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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.[1] 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.[2,3] Some of the possible reasons for difficulty in quitting include womens' greater concern about weight gain after cessation, difficulty with negative mood, and a greater need for social support to stop smoking.[2,4,5] 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.[6] 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.[7–9] 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.[7,10,11] 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.[12,13] Nicotine is quickly metabolized by the liver through a set of biochemical reactions that involve cytochrome p450 and aldehyde oxidase enzymes.[12,14–16] Approximately 80% is converted to cotinine and the rest to a variety of other metabolites.[13] Cotinine has a plasma half-life of 16 hours, much longer than that of nicotine (2 hours). Women's hormones influence nicotine metabolism.[17] Nicotine and cotinine metabolize faster in women than in men, and even faster in women taking oral contraceptives than in those who are not.[12,17,18] The rate women metabolize nicotine influences smoking behavior, causing more dependence and increasing the associated risks.

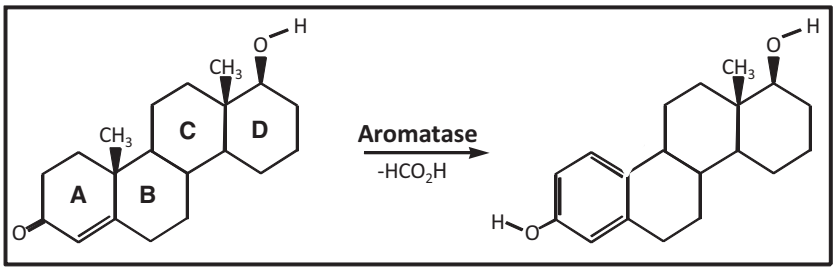
PRONOUNCED DETRIMENTAL EFFECTS OF NICOTINE IN WOMEN AS COMPARED WITH MEN

Nicotine adversely affects cerebral blood flow and blood–brain barrier function, induces peripheral thrombus formation, and alters cerebrovascular endothelial cell function.[19–25] Nicotine is also considered a procoagulant and proinflammatory because it induces massive leukocyte infiltration and up-regulates other proinflammatory factors.[26] Nicotine is also known to modify lipid metabolism in animals at concentrations similar to those found in a smoker's blood.[27] 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.[28–36] 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.[37–41] In addition, an unanswered question in the field of nicotine addiction is where synergistic deleterious effects of nicotine plus extra-ovarian 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.[42–44] 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.[43] The presence of aromatase in the hippocampus indicates the de novo synthesis of estradiol locally.[43] Regarding cell types in the hippocampus, studies have demonstrated gender differences in the expression and activity of aromatase in astrocytes.[45] It has been demonstrated that the astrocytes from women's brains produce more estradiol than the astrocytes from men's brains.[46,47] These newly synthesized estrogens regulate estrogen receptors for consequent para/autocrine estrogen action in the hippocampus,[48] maintain the hippocampal synapses,[49] and modulate interneuronal communication by acting in a paracrine manner.[48] It has been demonstrated that aromatase expression is induced after brain injury and is neuroprotective.[45,50,51] 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.



