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Role of estrogen in development of migraine

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Abstract

Migraines are benign conditions but negatively affects the quality of life of the migraineurs. Migraines are expressed as pain associated with vasodilatation of cerebral and meningeal arteries and are classified as occurring with or without a visual aura. Migraines are 3 times more common in women than in men. They may be associated with the menstrual period, ameliorated by pregnancy, diminished at menopause and may worsen with menopausal hormone treatment. These observations indicate that fluctuations in estrogen levels may be a precipitating factor for migraines. Several polymorphisms are associated with familial migraine including genetic variation in Estrogen Receptors (ER). ER stimulates NO production in vascular endothelium this causes direct modification of migraine. Migraine is a risk factor for stroke, thus, it is concluded that the elevated estrogen level is one of the main factors responsible for the development of migraine and its preponderance in females along with the polymorphisms of estrogen receptors that affect nitric oxide production therefore causing modulation of migraines.

Keywords: Estrogens, Migraines, Estrogen receptors, Nitric oxide

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Introduction

Migraines are benign conditions[1,2] but negatively affects the quality of life of the migraineurs. Neurovascular component is one of the main etiology of migraine. Migraines are expressed as pain associated with vasodilatation of cerebral and meningeal arteries and are classified as occurring with or without a visual aura, thus implicating different neuronal involvement between the two types of migraines.[1,2,34,5] Indeed, individuals who experience aura can be biochemically differentiated from those who do not.[6]

Migraines are 3 times more common in women than in men.[4,7] They may be associated with the menstrual period, ameliorated by pregnancy, diminished at menopause and may worsen with menopausal hormone treatment. These observations indicate that fluctuations in estrogen levels, may be a precipitating factor for migraines.[1,3,5] But, the differences in circulating levels of estrogen were not observed between women with and without menstrual migraine. Urinary excretion of estrone-3-glucuronide was double in women with migraine than in those who did not experience migraine, thus the ability to metabolize estrogen may be related to the development of migraine.[5] Therefore, further studies related to estrogen metabolism among women who experience migraines, with or without aura, and women who do not, need to be conducted especially related to the production of catecholestrogens that influence production and disposition of adrenergic neurotransmitters thus participating in neuronally induced cerebral vasospasm.[6,7]

Polymorphism of estrogen receptors

Several polymorphisms are associated with familial migraine including genetic variation in Estrogen Receptor alpha (ERα) (G594A polymorphism of exon 8).[8,,9,10] Estrogen receptors are located within brain nuclei innervating the cerebral vasculature as well as other nuclei regulating cardiovascular function.[7] Thus, besides influencing adrenergic mechanisms, estrogen may also modulate central opioidergic tone, release of peptidergic transmitters from trigeminal nuclei, and the GABAergic system, perhaps modulating NO.[11,12,4,7,13]

Estrogen receptors and Nitric Oxide (NO)

ERα stimulates NO production in vascular endothelium, this causes direct modification of migraine. Platelet production of NO was greater in women with menstrual migraine than in those without.[4] NO released from platelets contribute to decrease cerebral vascular tone. A polymorphism E298D in eNOS results in decreased activity of the enzyme and is also associated with increased risk for cardiovascular and cerebrovascular disease. The homozygous variant is an independent risk factor for stroke in persons with migraine with aura. Females participation in the studies related to migraine is about 80% which reflects that the condition is prominent in women.[14] More studies are needed to establish the association of genetic variation in eNOS with those of ERα in a larger population. If the genetic variant results in decreased activity of eNOS, the results are difficult to interpret within the context that increased production of NO may trigger migraine.[15] Some evidences suggest that neuronally derived NO is also involved in the etiology of migraine, but no association of migraine with genetic variation of

neuronal nitric oxide synthase was found.[11,12,14] Further research is required regarding estrogenic modulation of all three isoforms of nitric oxide synthase in the cerebrovascular unit.

In addition to estrogenic modulation of neuronal transmission associated with pain and endothelial NO[17,7,16] estrogen may induce migraine through direct effects on vascular smooth muscle cells. For example, estrogen increased the efflux of magnesium from cultured cerebral smooth muscle cells.[18]

Migraine and stroke

Migraine may be a risk factor for stroke, as revealed by Atherosclerosis Risk in Communities Study, according to which there is increased incidence of ischemic stroke in young women who experience migraine with aura.[19] This observation also points to an underlying pathological condition of the neurovascular unit contributing to migraine.[17,20,21] These observations point to the need to understand and differentiate factors contributing to stroke risk.[2,22] Several chronic alterations in small arterial anatomy and function, which may not show a sex difference in frequency, predispose an individual to ischemic stroke and migraine with aura.

Conclusion

Thus, the above studies indicate that the elevated estrogen level is one of the main factors responsible for the development of migraine and its preponderance in females along with the polymorphisms of estrogen receptors that affect nitric oxide production therefore causing modulation of migraines.

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