

Review (Narrative)

Is Sex Hormone a Risk Factor of Nociceptive Hypersensitivity in the Context of Cerebrovascular Diseases?

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SUMMARY

Cerebral vessel events have long been considered a leading cause in postmenopausal women with physiological changes in expressing and secreting of sex hormones. Hormone replacement therapy emerged as a supplementary therapeutic strategy under the risk of cerebrovascular accidents and bone loss. Epidemiological and genetic data showed that an interrelationship among hormone and cerebrovascular disorders exist. A battery of animal experiments and clinical observations received different results both positive and negative.. Recent studies still cannot give a once-for-all answer to whichever hormone, estrogen or progesterone overweighs the other in benefits. Here we review and analyze the two hormones' effects on cerebrovascular diseases and that of associated epidemiological and genetic evidences.■

KEYWORDS Cerebrovascular Disease; Sex Hormone; Estrogen; Progesterone; Inflammation

Sci Insights. 2018; 2018:e000151. doi:10.15354/si.18.re079

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Organisms have an astounding ability to rehabilitate from considerable external interference and internal overbalance. This potential has been manipulated throughout human beings' history. But such an underlying role will diminish with increasing age. As humans entering the society of elderly, cerebrovascular diseases have been increasingly one of the leading causes of morbidity and mortality after the severe infectious disease has been controlled. Cerebrovascular accidents, a part of the complex of vascular diseases, have their own origin. While various associated risk factors for stroke have been identified over the past several decades, the real approaches preventing this pathological process are still under the water.

Estrogen and progesterone, two members of the steroid hormone family, are well known for their roles in cerebrovascular function. Unfortunately, the administration of the two hormones in vascular diseases has been restricted due to the severe negative effects. But fortunately, what essence these two molecules really take has been re-evaluated, and what effects these chemicals exert in vascular diseases have been assessed.

EPIDEMIOLOGY FOR CEREBROVASCULAR DISEASES

The World Health Organization (WHO) defines a stroke as rapidly developing clinical signs of focal or global disturbance of cerebral function with symptoms lasting 24 hours or longer or leading to death, with no apparent cause except of vascular origin (1). The International Classification of Diseases (ICD) using etiology and pathology has divided stroke into nine major groups. In 1990, the National Institute of Neurological Disorders and Stroke (NINDS) group classified stroke in a broad way following its epidemiological, pathological and clinical purposes (2).

With the development and utilization of the medical imaging equipment such as the computed tomography (CT), magnetic resonance imaging (MRI), position emission tomography (PET) and transcranial Doppler cerebral flow assessment, stroke diagnosis has been changing dramatically. Through them, a far more detailed evaluation can be given and can reconsider the prognosis after the attack of the cerebral vasculature.

The high mortality of stroke is always a wake-up call every year in the world. It is maybe higher in the third world than in industrialized countries. Age is the strongest predictor of mortality in stroke people. The

average mortality rate is 7.6% for ischemic stroke and 37.5% for hemorrhagic stroke at 30 days after the accident (3).

In general, the stroke rate changes with various race, family history, gender, and age. Simultaneously, other so-called modifiable factors as smoking, obesity, physical activity, hypertension, hyperlipidemia, and other risk factors significantly affect the occurrence of stroke (4). Under the use of preventive therapies and interventions, the burden of cerebrovascular diseases is improving dramatically. Many kinds of educations to those risk populations play an important role in reducing stroke onset. But the precise mechanisms for cerebrovascular accidents are yet to be guaranteed.

GENETIC ASSOCIATED CAUSES OF CEREBROVASCULAR DISEASES

Accumulating evidence indicates that cerebrovascular diseases are strongly associated with genetic respects. Meschia JF (5) reviewed the major causes of cerebrovascular diseases that related directly or indirectly to the genetic reasons. Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a stroke syndrome, is resulted from a mutation in the gene of Notch 3 encoding the large Notch 3 transmembrane receptor (6). Normally, Notch 3 is composed of a 97kDa intracellular fragment and a 210kDa extracellular fragment. But a large number of the Notch 3 ectodomains (210kDa) are accumulated within the cerebral vessels in CADASIL patients and models. It strongly suggested that Notch 3 plays a crucial role in CADASIL cases. X-linked disorders as Fabry disease are caused by a mutation in the α -galactosidase A gene. After 30 or 40 years, patients with Fabry suffer a stroke, mainly a small-vessel ischemic one (7). Mostly such patients are accompanied with hypertension and cardiac abnormalities. Homocystinuria, an autosomal disorder, has a significant association with the defected gene that normally encoding the cystathionine β -synthase and the deficiency of methylenetetrahydrofolate reductase (MTHFR). Furthermore, mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) are caused by mutations in mitochondrial DNA (8). Additionally, sickle cell disease is caused by the mutation in the β -polypeptide chain of hemoglobin, in which glutamin acid replaced valine. Many such patients suffer their first stroke peak between ages 2 and 5 years (9).