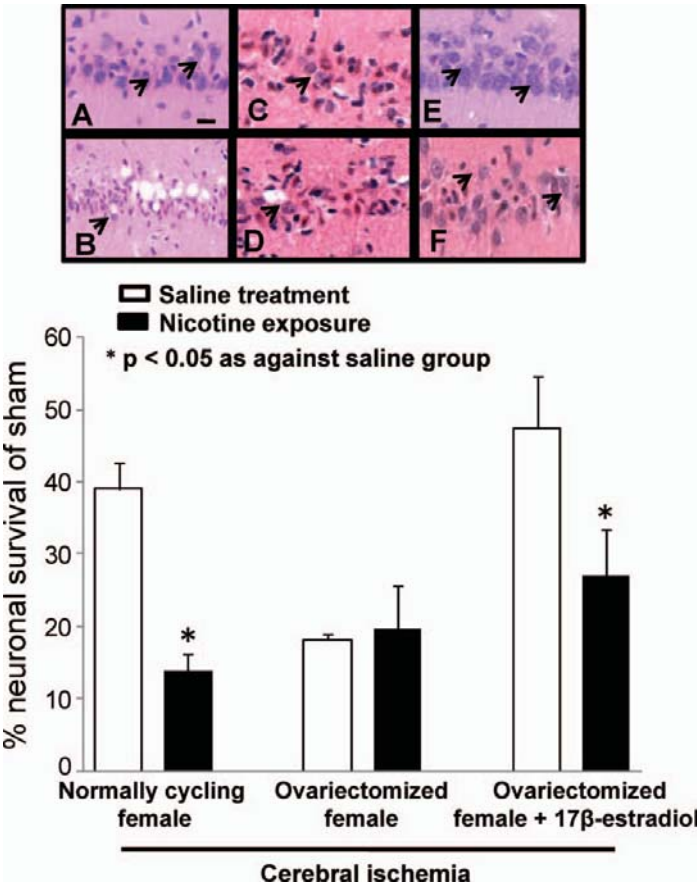
to oxygen-glucose deprivation.[46,47] Neuronal damage owing to mechanical or ischemic injury is enhanced in transgenic mice or after pharmacological inhibition of aromatase.[45,52] These findings underscore the fact that local de novo synthesis and release of estrogen regulate routine neuronal activities and are crucial for protection of neurons against stress.[53,54] Nicotine directly inhibits aromatase activity.[55] More definite evidence is presented by a recent study using positron emission tomography that demonstrated that nicotine directly interacts *in vivo* with primate brain aromatase in regions involved in mood, aggression, and sexual behavior.[56] Because brain aromatase is implicated in neuronal survival, cognition, mood, aggression, and sexual behavior,[57] its inhibition by nicotine reveals a novel additional mechanism through which nicotine and cigarette smoking can exert their effects on behavior and neurophysiology.[56]

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.[58,59] Although gender differences of the brain might be based on genetic constitution,[60–62] the role of sex hormones during development of neural tissue cannot be denied in observed gender differences in the neuropathological conditions.[63] For example, female are less susceptible to post-ischemic brain damage in experimental models, rodent as well as in humans.[64–67] 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.[66,68] 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.[69–73] In female rodents, the fluctuation in ovarian hormonal levels during the estrous cycle influences the response of brain to pathological insults.[58] 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.[74] 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.[74]

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.[75] Interestingly, neuroprotective effects of endogenous or exogenous

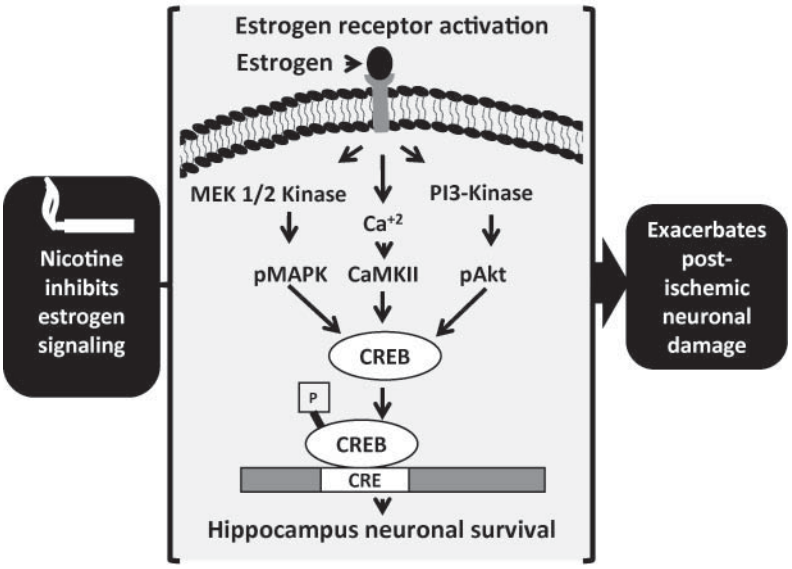
FIGURE 2. (A) Representative histological images in the hippocampal CA1 region 7 days after induction of cerebral ischemia: (a) cycling rat, (b) nicotine treated cycling rat, (c) ovariectomized, (d) nicotine treatment ovariectomized, (e) ovariectomized plus 17β-estradiol treated, and (f) nicotine exposed 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

