level of GSH is assessed. The second type of outcome measurement evaluates the clinical manifestation of autism in animal models.

Discussion

Given that LA has the following effects: scavenges free radicals [13], increases reduced GSH levels [14], increases SOD and catalase activities [18] and GSH-Px activity, and induces GSH synthesis enzymes and other antioxidant protective enzymes [19], and anti-inflammatory effects. In the meantime, autism is a disorder with enhanced oxidative stress [20,33], decreased antioxidant enzymes of SOD and GSH-Px [23,24], brain inflammation, apoptosis [27], increased the levels of pro-inflammatory cytokines TNF-α and IL-6 [27] and impaired mitochondrial energy production [26,32]. Therefore, it may at least partially improve some symptoms of autism. However, it needs to be noticed that some of ROS have the role of being as second messengers [34]. So, animal model studies are recommended. Further studies may investigate whether LA and gold nanoparticles may improve inflammation. In addition, it needs to be answered whether they should be administered together. The way that they might be administered should be discussed.

Conclusion

Considering the neurobiology of autism and the mechanism-based function of gold nanoparticles plus LA, it is hypothesised that gold nanoparticles plus LA improve autism symptoms through the enhancement of defence against oxidative stress.

Conflict of interest statement

The author has no conflicts of interest with regard to the content of this article.

References

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