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Nicotine Addiction Causes Unique Detrimental Effects on Women’s Brains

Ami P. Raval, PhD

ABSTRACT. Nicotine addiction produces diverse physiological effects common to both men and women because of activation of the nicotinic acetylcholine receptors. In addition to these effects, nicotine reduces circulating estrogen (the female sex hormone) levels and leads to early onset of menopause in women. Nicotine’s effect on estrogen metabolism has potential far-reaching consequences because endogenous circulating estrogen helps prevent cerebrovascular diseases in premenopausal women. In this article, the author presents a survey of literature showing that nicotine addiction causes unique deleterious effects in women’s brains by inhibiting estrogen signaling, which makes the brain more susceptible to ischemic brain damage.

KEYWORDS. Aromatase, birth control pills, cerebral ischemia, estrogen, estrogen receptors, stroke

INTRODUCTION

The increase in women’s smoking prevalence is a major public health concern in the United States. As per centers for disease control and prevention, currently 22 million (22%) women age 18 and older and approximately 1.5 million adolescent girls smoke cigarettes. The primary reason people consume tobacco products is because of nicotine addiction. Although the detrimental effects of smoking-derived nicotine on health are well-established, giving up a smoking habit is more difficult for women than for men. Some of the possible reasons for difficulty in quitting include women’s greater concern about weight gain after cessation, difficulty with negative mood, and a greater need for social support to stop smoking. The current perception among women who smoke is that tobacco-related cancers are their principal threat to health. However, according to statistics presented by American Heart Association, nearly twice as many women in the United States die of cardiovascular and cerebrovascular disease as from all forms of cancer, including breast cancer. In the current article, I briefly review gender differences in nicotine metabolism and the general deleterious effects of nicotine on health. The author then discusses the effects of nicotine addiction specific to women and the need to understand the consequences of nicotine addiction unique to women to treat or mitigate this epidemic.

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GENDER DIFFERENCES IN NICOTINE METABOLISM

Cigarette smoke is a complex chemical mixture containing 4,800 compounds. Nicotine is the major toxic and addictive agent in tobacco smoke responsible for the elevated risk of cardiovascular disease and sudden coronary death associated with smoking. In general, nicotine is rapidly absorbed by the lungs and distributed to body tissues during smoking. Nicotine plasma concentration in smokers ranges between 10 pM and 10 μM. Nicotine is quickly metabolized by the liver through a set of biochemical reactions that involve cytochrome p450 and aldehyde oxidase enzymes. Approximately 80% is converted to cotinine and the rest to a variety of other metabolites. Cotinine has a plasma half-life of 16 hours, much longer than that of nicotine (2 hours). Women’s hormones influence nicotine metabolism. Nicotine and cotinine metabolize faster in women than in men, and even faster in women taking oral contraceptives than in those who are not. The rate women metabolize nicotine influences smoking behavior, causing more dependence and increasing the associated risks.

PRONOUNCED DETRIMENTAL EFFECTS OF NICOTINE IN WOMEN AS COMPARED WITH MEN

Nicotine adversely affects cerebral blood flow and blood–brain barrier function, induces peripheral thrombus formation, and alters cerebrovascular endothelial cell function. Nicotine is also considered a procoagulant and proinflammatory because it induces massive leukocyte infiltration and up-regulates other proinflammatory factors. Nicotine is also known to modify lipid metabolism in animals at concentrations similar to those found in a smoker’s blood. In addition to these general deleterious effects of nicotine, in women nicotine addiction modulates estrogen metabolism, reduces circulating estrogen levels, disturbs normal periodicity of the menstrual cycle, and ultimately leads to early onset of menopause. However, whether this systemic effect of nicotine on circulating estrogen is the sole culprit or there are any direct effects of nicotine on brain estrogen signaling is not yet understood. Importantly, a synergistic detrimental effect exists between the use of oral contraceptives and those undergoing hormone replacement therapy (for post-menopausal women) and smoking/nicotine dependence on the risk of cardiovascular and cerebrovascular diseases, but the mechanism is unknown. In addition, an unanswered question in the field of nicotine addiction is where synergistic deleterious effects of nicotine plus extraovarian hormone are different from nicotine addiction.