FIGURE 3. Schematic diagrams depicting that the nicotine inhibits estrogen-signaling and exacerbates post-ischemic damage in women. It has been demonstrated that the estrogen mediated activation of cyclic-AMP response element binding protein occurs via calcium–calmodulin-dependent protein kinase, mitogen-activated protein kinase, and protein kinase B (Akt) pathways.[75,85]



estrogen are triggered by secondary messenger calcium;[89] 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.[88,90,91] Studies demonstrated that estrogen receptors facilitate L-type voltage-gated Ca^{2+} channels in the hippocampal neurons.[88,89] It has been demonstrated that 17β-estradiol rescues the hippocampal CA1 region from subsequent ischemic damage via $Ca^{+2} \rightarrow$ mitogen-activated protein kinase and calcium–calmodulin-dependent protein kinase $\rightarrow$ cyclic-AMP response element binding protein activation.[71,72,75,85,92] 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.[93–95] In hippocampus, ER-β regulates estrogen-mediated cyclic-AMP response element binding protein phosphorylation.[96] 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).[76,97] 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.[95] A recent study from Noppens et al. demonstrated that estradiol treatment after cardiac arrest and cardiopulmonary resuscitation was neuroprotective and mediated through ER-β.[98] On the other hand, studies from other groups demonstrate that estradiol attenuates injury require ER-α-activation.[72,99,100] Estrogen-mediated vascular protection after ischemia is achieved via ER-α, which increased vascular expression of angiopoietin-1 and stimulated angiogenesis in the brain.[101,102] 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.[103,104] A previous study suggests a prominent role for ER-β in post-ischemic neuroprotection and not for ER-α,[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.[105–107]

Finally, most previous studies of the mechanisms of nicotine dependence were performed on male experimental animals and were focused on identifing 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 the 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.[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.[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.

REFERENCES

1. Benowitz NL. Clinical pharmacology of nicotine. Ann Rev Med 1986; 37:21–32.

2. Osler M, Prescott E, Godtfredsen N, Hein HO, Schnohr P. Gender and determinants of smoking cessation: a longitudinal study. Prev Med 1999; 29:57–62.

3. Prescott E, Osler M, Andersen PK, Hein HO, Borch-Johnsen K, Lange P, Schnohr P, Vestbo J. Mortality in women and men in relation to smoking. Int J Epidemiol 1998; 27:27–32.

4. Orlandi MA. Gender differences in smoking cessation. Women Health 1986; 11:237–51.

5. Can G, Oztuna F, Topbas M. Complaints related to smoking cessation. Tuberk Toraks 2007; 55:364–9.

6. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, Carnethon MR, Dai S, de Simone G, Ford ES, Fox CS, Fullerton HJ, Gillespie C, Greenlund KJ, Hailpern SM, Heit JA, Ho PM, Howard VJ, Kissela BM, Kittner SJ, Lackland DT, Lichtman JH, Lisabeth LD, Makuc DM, Marcus GM, Marelli A, Matchar DB, McDermott MM, Meigs JB, Moy CS, Mozaffarian D, Mussolino ME, Nichol G, Paynter NP, Rosamond WD, Sorlie PD, Stafford RS, Turan TN, Turner MB, Wong ND, Wylie-Rosett J, Roger VL, Turner MB. Heart disease and stroke statistics–2011 update: a report from the American Heart Association. Circulation; 123(4):e18–e209.

7. Hoffmann D, Hoffmann I, El-Bayoumy K. The less harmful cigarette: a controversial issue. A tribute to Ernst L. Wynder. Chem Res Toxicol 2001; 14:767–90.

8. Rodgman A, Smith CJ, Perfetti TA. The composition of cigarette smoke: a retrospective, with emphasis on polycyclic components. Hum Exp Toxicol 2000; 19:573–95.

9. Borgerding M, Klus H. Analysis of complex mixtures: cigarette smoke. Exp Toxicol Pathol 2005; 57(Suppl 1):43–73.

10. Wang H, Shi H, Wang Z. Nicotine depresses the functions of multiple cardiac potassium channels. Life Sci 1999; 65:PL143–9.

11. Keeley EC, Pirwitz MJ, Landau C, Lange RA, Hillis LD, Foerster EH, Conrad K, Willard JE. Intranasal nicotine spray does not augment the adverse effects of cigarette smoking on myocardial oxygen demand or coronary arterial dimensions. Am J Med 1996; 101:357–63.

12. Hukkanen J, Jacob P 3rd, Benowitz NL. Metabolism and disposition kinetics of nicotine. Pharmacol Rev 2005; 57:79–115.