RECOVERY FROM CEREBROVASCULAR DISEASES

Though a good number of probes have been made in cerebrovascular accidents, the results are relatively hopeless. Even so, a little change over the therapeutic approach to stroke has been seen.

Stroke rehabilitation has been defined by different individual structure, process, and outcome as well (10). The basic stroke-peculiar measure comprises motor, sensory, visual and impairments. Many assessment systems exist for measuring stroke patients' abilities recovering from the hit. But the two most widely used assessments are the Functional Independence Measure (FIM) (11) and the Barthel Activities of Daily Living (LDL) index (12).

Several major respects are the goals of stroke recovery. Rehabilitating from motor deficits is the most common case characterized by muscle weakness, clumsiness, and fatigue. The individualized therapeutic techniques must be adapted to the patients with different stages of motor recovery (13). Pain in the shoulder of the affected side is very common after the accidents of brain vessels. But unfortunately, no effective way has been described. Besides, neuropsychological deficits are another aspect that needs to be considered. Such practice needs an empirical therapist working patiently with verbal or/and non-verbal material and approaches (14).

BASIC ACTIONS OF ESTROGEN

The physiological estrous cycle plays a pivotal role in regulating secreting and signaling of estrogen, which is mainly expressed in ovarian. It has the basic molecular structure of perhydrocyclopentanophenanthrene, and exerts effects the same way as glucocorticoid. The estrogen receptor is a member of the steroid-hormone-receptor family of proteins. It has two structurally distinct receptors, ER- α and ER- β . Three different receptor complexes exist either as a homodimer α/α or β/β or a heterodimer α/β , with each processing respective unique properties.

When estrogen transports through the cell membrane, it binds with high affinity to ER. They bond, with the help of several receptor accessory proteins, on the one hand, it promotes the dissociation of some molecular chaperones from the receptor; on the other hand, it recruits some other assistant proteins to the receptor.

Finally, it is carried and translocated to the nucleus and binds to associated DNA response domain. Consequently, transcription and translation are followed (Figure 1. A, B, C, D). Estrogen increases the expression of vasodilators, and promotes the formation of anti-inflammatory molecules and decreases the pro-inflammatory proteins after the challenge of lipopolysaccharide (LPS) in rodent models. As a result, estrogen produces the effects on cardiac or cerebral vessels and inflammatory responses.

PROGESTERONE FUNCTIONS IN BRAIN VESSEL DISORDERS

A widely-accepted function of progesterone is the neuroprotective role in traumatic brain injury. A battery of evidence showed that progesterone functions as a protector in middle cerebral artery occlusion (MCAO) and ischemic brain damage (15-20). However, Murphy (21) demonstrated that progesterone does not ameliorate histological injury after MCAO in previously ovariectomized adult female rats and chronic administration can exacerbate infarction in subcortical regions.

Comparatively, whether the benefits of progesterone administration outweighed the adverse effects in cerebrovascular diseases is undertaking (22). The natural progestins, usually progesterone and testosterone, are salvaged for their use due to their negative effects. So many new progesterones including nomegestrol acetate (NOMAc) and trimegestone (TMG) that are derived from the parent molecule of progesterone are synthesized (23). Given the fewer side effects, better physiological activities and self-owned pharmacological properties, it is likely these new derivatives have perspective therapeutic values in cerebrovascular disorders (Figure. 1 E).

ESTROGEN OR PROGESTERONE, WHICH IS THE BETTER?

Estrogen and progesterone have long been considered as primary hormones in reproductive and maternal behaviors. An emerging data have shown that the two sex hormones function as neuroprotective and neuro-regenerative agents in traumatic brain injury and stroke. With the progress of insight probes, different, even opposite results are collected.

