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Role of Progesterone in Nicotine Addiction: Evidence From Initiation to Relapse

Wendy J. Lynch and

Department of Psychiatry and Neurobehavioral Research, University of Virginia, Charlottesville, Virginia

Mehmet Sofuoglu

Department of Psychiatry and VA Connecticut Healthcare System, West Haven, Connecticut

Abstract

Nicotine addiction continues to be the main cause of preventable death in developed countries. Women and teen girls appear to be more vulnerable on certain aspects of nicotine addiction compared with men and boys. While the mechanism of gender differences in nicotine addiction is not yet clear, evidence suggests that while estrogen may underlie enhanced vulnerability in females, progesterone may protect females. Thus, progesterone may have therapeutic use for tobacco addiction, especially in female smokers. A greater understanding of the role of progesterone in nicotine addiction is important not only from a treatment standpoint, but also from a prevention standpoint: hormone transition phases, such as those that occur at adolescence, and during pregnancy and following birth, as well as following hormonal manipulation (e.g., using methods of hormonal birth control), may all contribute to changes in vulnerability to nicotine addiction. In this review, we summarize recent evidence from clinical and preclinical studies examining the role of progesterone in nicotine addiction focusing on its role during initiation of use and during later phases of the addiction process as a potential relapse prevention treatment. We conclude with future directions including further examination of progesterone as a potential intervention and treatment of nicotine addiction.

Keywords

progesterone; nicotine; tobacco; sex differences; translational research

Nicotine addiction continues to be the main cause of preventable death in developed countries, with an estimated 435,000 premature deaths in the United States and 5 million deaths worldwide. Although nicotine use has leveled off in recent years, some studies suggest that cigarette smoking is on the rise in young women and teen girls (Perkins, 2001). Females aged 12–17 are also more likely than males initiate smoking (SAMHSA, 2008), and they take less time to develop tobacco dependence symptoms after initial use (DiFranza et al., 2002; Ridenour, Lanza, Donny, & Clark, 2006; Thorner, Jaszyna-Gasior, Epstein, & Moolchan, 2007). Similar reports of enhanced vulnerability in females versus males have been reported among adult smokers. For example, among adults (18 years and over), although more men than women smoke, women take less time to become dependent after initial use, report shorter and less frequent abstinence periods (for review, see Pierce & Gilpin, 1996), and smoke for longer periods of time in their lives compared with men with

the median cessation age of 33 years for males versus 37 years for females (Cepeda-Benito, Reynoso, & Erath, 2004). Women also appear to respond less favorably to smoking cessation treatments (Cepeda-Benito et al., 2004; Scharf & Shiffman, 2004), despite maintaining their nicotine addiction with lower levels of nicotine intake than men (Battig, Buzzi, & Nil, 1982; Eissenberg, Adams, Riggins, & Likness, 1999; Hofer, Nil, Wyss, & Battig, 1992; Zeman, Hiraki, & Sellers, 2002). Consistent with these findings, in preclinical studies, adolescent and adult female rats showed faster acquisition of intravenous nicotine self-administration and higher break points on a progressive-ratio schedule compared with adolescent and adult males (Donny et al., 2000; Lynch, 2009). Similarly, female mice showed a greater preference for nicotine in a two-bottle choice task compared with male mice (Klein, Stine, Vandenberg, Whetzel, & Kamens, 2004; Meliska, Bartke, McGlacken, & Jensen, 1995), indicating greater sensitivity of females to nicotine's reinforcing effects. These studies point to important gender differences in initiation and maintenance of nicotine use that may contribute to smaller gains in curbing nicotine addiction in women.