13. Gritz ER, Baer-Weiss V, Benowitz NL, Van Vunakis H, Jarvik ME. Plasma nicotine and cotinine concentrations

in habitual smokeless tobacco users. Clin Pharmacol Ther 1981; 30:201–9.

14. Cashman JR, Park SB, Yang ZC, Wrighton SA, Jacob P 3rd, Benowitz NL. Metabolism of nicotine by human liver microsomes: stereoselective formation of trans-nicotine n'-oxide. Chem Res Toxicol 1992; 5:639–46.

15. Mwenifumbo JC, Tyndale RF. Molecular genetics of nicotine metabolism. Handb Exp Pharmacol 2009:235–59.

16. von Weymarn LB, Brown KM, Murphy SE. Inactivation of cyp2a6 and cyp2a13 during nicotine metabolism. J Pharmacol Exp Ther 2006; 316:295–303.

17. Benowitz NL, Lessov-Schlaggar CN, Swan GE, Jacob P 3rd. Female sex and oral contraceptive use accelerate nicotine metabolism. Clin Pharmacol Ther 2006; 79:480–8.

18. Berlin I, Gasior MJ, Moolchan ET. Sex-based and hormonal contraception effects on the metabolism of nicotine among adolescent tobacco-dependent smokers. Nicotine Tob Res 2007; 9:493–8.

19. Abbruscato TJ, Lopez SP, Mark KS, Hawkins BT, Davis TP. Nicotine and cotinine modulate cerebral microvascular permeability and protein expression of zo-1 through nicotinic acetylcholine receptors expressed on brain endothelial cells. J Pharm Sci 2002; 91:2525–38.

20. Hawkins BT, Abbruscato TJ, Egleton RD, Brown RC, Huber JD, Campos CR, Davis TP. Nicotine increases in vivo blood-brain barrier permeability and alters cerebral microvascular tight junction protein distribution. Brain Res 2004; 1027:48–58.

21. Hioki H, Aoki N, Kawano K, Homori M, Hasumura Y, Yasumura T, Maki A, Yoshino H, Yanagisawa A, Ishikawa K. Acute effects of cigarette smoking on platelet-dependent thrombin generation. Eur Heart J 2001; 22:56–61.

22. Lilienberg G, Venge P. Platelet adhesion in patients prone to arterial and venous thrombosis: the impact of gender, smoking and heredity. Scand J Clin Lab Invest 1998; 58:279–86.

23. Lindenblatt N, Platz U, Hameister J, Klar E, Menger MD, Vollmar B. Distinct effects of acute and chronic nicotine application on microvascular thrombus formation and endothelial function in male and female mice. Langenbecks Arch Surg 2007; 392:285–295.

24. Powell JT. Vascular damage from smoking: disease mechanisms at the arterial wall. Vasc Med 1998; 3:21–8.

25. Rahman MM, Laher I. Structural and functional alteration of blood vessels caused by cigarette smoking: an overview of molecular mechanisms. Curr Vasc Pharmacol 2007; 5:276–92.

26. Ikonomidis I, Lekakis J, Vamvakou G, Andreotti F, Nihoyannopoulos P. Cigarette smoking is associated with increased circulating proinflammatory and procoagulant markers in patients with chronic coronary artery disease: effects of aspirin treatment. Am Heart J 2005; 149:832–9.

27. Booyse FM, Osikowicz G, Quarfoot AJ. Effects of chronic oral consumption of nicotine on the rabbit aortic endothelium. Am J Pathol 1981; 102:229–38.

28. Cassidenti DL, Vijod AG, Vijod MA, Stanczyk FZ, Lobo RA. Short-term effects of smoking on the pharmacokinetic profiles of micronized estradiol in postmenopausal women. Am J Obstet Gynecol 1990; 163:1953–60.

29. Cramer DW, Harlow BL, Xu H, Fraer C, Barbieri R. Cross-sectional and case-controlled analyses of the association between smoking and early menopause. Maturitas 1995; 22:79–87.

30. Damaj MI. Influence of gender and sex hormones on nicotine acute pharmacological effects in mice. J Pharmacol Exp Ther 2001; 296:132–40.

31. Grainge MJ, Coupland CA, Cliffe SJ, Chilvers CE, Hosking DJ. Cigarette smoking, alcohol and caffeine consumption, and bone mineral density in postmenopausal women: the Nottingham Epic Study Group. Osteoporos Int 1998; 8:355–63.