Usually, estrogen exerts function as a prophylactic treatment for ischemic brain injury, while progesterone as a post-injury treatment for the acute, ischemic and

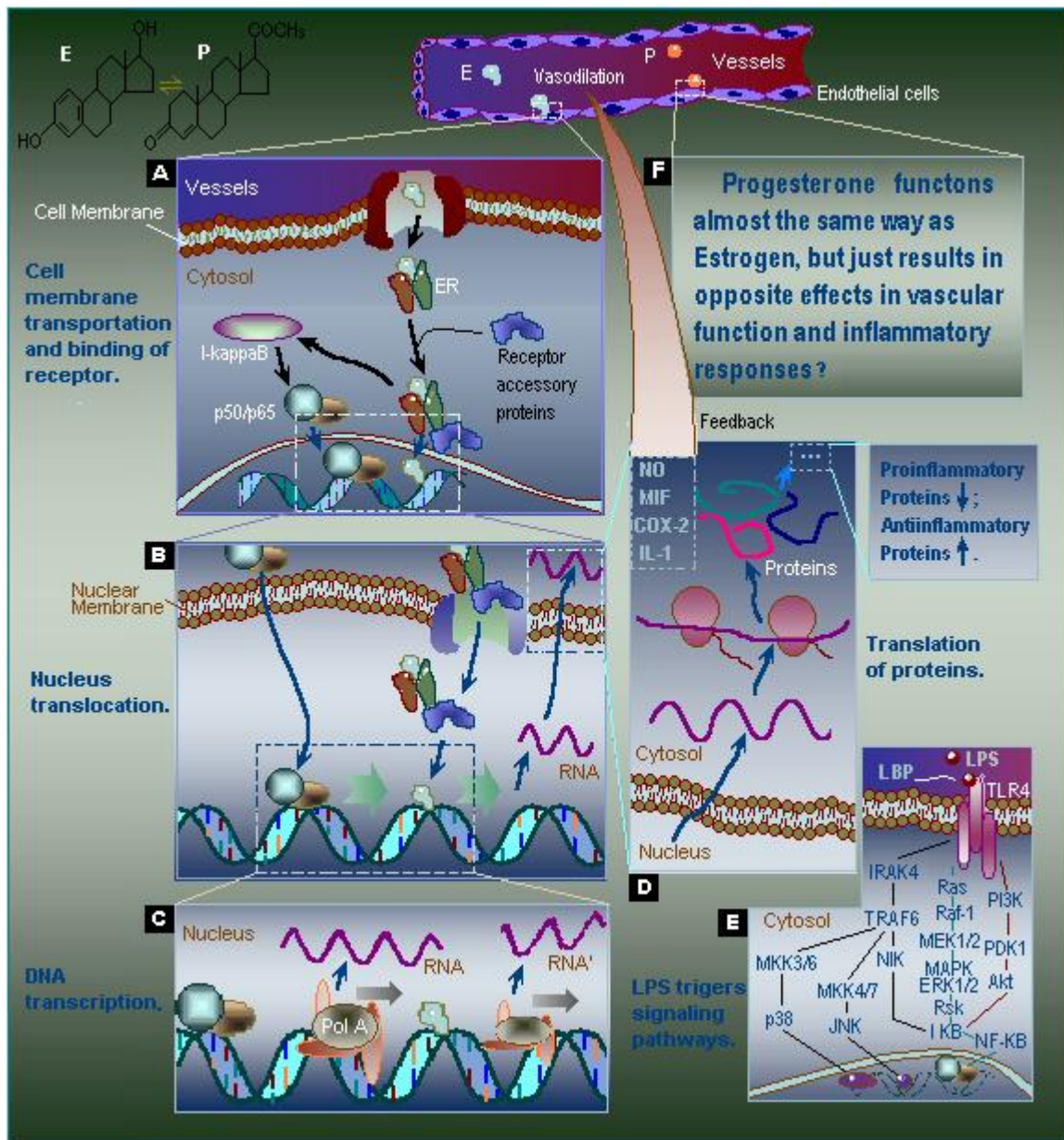


Figure 1. General activities of sex hormones in endothelial cells and LPS trigger signaling. Estrogen (E) transports through cell membrane molecular channel, and binds to ER with the help of series receptor accessory proteins and regulates the function of NF- κ B via I- κ B (panel A). ER carries estrogen and translocates into nucleus, then ER dissociated with estrogen, meanwhile, NF- κ B translocates through the nuclear membrane to DNA (panel B). Estrogen and NF-B function after connecting with respective DNA domain, the rRNA produced and out of the nucleus (panel C). rRNA modification and proteins translation in cytosol (panel D). General pathways triggered by lipopolysaccharide (LPS) in cellular signaling transduction (panel E). Progesterone (P) exerts functions almost the same way with E, but the effects may be complex (panel F). *Copyright: Insights Publisher.*