The mechanisms of these gender differences in nicotine addiction are not clear and may include the influence of cyclic changes in levels of the gonadal hormones estradiol and progesterone across the menstrual cycle and at different hormone transition phases (i.e., adolescence, pregnancy, menopause). Both estradiol and progesterone have well-documented actions on brain functioning, including interactions with multiple neurotransmitter systems affecting the brain reward circuit (Jackson, Robinson, & Becker, 2006). Cumulative evidence from preclinical and clinical studies suggest that gonadal hormones, especially progesterone, may protect females during initiation and maintenance of tobacco addiction, and may have therapeutic use for tobacco addiction, especially in female smokers (Allen, Bade, Center, Finstad, & Hatsukami, 2008; Sofuoglu, Mitchell, & Mooney, 2009; Sofuoglu, Mouratidis, & Mooney, 2010). This is a particularly important question to address not only from a treatment standpoint, but also from a prevention standpoint: hormone transition phases, such as those that occur at adolescence, and during pregnancy and following birth, as well as following hormonal manipulation (e.g., using methods of hormonal birth control), may all contribute to changes in vulnerability to nicotine addiction. The aim of this paper is to summarize recent progress in our understanding of progesterone's contribution to nicotine addiction during both initial phases and as a potential relapse prevention treatment. To reach this goal, we will first review the physiological, pharmacological, and neurobiological functions of progesterone that are relevant for nicotine addiction. Next, we review the preclinical and clinical studies examining the role of progesterone in nicotine addiction. We conclude with future directions including the potential role of progesterone for the treatment of nicotine addiction.

Clinical Pharmacology of Progesterone

Progesterone is a steroid hormone synthesized in the ovaries, as well as in the adrenal glands. Cyclic changes in progesterone take place during the menstrual cycle, which is divided into four phases: menstruation, follicular, ovulatory, and luteal (Figure 1a). During the follicular phase, women have low progesterone levels that are comparable to those in men, less than 1 ng/ml (Pearson Murphy & Allison, 2000; Zumoff et al., 1990). Women have higher progesterone levels than men during the luteal phase of the menstrual cycle (2–28 ng/ml), and especially high levels during pregnancy (9–200 ng/ml; Chabbert Buffet, Djakoure, Maitre, & Bouchard, 1998). The high levels of progesterone and progesterone metabolites fall rapidly and dramatically within 2 weeks following childbirth (Cunningham et al., 2005). Progesterone levels are also low during adolescence, both before menarche, and for several years following its onset (Dohler & Wuttke, 1975).

Similarly, in rodents progesterone levels vary with estrous cycle phase and at different reproductive stages. The rat estrous phase is divided into four phases: diestrus, proestrus, estrus, and metestrus (Figure 1b). Progesterone levels are low during estrus, the time of sexual receptivity, and peak to their highest levels during proestrus with a secondary peak during the transition from metestrus to diestrus (Knobil & Neill, 2006). As in humans, in rodents progesterone levels are greatly elevated during pregnancy, showing a progressive increase throughout but then a rapid decline in the days preceding birth (Rosenblatt, Mayer, & Giordano, 1988). Progesterone levels are also low during early adolescence, but peak on the day of vaginal opening (a marker of puberty in the rodent) and further increase to adult levels over the next several days (Dohler & Wuttke, 1975).

Progesterone has been used for over 50 years in the treatment of various disorders including ovarian failure, premenstrual symptoms, amenorrhea, dysfunctional uterine bleeding, menopausal symptoms, and for contraception (de Lignieres, 1999). Progesterone is also under investigation for the treatment of seizure disorder, and traumatic brain injury (Herzog, 2008; Stein, 2008). Because it is poorly absorbed and has extensive first pass metabolism, several synthetic progesterone derivatives have been synthesized and marketed. However, these synthetic progesterone derivatives have additional androgenic, corticosteroid and anabolic effects and have been associated with unfavorable side effects including fluid retention, androgenic effects and alterations in lipid profile (Goodman, Gilman, Hardman, Gilman, & Limbird, 1996). Recently, micronized progesterone formulations that can be taken orally have been developed to overcome the poor absorption of progesterone and the unfavorable side effects of the synthetic progestogens (McAuley, Kroboth, & Kroboth, 1996; Simon, 1995). The safety, tolerability and efficacy of micronized progesterone have been demonstrated in multiple studies. Acute effects of micronized progesterone on physiological, performance, and subjective measures have been investigated over a wide dose range, from 200 to 2,000 mg/day in both women and men (Freeman, Rickels, Sondheim, & Polansky, 1995; Gron, Friess, Herpers, & Rupprecht, 1997; Schweizer, Case, Garcia-Espana, Greenblatt, & Rickels, 1995). Micronized progesterone provides a specific pharmacological tool to investigate the effects of this hormone, devoid of the additional pharmacological effects that synthetic progesterone derivatives have. After oral administration, 50% to 60% of micronized progesterone is absorbed, reaching peak plasma levels within two to three hours. The elimination half-life of progesterone is 3 to 4 hr, necessitating twice or three times daily dosing to achieve stable plasma (McAuley et al., 1996). Progesterone may potentially be used for short periods (i.e., 2 to 3 weeks), alone or in combination with other treatments. However, prolonged treatment with progesterone is likely to inhibit ovulation and disrupt menstrual cycle. Progesterone is metabolized by the liver to several steroids including pregnanediol, pregnanolone, allopregnanolone, pregnanediolone, 20 α -dihydroprogesterone, and 17-OH progesterone and is excreted mainly in the urine.