32. Greenberg G, Thompson SG, Meade TW. Relation between cigarette smoking and use of hormonal replacement therapy for menopausal symptoms. J Epidemiol Community Health 1987; 41:26–9.

33. Jensen J, Christiansen C, Rodbro P. Cigarette smoking, serum estrogens, and bone loss during hormone-replacement therapy early after menopause. N Engl J Med 1985; 313:973–5.

34. Michnovicz JJ, Naganuma H, Hershcopf RJ, Bradlow HL, Fishman J. Increased urinary catechol estrogen excretion in female smokers. Steroids 1988; 52:69–83.

35. Mueck AO, Seeger H. Smoking, estradiol metabolism and hormone replacement therapy. Curr Med Chem Cardiovasc Hematol Agents 2005; 3:45–54.

36. Windham GC, Elkin EP, Swan SH, Waller KO, Fenster L. Cigarette smoking and effects on menstrual function. Obstet Gynecol 1999; 93:59–65.

37. Baillargeon JP, McClish DK, Essah PA, Nestler JE. Association between the current use of low-dose oral contraceptives and cardiovascular arterial disease: a meta-analysis. J Clin Endocrinol Metab 2005; 90:3863–70.

38. Escobedo LG, Caspersen CJ. Risk factors for sudden coronary death in the United States. Epidemiology 1997; 8:175–180.

39. Goldstein LB, Adams R, Alberts MJ, Appel LJ, Brass LM, Bushnell CD, Culebras A, DeGraba TJ, Gorelick PB, Guyton JR, Hart RG, Howard G, Kelly-Hayes M, Nixon JV, Sacco RL. Primary prevention of ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council: cosponsored by the atherosclerotic peripheral vascular disease interdisciplinary working group; cardiovascular nursing council; clinical cardiology council; nutrition, physical activity, and metabolism council; and the quality of care and outcomes research interdisciplinary working group. Circulation 2006; 113:e873–923.

40. Tanis BC, van den Bosch MA, Kemmeren JM, Cats VM, Helmerhorst FM, Algra A, van der Graaf Y, Rosendaal

FR. Oral contraceptives and the risk of myocardial infarction. N Engl J Med 2001; 345:1787–93.

41. Girolami A, Tezza F, Allemand E, Girolami B. Arterial thrombosis and drospirenone-containing pill (yasmin): is the pill to be absolutely avoided by women who smoke? J Thromb Thrombolysis 2008; 26:163–4.

42. Roselli CE, Horton LE, Resko JA. Distribution and regulation of aromatase activity in the rat hypothalamus and limbic system. Endocrinology 1985; 117:2471–7.

43. Rune GM, Frotscher M. Neurosteroid synthesis in the hippocampus: role in synaptic plasticity. Neuroscience 2005; 136:833–42.

44. Ryan KJ, Naftolin F, Reddy V, Flores F, Petro Z. Estrogen formation in the brain. Am J Obstet Gynecol 1972; 114:454–60.

45. Azcoitia I, Sierra A, Veiga S, Garcia-Segura LM. Aromatase expression by reactive astroglia is neuroprotective. Ann N Y Acad Sci 2003; 1007:298–305.

46. Liu M, Oyarzabal EA, Yang R, Murphy SJ, Hurn PD. A novel method for assessing sex-specific and genotype-specific response to injury in astrocyte culture. J Neurosci Methods 2008; 171:214–7.

47. Liu M, Hurn PD, Roselli CE, Alkayed NJ. Role of p450 aromatase in sex-specific astrocytic cell death. J Cereb Blood Flow Metab 2007; 27:135–41.

48. Prange-Kiel J, Wehrenberg U, Jarry H, Rune GM. Para/autocrine regulation of estrogen receptors in hippocampal neurons. Hippocampus 2003; 13:226–34.

49. Hojo Y, Hattori TA, Enami T, Furukawa A, Suzuki K, Ishii HT, Mukai H, Morrison JH, Janssen WG, Kominami S, Harada N, Kimoto T, Kawato S. Adult male rat hippocampus synthesizes estradiol from pregnenolone by cytochromes p45017alpha and p450 aromatase localized in neurons. Proc Natl Acad Sci U S A 2004; 101:865–70.

50. Azcoitia I, Sierra A, Veiga S, Honda S, Harada N, Garcia-Segura LM. Brain aromatase is neuroprotective. J Neurobiol 2001; 47:318–29.

