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New Insight into Role of Estrogens in Central Nervous System

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Abstract

17β-estradiol is female sex steroid that belongs to estrogens. It is formed from cholesterol, whereas its direct precursors are androgens such as testosterone. There are experimental data providing neuroprotective properties of 17β-estradiol in animals' models. Additionally, several clinical experiments prove that estrogens replacement therapy in postmenopausal women decrease the risk of neurodegenerative disorders such as Alzheimer's, Parkinson's disease. 2-methoxyestradiol is a physiological metabolite of 17β-estradiol which is mainly known due to its anticancer and antiproliferative properties, whereas some studies reported its neurotoxic activity. 2-ME selectively increase level of neuronal nitric oxide synthase leading to generation of nitric oxide and its derivatives within hippocampal cells. Generation of reactive nitrogen species and reactive oxygen species leads to DNA damage in hippocampal cells and cell death.

Keywords: *17β-Estradiol; Estrogens; 2-Metoxyestradiol; Neuroprotection; Neurodegeneration; Oxidative Stress*

Abbreviations

E2: 17β-Estradiol; 2-ME: 2-Methoxyestradiol; nNOS: Neuronal Nitric Oxide Synthase; RNS: Reactive Nitrogen Species; ROS: Reactive Oxygen Species

Introduction

17β-estradiol (E2) is female sex steroid that belongs to estrogens. It is formed from cholesterol, whereas its direct precursors are androgens such as testosterone [1]. There are experimental data providing neuroprotective properties of E2 in animals' models. This hormone increases neuronal survival after brain injury *in vivo*. Moreover, it protects neuronal cells from anoxia and oxidative stress [2-5]. Some studies confirm that sex hormones are involved in hippocampus-dependent cognition and neuroplasticity [1,6]. On the other hand, there are some data considering neurodegenerative influence of E2 derivatives [1,2,7].

Estradiol as a neuroprotector

E2 is a female hormone that is also known as a neuroprotective factor. Several clinical experiments prove that estrogens replacement therapy in postmenopausal women decrease the risk of neurodegenerative disorders such as Alzheimer's, Parkinson's disease, memory and cognitive dysfunctions. Interestingly, estrogens supplementary even improve memory and cognition [5].

According to numerous *in vivo* studies, E2 exhibits protective properties in a brain injury. Administration of estrogens protects against stroke, decrease the extent of injury, and reduce number of deaths [5]. The neuroprotective effects of estrogens are reduced oxidative stress, anti-inflammation activity, improved post-stroke recovery, beneficial vascular effects, decreased apoptosis and attenuated

excitotoxicity [8]. E2-mediated mechanism of neuroprotection is due to the presence of estrogen receptors (ER) in cerebral cortex [9]. What is more, Wise., *et al*. proved that ERα is responsible for protective mechanism of estradiol in a brain injury [10]. Selective targeting of ERα may help in prevention and therapy of neuronal dysfunctions associated with aging or brain injury [5].

In general oxidative stress is the most important mechanism in cellular damage. Estrogens have been reported to exhibit some anti-oxidative properties such as prevention of peroxide accumulation, reduction of ROS production, limitation of lipid peroxidation and decrease level of hydrogen peroxide [11-14]. What is more, estrogens are engaged in redox cycle in which they turn into quinol when eliminating a radical, and then they are converted back to estrogen form by a reducing agent – NADPH [15].

Large number of studies have demonstrated a wide range of anti-inflammatory properties of estrogens. They have an ability to reduce leukocyte adhesion, cytokine production and monocyte activation [16-18]. These mechanisms are very important as they play a key role in estrogens' neuroprotective effects in stroke [19].

2-methoxyestradiol as an active metabolite of 17β-estradiol

2-methoxyestradiol (2-ME) is a physiological metabolite of E2. Physiological concentrations of 2-ME range from pM in men up to nM in women [1]. The first step of 2-ME synthesis is hydroxylation of 2E to 2-hydroxyestradiol by a NADPH-dependent cytochrome P-450-linked monooxygenase system. Then 2-hydroxyestradiol rapidly follows subsequent O-methylation catalysed by catechol-O-methyltransferase (COMT) leading to the synthesis of monomethyl ether – 2ME [1,2,7].