INHIBITORY EFFECTS OF NICOTINE ON ESTROGEN BIOSYNTHESIS IN THE BRAIN

The brain is an important target for ovarian hormones and the site of estrogen synthesis in vertebrates. The brain also expresses several steroidogenic enzymes, including aromatase, which catalyzes the conversion of androgens into estrogens (Figure 1) and is the most crucial step in estrogen biosynthesis. The presence of aromatase in the hippocampus indicates the de novo synthesis of estradiol locally. Regarding cell types in the hippocampus, studies have demonstrated gender differences in the expression and activity of aromatase in astrocytes. It has been demonstrated that the astrocytes from women’s brains produce more estradiol than the astrocytes from men’s brains. These newly synthesized estrogens regulate estrogen receptors for consequent para/autocrine estrogen action in the hippocampus, maintain the hippocampal synapses, and modulate interneuronal communication by acting in a paracrine manner. It has been demonstrated that aromatase expression is induced after brain injury and is neuroprotective. The gender difference in availability of aromatase in astrocytes also reflects the resistance of women’s astrocytes
FIGURE 1. Aromatase enzyme converts testosterone to estradiol.

NICOTINE ADDICTION AND INCREASED POST-ISCHEMIC BRAIN DAMAGE IN WOMEN

To date, the presentation and outcome of several neuropathological conditions (e.g., Alzheimer’s disease, Huntington’s disease, multiple sclerosis, traumatic brain injury, autism, schizophrenia, mood disorders, and stroke, including cerebral ischemia) for which gender differences have been identified. Although gender differences of the brain might be based on genetic constitution, the role of sex hormones during development of neural tissue cannot be denied in observed gender differences in the neuropathological conditions. For example, female are less susceptible to post-ischemic brain damage in experimental models, rodent as well as in humans. This natural neuroprotection against ischemic injury is considered to be due to the effects of circulating ovarian hormones that are lost after ovariectomy or reproductive senescence. Exogenous administration of estrogen to ovariectomized (ovarian hormone deprivation) rats has been demonstrated to improve neuronal survival after ischemia, thus attributing a protective role to estrogen against ischemia.

In female rodents, the fluctuation in ovarian hormonal levels during the estrous cycle influences the response of brain to pathological insults. It has been demonstrated that the neurotoxic effect of kainic acid on hippocampal neurons in female rats is different depending on the day of the estrous cycle on which the neurotoxin was injected. This study demonstrated that the injection of neurotoxin on the morning of estrus (1 day after estradiol peak) resulted in no neuronal loss but significant loss in hilar neurons was noted when neurotoxin was given at the early proestrus, specifically before the peak of estradiol.

In this context, the author demonstrated that the higher serum levels of endogenous 17β-estradiol during the proestrus and estrus stages of the estrous cycle protected the brain against global cerebral ischemia in normally cycling female rats. Interestingly, neuroprotective effects of endogenous or exogenous
FIGURE 2. (A) Representative histological images in the hippocampal CA1 region 7 days after induction of cerebral ischemia: (a) cycling rat, (b) nicotine treated cycling rat, (c) ovariectomized, (d) nicotine treatment ovariectomized, (e) ovariectomized plus 17β-estradiol treated, and (f) nicotine exposed ovariectomized plus 17β-estradiol treated group. Arrow shows normal neurons (Scale bar = 20 μm). (B) Presence of normal neurons in the CA1 region (which includes the middle, medial, and lateral subregion) of rat hippocampus 7 days after induction of cerebral ischemia in different experimental groups. *p < 0.05 as against saline treated group. (Reproduced from Raval et al., 2009, Neuroscience letters, with permission from Elsevier).

Estrogen in nicotine-exposed female rats could not be reproduced (Figure 2). In this study, chronic nicotine exposure abrogated endogenous estrogen-conferred neuroprotection in the CA1 region of the hippocampus against cerebral ischemia in normally cycling female rats was demonstrated.76 Furthermore, the authors demonstrated that a bolus of 17β-estradiol to nicotine-exposed ovariectomized rats failed to rescue CA1 neurons following cerebral ischemia.76 These results clearly suggest that nicotine inhibited the beneficial effects of estrogen on cerebrovascular heath, the mechanism of which is not identified yet.