51. Garcia-Segura LM, Veiga S, Sierra A, Melcangi RC, Azcoitia I. Aromatase: a neuroprotective enzyme. Prog Neurobiol 2003; 71:31–41.

52. McCullough LD, Blizzard K, Simpson ER, Oz OK, Hurn PD. Aromatase cytochrome p450 and extragonadal estrogen play a role in ischemic neuroprotection. J Neurosci 2003; 23:8701–5.

53. Roselli CE, Liu M, Hurn PD. Brain aromatization: classic roles and new perspectives. Semin Reprod Med 2009; 27:207–17.

54. Saldanha CJ, Duncan KA, Walters BJ. Neuroprotective actions of brain aromatase. Front Neuroendocrinol 2009; 30:106–18.

55. Barbieri RL, Gochberg J, Ryan KJ. Nicotine, cotinine, and anabasine inhibit aromatase in human trophoblast in vitro. J Clin Invest 1986; 77:1727–33.

56. Biegon A, Kim SW, Logan J, Hooker JM, Muench L, Fowler JS. Nicotine blocks brain estrogen synthase (aromatase): in vivo positron emission tomography studies in female baboons. Biol Psychiatry 2010; 67:774–7.

57. Roselli CE, Resko JA. Cytochrome p450 aromatase (cyp19) in the non-human primate brain: distribution, regulation, and functional significance. J Steroid Biochem Mol Biol 2001; 79:247–53.

58. Cosimo Melcangi R, Garcia-Segura LM. Sex-specific therapeutic strategies based on neuroactive steroids: in search for innovative tools for neuroprotection. Horm Behav 2010; 57:2–11.

59. Gillies GE, McArthur S. Estrogen actions in the brain and the basis for differential action in men and women: a case for sex-specific medicines. Pharmacol Rev 2010; 62:155–98.

60. Dulac C. Brain function and chromatin plasticity. Nature 2010; 465:728–35.

61. Xu J, Watkins R, Arnold AP. Sexually dimorphic expression of the x-linked gene eif2s3x mrna but not protein in mouse brain. Gene Expr Patterns 2006; 6:146–55.

62. Reisert I, Pilgrim C. Sexual differentiation of monoaminergic neurons: genetic or epigenetic? Trends Neurosci 1991; 14:468–73.

63. Gagnidze K, Pfaff DW. Sex on the brain. Cell 2009; 139:19–21.

64. Bramlett HM. Sex differences and the effect of hormonal therapy on ischemic brain injury. Pathophysiology 2005; 12:17–27.

65. Roof RL, Hall ED. Gender differences in acute cns trauma and stroke: neuroprotective effects of estrogen and progesterone. J Neurotrauma 2000; 17:367–88.

66. Zhang YQ, Shi J, Rajakumar G, Day AL, Simpkins JW. Effects of gender and estradiol treatment on focal brain ischemia. Brain Res 1998; 784:321–4.

67. Li R, Shen Y. Estrogen and brain: synthesis, function and diseases. Front Biosci 2005; 10:257–67.

68. McCullough LD, Hurn PD. Estrogen and ischemic neuroprotection: an integrated view. Trends Endocrinol Metab 2003; 14:228–35.

69. Rusa R, Alkayed NJ, Crain BJ, Traystman RJ, Kimes AS, London ED, Klaus JA, Hurn PD. 17beta-estradiol reduces stroke injury in estrogen-deficient female animals. Stroke 1999; 30:1665–70.

70. Pelligrino DA, Santizo R, Baughman VL, Wang Q. Cerebral vasodilating capacity during forebrain ischemia: effects of chronic estrogen depletion and repletion and the role of neuronal nitric oxide synthase. Neuroreport 1998; 9:3285–91.

71. Jover T, Tanaka H, Calderone A, Oguro K, Bennett MV, Etgen AM, Zukin RS. Estrogen protects against global ischemia-induced neuronal death and prevents activation of apoptotic signaling cascades in the hippocampal ca1. J Neurosci 2002; 22:2115–24.

72. Lebesgue D, Chevaleyre V, Zukin RS, Etgen AM. Estradiol rescues neurons from global ischemia-induced cell death: multiple cellular pathways of neuroprotection. Steroids 2009; 74:555–61.