Progesterone as a Neurosteroid

In addition to its reproductive effects, progesterone and its active metabolites, allopregnanolone and pregnanolone regulate neuronal signaling. These effects are mediated by two different mechanisms: classic steroid (genomic) and neuroactive steroid (nongenomic) action. The classic steroid mechanism involves binding of progesterone to intracellular progesterone receptors, which then migrate to the nucleus and activate the promoter region of several different genes (Brinton et al., 2008). Because gene transcription is a slow process, these responses are slow, ranging from minutes to days. The nongenomic effects are mediated by membrane receptors and are typically faster, ranging from seconds to minutes, because genetic transcription is not involved. Steroid hormones with these nongenomic effects are called “neuroactive steroids.”

Progesterone and its metabolites interact with multiple neurotransmitter receptors including GABA_A, glycine, sigma1, kainate, serotonin3, and nicotinic cholinergic receptors (Cyr, Ghribi, & Di Paolo, 2000; Romieu, Martin-Fardon, Bowen, & Maurice, 2003; Smith, 1991; Smith, Shen, Gong, & Zhou, 2007). Perhaps, most relevant for nicotine addiction are interactions with GABA. Progesterone's active metabolites, pregnanolone and allopregnanolone, have positive modulatory effects on GABA_A receptors which enhance GABAergic transmission. GABA is the main inhibitory neurotransmitter in the brain and has significant influence on multiple central nervous system (CNS) function. The positive modulatory effects of progesterone metabolites on the GABA_A receptors have been proposed to attenuate drug reward. Notably, the effects of progesterone and its metabolites on GABAergic signaling vary with menstrual/estrous cycle phase and at hormone transition phases including during adolescence and during pregnancy. For example, during puberty, allopregnanolone's effects on GABAergic transmission are opposite to those seen before and after puberty with results showing a reduction in GABAergic transmission (Smith, Aoki, & Shen, 2009). The expression of GABA-A receptors at extrasynaptic sites also varies markedly at the onset of puberty in female mice and changes in the $\alpha 4\beta 8$ GABA receptors are thought to underlie the increased responsiveness to stress reported during adolescence (Smith et al., 2009).

Progesterone also affects signaling at nicotinic receptors. Specifically, both progesterone and allopregnanolone are negative modulators of the $\alpha 4\beta 2$ nicotinic receptors (Bertrand, Valera, Bertrand, Ballivet, & Rungger, 1991; Bullock et al., 1997; Dar & Zinder, 1997; Valera, Ballivet, & Bertrand, 1992). Progesterone has also been reported to increase mRNA expression of $\alpha 5$ nicotinic receptors (Gangitano, Salas, Teng, Perez, & De Biasi, 2009). Blockage of nicotinic receptors is shared by several smoking cessation medications including varenicline and bupropion and may contribute to progesterone's proposed therapeutic role for nicotine addiction (Fant, Buchhalter, Buchman, & Henningfield, 2009; Henningfield, Shiffman, Ferguson, & Gritz, 2009). Although less is known regarding the effects of progesterone on nicotinic signaling at hormone transition phases, results from one study indicate that there are estrous cycle phase differences in progesterone's modulation of $\alpha 5$ nicotinic receptors that may influence anxiety-related behavior (Gangitano et al., 2009).

In addition to these mechanisms, progesterone also facilitates synaptic plasticity through its effects on intracellular signaling, synaptic proteins, and spine density in the hippocampus (Choi et al., 2003; Nilsen & Brinton, 2003; Woolley & McEwen, 1993). These synaptic effects may possibly contribute to the cognitive functions mediated by progesterone.