Estrogen is a multi-factorial agent spanning a broad spectrum of anti-oxidant,77–79 anti-excitatory,80–82 and anti-apoptotic mechanisms.83–85 Apart from direct genomic action, estrogen has been suggested to activate rapid intracellular signaling pathways that indirectly affect genomic activity via other transcription regulators such as cyclic adenosine monophosphate (cAMP) response element binding protein.86–88 These effects of
estrogen are triggered by secondary messenger calcium; calcium in turn activates numerous kinases like calcium–calmodulin-dependent protein kinase, protein kinase A, protein kinase c, mitogen-activated protein kinase, or phosphoinositide 3-kinase. Studies demonstrated that estrogen receptors facilitate L-type voltage-gated Ca\^{2+} channels in the hippocampal neurons. It has been demonstrated that 17β-estradiol rescues the hippocampal CA1 region from subsequent ischemic damage via Ca\^{2+} → mitogen-activated protein kinase and calcium–calmodulin-dependent protein kinase → cyclic-AMP response element binding protein activation. These rapid, diverse, non-genomic actions of estrogen are mediated via estrogen receptors.

The literature suggests there are four distinct receptors for estrogen: two ligand-activated receptors (ER-α and ER-β), one G protein-coupled estrogen receptor, and one putative receptor ER-X. In hippocampus, ER-β regulates estrogen-mediated cyclic-AMP response element binding protein phosphorylation. A recent study demonstrated that the reduced availability of ER-β following nicotine exposure subsequently decreased neuronal survival after cerebral ischemia in nicotine-treated normally cycling or estrogen-treated ovariectomized female rats compared with untreated groups (Figure 3). These studies showed that ER-β is a key mediator of beneficial effects of estrogen on neurovascular parenchyma and nicotine dependence resulted in loss of ER-β signaling. In support, Gustafsson, a pioneer in the area of estrogen receptor signaling, emphasized the role of ER-β as a target for candidate diseases and suggested to explore ER-β as a marker for clinical decision making and treatment. A recent study from Noppens et al. demonstrated that estradiol treatment after cardiac arrest and cardiopulmonary resuscitation was neuroprotective and mediated through ER-β. On the other hand, studies from other groups demonstrate that estradiol attenuates injury require ER-α-activation. Estrogen-mediated vascular protection after ischemia is achieved via ER-α, which increased vascular expression of angiopoietin-1 and stimulated angiogenesis in the brain. This contradiction suggests that both ligand-activated estrogen receptors (α and β) are crucial for neuronal survival and work via different
mechanisms that require in-depth investigation. Despite the presence of ER-β in cerebral arteries, information about the role of ER-β in the cerebral vasculature is limited.\textsuperscript{103,104} A previous study suggests a prominent role for ER-β in post-ischemic neuroprotection and not for ER-α,\textsuperscript{76} but a role for ER-α cannot be totally excluded, especially because ER-α is present in both the smooth muscle and endothelial cell layers of cerebral blood vessels.\textsuperscript{105–107}

Finally, most previous studies of the mechanisms of nicotine dependence were performed on male experimental animals and were focused on identifying effects of nicotine on its receptors. Here, the author presented a review of the literature on nicotine-related consequences unique to women. Therefore, a better understanding of the consequences of nicotine dependence is sorely required to develop alternative therapies based on women’s physiology to overcome deleterious effects of nicotine in women. Importantly, the sex-specific effects of nicotine on women’s brains discussed in this review emphasize a greater need to develop a sex-based pharmacological approach to overcome deleterious effects of nicotine addiction.

CONCLUSIONS

Under normal conditions, women suffer less ischemic brain damage than do men. This natural brain protection against ischemic injury in women is considered to be due to the effects of circulating ovarian hormones that are lost after either menopause or removal of the ovaries. The results of our research indicate that nicotine addiction makes female more susceptible to ischemic brain damage.\textsuperscript{76,97} More importantly, women taking oral contraception who are smokers increase their risk for cardiovascular and cerebrovascular events by 30-fold compared with women who are not smoking or using oral contraceptives.\textsuperscript{40,41} Therefore, it is critical to understand the effects of nicotine on hippocampal damage in women during their normal reproductive phase and while taking oral contraceptives or undergoing hormone-estrogen replacement therapy. Finally, smoking dependence poses unique and severe risks for nicotine-attributed chronic cerebrovascular diseases in women, and a better understanding of the consequences of nicotine addiction unique to women is sorely required to treat or mitigate this epidemic.

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