2-ME is mainly known due to its anticancer and antiproliferative properties [20,21]. An anticancer activity of 2-ME is strictly related to the inhibition of angiogenesis and induction of cell death in both proliferating and cancer cells. Branded as Panzem is evaluated in ongoing clinical trials in anticancer treatment of breast, ovarian, prostate cancers and multiple myeloma [1].

Unlikely to E2, 2-ME activity seems to be estrogen receptor independent [22,23]. Its anticancer properties are due to induction of nitro-oxidative stress, which is described as an imbalance between production and reduction of reactive nitrogen species (RNS) and reactive oxygen species (ROS) [1]. 2-ME has an ability to generate ROS and RNS. This process results in nitro-oxidative stress-induced apoptosis [1,24,25]. Anticancer mechanism of action of 2-ME is also associated with microtubule polymerization [1].

Notably, we have previously demonstrated that 2-ME both at pharmacological and physiological relevant concentrations increases nuclear fraction of neuronal nitric oxide synthase (nNOS) in osteosarcoma cell death model (143b) [20]. Interestingly, nNOS has been suggested as molecular messenger of 2-ME. NOS has an ability to catalyse an oxidation of L-arginine to citrulline that leads to nitric oxide (NO) molecule release. This activity results in increased level of NO that leads to DNA strand breaks and finally, cell death [20,26].

Neurotoxic influence of 2-methoxyestradiol

2-ME is an antiproliferative agent that induces apoptosis in actively dividing cells, such as cancers, whereas non-proliferating cells seems to be resistant to 2-ME [27]. Interestingly, adult neurogenesis undergoes in two regions of the brain – olfactory bulb and

dentate gyrus of the hippocampus – a structure responsible for memory formation and cognitive functions [28]. Disturbed adult neurogenesis leads to neuronal loss, what may result in neurodegenerative diseases such as Parkinson Disease or Alzheimer Disease. Initial symptoms are cognitive impairment and mood disorders like anxiety and depression, which are strictly related with hippocampal dysfunctions [28].

2-ME synthesis begins with E2 hydroxylation and then follows subsequent O-methylation catalyzed by COMT [7]. COMT is widely distributed in hippocampus and thus, this brain structure seems to be especially exposed to potential neurotoxic activity of 2-ME [1].

According to Picazo., *et al*. endogenous metabolism of E2 to 2-ME may counterbalance the neuroprotective effects of the hormone [2]. In their study, number of hilar neurons in rats was decreased after treatment with 2-ME and was comparable to results observed after kainic acid. Interestingly, E2 prevented hilar neuronal loss in rats treated with kainic acid. These findings may suggest that neuroprotective activity of E2 is not mediated by its metabolism to catocholestrogens and endogenous conversion to 2-ME may be neurotoxic [2].

In addition, we have previously demonstrated that 2-ME induce apoptosis and DNA damage in hippocampal HT22 cells [7]. 2-ME at pharmacologically and physiologically relevant concentrations was found to increase nuclear localization of (nNOS). Induction of nNOS is strongly correlated with elevated nitic oxide production. NO easily react with oxygen radicals to generate reactive nitrogen species (RNS) such as peroxynitrite and nitrogen dioxide [29]. Elevated level of NO and RNS is directly correlated with DNA damage and cell death. Moreover, we observed single and double strand breaks in HT22 cells caused by 2-ME [7].

It is well known that nitro-oxidative stress may contribute to neurodegenerative disorders such as stroke, multiple sclerosis, Alzheimer's and Parkinson's diseases. Increased level of RNS and ROS leads to cell death via DNA, protein and lipids damage [29-31]. Due to the above the role of 2-ME in cancer cell death and neurodegenerations development may be suggested. Moreover, patients treated for long periods with 2-ME as anticancer drug, may in future suffer some changes in hippocampal functions, including memory impairment or mood disorders such as depression or anxiety.

Conclusion

E2 is a female sex hormone that exhibits neuroprotective properties. Numerous of studies show that E2 protects against stroke, decrease the extent of brain injury, and reduce number of neuronal cell deaths. Nevertheless, its derivative, 2-ME has been suggested as neurotoxic factor. 2-ME induce oxidative stress that is significant in development of neurodegenerative diseases. Interestingly, 2-ME, branded as Panzem, is used in clinical trials as efficient anti-cancer drug. Role of 2-ME in neurodegeneration development is currently under our investigation.

Conflict of Interest

The authors confirm that this article content has no conflict of interest.

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