73. Lebesgue D, Traub M, De Butte-Smith M, Chen C, Zukin RS, Kelly MJ, Etgen AM. Acute administration of non-classical estrogen receptor agonists attenuates ischemia-induced hippocampal neuron loss in middle-aged female rats. PLoS One5:e8642.

74. Azcoitia I, Fernandez-Galaz C, Sierra A, Garcia-Segura LM. Gonadal hormones affect neuronal vulnerability to excitotoxin-induced degeneration. J Neurocytol 1999; 28:699–710.

75. Raval AP, Saul I, Dave KR, DeFazio RA, Perez-Pinzon MA, Bramlett H. Pretreatment with a single estradiol-17beta bolus activates cyclic-amp response element binding protein and protects ca1 neurons against global cerebral ischemia. Neuroscience 2009; 160:307–18.

76. Raval AP, Bhatt A, Saul I. Chronic nicotine exposure inhibits 17beta-estradiol-mediated protection of the hippocampal ca1 region against cerebral ischemia in female rats. Neurosci Lett 2009; 458:65–69.

77. Prokai L, Prokai-Tatrai K, Perjesi P, Zharikova AD, Perez EJ, Liu R, Simpkins JW. Quinol-based cyclic antioxidant mechanism in estrogen neuroprotection. Proc Natl Acad Sci U S A 2003; 100:11741–6.

78. Kumar S, Lata K, Mukhopadhyay S, Mukherjee TK. Role of estrogen receptors in pro-oxidative and anti-oxidative actions of estrogens: a perspective. Biochim Biophys Acta 2010; 1800(10): 1127–35.

79. Sribnick EA, Ray SK, Banik NL. Estrogen as a multi-active neuroprotective agent in traumatic injuries. Neurochem Res 2004; 29:2007–14.

80. Weaver CE Jr, Park-Chung M, Gibbs TT, Farb DH. 17beta-estradiol protects against nmda-induced excitotoxicity by direct inhibition of nmda receptors. Brain Res 1997; 761:338–41.

81. Wojtowicz T, Mozrzymas JW. Estradiol and gabaergic transmission in the hippocampus. Vitam Horm 82:279–300.

82. Ma XM, Huang JP, Kim EJ, Zhu Q, Kuchel GA, Mains RE, Eipper BA. Kalirin-7, an important component of excitatory synapses, is regulated by estradiol in hippocampal neurons. Hippocampus 2010 (in press).

83. Dubal DB, Shughrue PJ, Wilson ME, Merchenthaler I, Wise PM. Estradiol modulates bcl-2 in cerebral ischemia: a potential role for estrogen receptors. J Neurosci 1999; 19:6385–93.

84. Alkayed NJ, Goto S, Sugo N, Joh HD, Klaus J, Crain BJ, Bernard O, Traystman RJ, Hurn PD. Estrogen and bcl-2: gene induction and effect of transgene in experimental stroke. J Neurosci 2001; 21:7543–50.

85. Jover-Mengual T, Zukin RS, Etgen AM. Mapk signaling is critical to estradiol protection of ca1 neurons in global ischemia. Endocrinology 2007; 148:1131–43.

86. Wade CB, Dorsa DM. Estrogen activation of cyclic adenosine 5'-monophosphate response element-mediated transcription requires the extracellularly regulated kinase/mitogen-activated protein kinase pathway. Endocrinology 2003; 144:832–8.

87. Lee SJ, Campomanes CR, Sikat PT, Greenfield AT, Allen PB, McEwen BS. Estrogen induces phosphorylation of cyclic amp response element binding (pcreb) in primary hippocampal cells in a time-dependent manner. Neuroscience 2004; 124:549–60.

88. Wu TW, Wang JM, Chen S, Brinton RD. 17beta-estradiol induced ca2+ influx via l-type calcium channels activates the src/erk/cyclic-amp response element binding protein signal pathway and bcl-2 expression in rat hippocampal neurons: a potential initiation mechanism for estrogen-induced neuroprotection. Neuroscience 2005; 135:59–72.

89. Sarkar SN, Huang RQ, Logan SM, Yi KD, Dillon GH, Simpkins JW. Estrogens directly potentiate neuronal l-type ca2+ channels. Proc Natl Acad Sci U S A 2008; 105:15148–53.

90. Dolmetsch RE, Pajvani U, Fife K, Spotts JM, Greenberg ME. Signaling to the nucleus by an l-type calcium channel-calmodulin complex through the map kinase pathway. Science 2001; 294:333–9.