traumatic injuries of the brain and spinal cord (24). Estrogen plays roles in preserving the antioxidant effect, reducing in amyloid-beta (A- β) production and neurotoxicity, increasing in expression of the antiapoptotic factor bcl-2, and activating mitogen activated protein

kinase (MAPK) pathways. Progesterone has a membrane stabilizing effect and suppressing role in neuronal hyperexcitability (25). ZYC-26 (2-(1-adamantyl)-4-methylestrone), a non-feminizing estrogen, takes part of the antioxidant activity, rather than ER binding of non-

feminizing estrogens, and mediates their potent neuroprotective activity. And because of the now known toxicities of chronic feminizing estrogen use in older women, non-feminizing estrogens may be a useful alternative for estrogen-induced brain protection (26). Estrogen provides a protective role in increased vulnerability of males and menopausal females to cerebral ischemia by affecting amino acids (27). Transdermal HRT, 17-estradiol patch [36 µg/day] plus cyclic oral medroxyprogesterone acetate [2.5 mg/day, for 12 days/month] for 12 months, reduced carotid artery wall thickness, and this reduction may have been induced by an antiatherosclerotic effect combined with the direct effect of estrogen and decreased levels of estrogen-induced E-selectin (28).

Nonetheless, Gordon and colleagues published that two week's pre-treatment with a high physiological dose of 17β-oestradiol increased infarct volume after permanent MCAO (29). This, in contrast, shows that oestrogen does have the capacity to promote detrimental actions in the stroke-injured brain. And to some point, estrogen replacement therapy exacerbates the cerebral ischemia-reperfusion (I/R) injury in diabetic ovariectomized female rats through upregulated inflammation after tMCAO (30). In fact, maybe the influence of I/R on vessel function was more prominent than that of estrogen therapy (31). Moreover, a clinical trial showed that estradiol replacement therapy in elderly women suffered cerebrovascular disease could not protect against a reoccurrence of ischemia or to reduce the mortality compared to a placebo (32).

Progesterone exerts its neuroprotective role not merely for interfering with some late pathophysiological mechanisms leading both to selective neuronal damage in the hippocampal CA1 and CA2 subfields, and to shrinkage of the cerebral cortex (33), but for suppressing specific aspects of the inflammatory response and nitric oxide synthase-2 expression in both permanent and transient ischemia (34). Synthetic progestins caused endothelial disruption, accumulation of monocytes in the vessel wall, platelet activation and clot formation. All these actions seem to be associated with the combined administration of estrogen and progestin (35). As such, the therapeutic strategies on cerebrovascular diseases should be weighed wisely. Using progesterone with minimal vascular toxicity might result in much safer estrogen preparations for those people who under the risk of cerebral vessel accidents.

The inflammatory responses have been proved to participate in neuropathological changes. Estrogen functions through regulating the expression of adhesion molecules, inducible nitric oxide synthase (iNOS) and other inflammatory proteins (36). Estrogen protects the cerebral blood vessels from endothelial dysfunction induced by A-βin Alzheimer's disease (AD) (37). Furthermore, 17β-estradiol favorably affects the vascular inflammation processes by affecting high sensitivity C-reactive protein (hs-CRP) and reduction of cell adhesion molecules (38). Estrogen (17β-estradiol) exerts protective function in infarcted cerebral cortex via reducing heat shock protein 27 (HSP-27) synergistically with 1α,25-(OH)₂-vitamin-D₃ (1,25-D₃) (39), inhibits the migration of inflammatory cell, particularly granulocytes, into the rat carotid arteries after acute endoluminal injury, but the progestin medroxyprogesterone acetate (MPA), a synthetic analog of progesterone, blocks this effect (40), attenuates blood-brain barrier (BBB) disruption by down-regulation of matrix metalloproteinases (MMP2 and MMP9) expression after I/R injury (41). Meanwhile, the presence of progesterone would diminish the anti-inflammatory effects of estrogen in ischemic brain injury after the rodent challenged with lipopolysaccharide (LPS) (42). What the real effect of estrogen or progesterone takes in the inflammatory process after cerebrovascular accidents remain to be proved with large-sample, evidence-based and randomized clinical trials and meta-analysis.

In addition to estrogen and progesterone, testosterone may have a beneficial effect on axonal regeneration after injury in the central nervous system. Testosterone replacement post-MCAO accelerated functional recovery in castrated rats, suggesting a potential therapeutic role for testosterone replacement in stroke recovery (43).

Brass LM reviewed and analyzed that the only estrogen replacement therapy in postmenopausal women is not effective for reducing the risk of a first or a recurrent stroke or death with established vascular disease. In contrast, there may be an increased risk of fatal stroke among those who took hormone replacement therapy (HRT) (44). Consistent with a meta-analysis on the association between hormone replacement therapy and subsequent stroke, the use of HRT would increase the risk of stroke, typically ischemic cerebrovascular events (45).

It is certain that we could say the HRT has mixed results. Different studies received different conclusions from subjective or objective reasons. Opposite results

from animal experiments or clinical trials, though, and even some scientists' attempts to put forward to give up the HRT (46, 47), the essence of HRT is clear and associated risks are yet to be warranted. Estrogen and progesterone might function alone or together in a cerebral vessel condition, any efforts to welcome or against their roles in vascular-associated events in the elderly be necessary to be weighed wisely.

EFFECT OF SEX HORMONE USE ON THE CHANGES IN NOCICEPTION IN PATIENTS WITH CEREBROVASCULAR RISKS

One of the intriguing phenomena is the potential relationship between sex hormone and nociception. The basic idea for this is the different nociceptive threshold and perception definitely exist between females and males (48, 49), which makes researchers suspect the probable contribution of sex hormone to the development of pain in this gender-related condition. Cumulating evidence indicated that sex hormones absolutely play roles in pain modulation through involving into various aspects of pain. Such kind of phenomenon becomes more common in postmenopausal women whom undergoing absolutely different impaction from sex hormonal in comparison to premenopausal women (50), though some studies did not find a conclusive association between sex hormonal factors and chronic widespread pain (51). However, some studies considered that sex hormone-related pain changes are strongly associated with the distinctive role of sex hormones in individuals who had psychological or psychiatric changes (52).

Another interesting fact is the linear relationship between sex hormone and cerebrovascular incidences (CVIs) with the aging of women (53), and that followed

by increased possibility of central neuropathic pain (54). Therefore, a strong contribution of sex hormone to this kind pain was suspected that sex hormone-induced alterations in neural plasticity makes these patients be much sensitive to CVIs and easier to develop neuropathic pain condition (55). Even it is still not confirmed by solid scientific evidence though, we still believe that in the context of CVIs, females are far easier to develop complex pain condition.

Under such kind conditions, we further suspect whether external HRT can benefit those under the influence of post menopause. It is too early giving a definite answer to this question because the external HRT itself has plenty of negative effects on the CVIs, and it is also absolutely different to the hormones produced by the body itself, which means we cannot get a definite answer so far about the mixed relationship between sex hormones and nociceptive perception in the context of CVIs.

CONCLUSIONS

There is also a need to better understand the role of hormones in cerebrovascular events. It is ironic that one way the HRT provides neuroprotective effects on menopausal women after or on stroke, but it also shows a problem in this context. Past successful knowledge should help to intelligently guide the future. No matter what results from the HRT, further exploration should be processed to clarify the exact role of hormones in cerebrovascular-risk factors for the elderly. Possible answers to this question may come by extending the research, where new roles for hormones in cerebrovascular diseases are prime for probation. ■

ARTICLE INFORMATION

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Author Contributions: Bao had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Drafting of the manuscript: Bao and Jiang.
Critical revision of the manuscript for important intellectual content: Bao, Li, Ma.
Statistical analysis: N/A.
Obtained funding: Bao.

Administrative, technical, or material support: Bao.
Study supervision: Bao.

Conflict of Interest Disclosures: The author declared no competing interests of this manuscript submitted for publication.

Acknowledgement: None.

Funding/Support: This work is supported by the National Natural Scientific Foundation of China (81560200).

Role of the Funder/Sponsor: The funding sponsor does not have any role in the conduction and publication of the work.

How to Cite This Paper: Bao S, Lei Y, Luo C; Song S, Yang F, Jiang Y, Li S, Ma J. Is sex hormone a risk factor of nociceptive hypersensitivity in the context of cerebrovascular diseases? *Sci Insig*. 2018; 2018:e000151.

Digital Object Identifier (DOI):

<http://dx.doi.org/10.15354/si.18.RE079>.

Article Submission Information: Received, July 8, 2018; Revised: August 26, 2018; Accepted: September 6, 2018. ■

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