91. Vaillant AR, Mazzoni I, Tudan C, Boudreau M, Kaplan DR, Miller FD. Depolarization and neurotrophins converge on the phosphatidylinositol 3-kinase-akt pathway to synergistically regulate neuronal survival. J Cell Biol 1999; 146:955–66.

92. Raval AP, Bramlett H, Perez-Pinzon MA. Estrogen preconditioning protects the hippocampal ca1 against ischemia. Neuroscience 2006; 141:1721–30.

93. Toran-Allerand CD. Estrogen and the brain: beyond er-alpha and er-beta. Exp Gerontol 2004; 39:1579–86.

94. Heldring N, Pike A, Andersson S, Matthews J, Cheng G, Hartman J, Tujague M, Strom A, Treuter E, Warner M, Gustafsson JA. Estrogen receptors: how do they signal and what are their targets. Physiol Rev 2007; 87:905–31.

95. Zhao C, Dahlman-Wright K, Gustafsson JA. Estrogen receptor beta: an overview and update. Nucl Recept Signal 2008; 6:e003.

96. Liu F, Day M, Muniz LC, Bitran D, Arias R, Revilla-Sanchez R, Grauer S, Zhang G, Kelley C, Pulito V, Sung A, Mervis RF, Navarra R, Hirst WD, Reinhart PH, Marquis KL, Moss SJ, Pangalos MN, Brandon NJ. Activation of estrogen receptor-beta regulates hippocampal synaptic plasticity and improves memory. Nat Neurosci 2008; 11:334–43.

97. Raval AP, Hirsch N, Dave KR, Yavagal DR, Bramlett H, Saul I. Nicotine and estrogen synergistically exacerbate cerebral ischemic injury. Neuroscience 2011; In press.

98. Noppens RR, Kofler J, Grafe MR, Hurn PD, Traystman RJ. Estradiol after cardiac arrest and cardiopulmonary resuscitation is neuroprotective and mediated through estrogen receptor-beta. J Cereb Blood Flow Metab 2009; 29:277–86.

99. Zhang QG, Raz L, Wang R, Han D, De Sevilla L, Yang F, Vadlamudi RK, Brann DW. Estrogen attenuates ischemic oxidative damage via an estrogen receptor

alpha-mediated inhibition of nadph oxidase activation. J Neurosci 2009; 29:13823–36.

100. Dubal DB, Rau SW, Shughrue PJ, Zhu H, Yu J, Cashion AB, Suzuki S, Gerhold LM, Bottner MB, Dubal SB, Merchanthaler I, Kindy MS, Wise PM. Differential modulation of estrogen receptors (ers) in ischemic brain injury: a role for eralpha in estradiol-mediated protection against delayed cell death. Endocrinology 2006; 147:3076–84.

101. Ardelt AA, McCullough LD, Korach KS, Wang MM, Munzenmaier DH, Hurn PD. Estradiol regulates angiopoietin-1 mrna expression through estrogen receptor-alpha in a rodent experimental stroke model. Stroke 2005; 36:337–41.

102. Jesmin S, Hattori Y, Sakuma I, Liu MY, Mowa CN, Kitabatake A. Estrogen deprivation and replacement modulate cerebral capillary density with vascular expression of angiogenic molecules in middle-aged female rats. J Cereb Blood Flow Metab 2003; 23:181–9.

103. Krause DN, Duckles SP, Pelligrino DA. Influence of sex steroid hormones on cerebrovascular function. J Appl Physiol 2006; 101:1252–61.

104. Turtzo LC, McCullough LD. Sex differences in stroke. Cerebrovasc Dis 2008; 26:462–74.

105. Miller VM, Duckles SP. Vascular actions of estrogens: functional implications. Pharmacol Rev 2008; 60:210–41.

106. Guo J, Krause DN, Horne J, Weiss JH, Li X, Duckles SP. Estrogen-receptor-mediated protection of cerebral endothelial cell viability and mitochondrial function after ischemic insult in vitro. J Cereb Blood Flow Metab 2010; 30:545–54.

107. Bake S, Ma L, Sohrabji F. Estrogen receptor-alpha overexpression suppresses 17beta-estradiol-mediated vascular endothelial growth factor expression and activation of survival kinases. Endocrinology 2008; 149: 3881–9.