Neurobiological Functions of Progesterone

Progesterone and its active metabolites modulate many CNS functions including memory, learning, sensory and attentional processes, stress response, mood, motivation, reward, pain, neuronal injury (Frye, 2007; Solis-Ortiz & Corsi-Cabrera, 2008; Stein, 2008). In this review, we will focus on the functions of progesterone that are most relevant for nicotine addiction including reward and cognitive function. It is important to note that nicotine, like other drugs of abuse, can also modulate neuroendocrine systems and impact levels of ovarian hormones, including progesterone. These actions have been the focus of several excellent reviews (Mello, 2010; Mello & Mendelson, 1997; Mello, Mendelson, & Teoh, 1989).

Reward

Preclinical and clinical studies have shown that progesterone modulates the reward system and responses to stimulant drugs. The majority of the preclinical work in this area has been conducted with cocaine with results showing that progesterone, and its active metabolite allopregnanolone, attenuates the rewarding effects of drugs of abuse (for reviews, see Anker

& Carroll, 2010; Carroll & Anker, 2010). Animal studies have mainly focused on the ratio of estradiol to progesterone as a predictor of sensitivity to drug reward with results generally showing that when levels of estradiol are high and relatively unopposed by progesterone (i.e., during adolescence and during estrus; Knobil & Neill, 2006; Dohler & Wuttke, 1975) drug reward is heightened. For example, adolescent females acquire cocaine self-administration faster and show a greater level of motivation to obtain cocaine compared with adolescent males (Lynch, 2008). Although little information is available on the effect of estrus cycle phase on speed of acquisition, studies have shown that vulnerability during later phases of the addiction process are increased in estrus females compared with females in other phases of their estrous cycle. For example, estrus females show a greater level of motivation to obtain cocaine (Roberts, Bennett, & Vickers, 1989), as well as subsequent reinstatement of cocaine-seeking behavior (Feltenstein & See, 2007; Kerstetter & Kantak, 2007) compared with females in other phases of the estrous cycle. Estrus is also characterized as a time when levels of progesterone have just dropped from peak levels and are at a low level (see Figure 1; also see Feltenstein & See, 2007), and more recent studies have examined the potential for progesterone to both counter the reward enhancing effects of estradiol (Anker & Carroll, 2010; Carroll & Anker, 2010) and, as predicted by human studies, to serve as a potential treatment. In order to examine these questions, progesterone is administered to ovariectomized (OVX) females with and without estradiol treatment and to intact animals, respectively. Results show that progesterone, when coadministered with estradiol in OVX females, attenuates acquisition of cocaine self-administration (Jackson et al., 2006) as well as subsequent cocaine-seeking behavior (Anker, Larson, Gliddon, & Carroll, 2007) compared with OVX rats with estradiol only. Progesterone administration alone also appears to reduce the reinforcing effects of drugs of abuse with evidence showing that OVX rats treated with progesterone only show an attenuated preference for a cocaine-associated environment compared with OVX females receiving vehicle (Russo et al., 2003). Progesterone treatment in intact females has been shown to attenuate cocaine self-administration under both short (i.e., 1–2-hr access/day; (Larson, Anker, Gliddon, Fons, & Carroll, 2007) and extended access conditions (6-hr access/day; (Larson et al., 2007), and to reduce subsequent cocaine-seeking behavior (Feltenstein, Byrd, Henderson, & See, 2009). Similar effects have recently been reported following treatment with allopregnanolone for both cocaine self-administration and for subsequent cocaine-seeking behavior (Anker & Carroll, 2010; Anker, Holtz, Zlebnik, & Carroll, 2009; Anker et al., 2007; Carroll & Anker, 2010). Further support for the idea that progesterone protects females is provided by results showing that during pregnancy, wherein progesterone levels progressively increase until a few days preceding birth, rats show a progressive decline in motivation for cocaine which rebounds in the few days preceding birth (Hecht, Spear, & Spear, 1999).

Similar findings have been observed in humans supporting an inhibitory effect of progesterone on the reward pathways. For example, in the midfollicular phase of the human menstrual cycle (when progesterone is low and estrogen is high), compared with the progesterone dominant luteal phase, the reward circuitry (midbrain, striatum and left frontopolar cortex) is more highly activated (Dreher et al., 2007). In two studies, female cocaine users who were in the luteal phase of their menstrual cycle showed attenuated responses to the subjective effects of cocaine, compared with those who were in the follicular phase of their menstrual cycle or with men (Evans, Haney, & Foltin, 2002; Sofuoglu et al., 1999). Because the luteal phase of the menstrual cycle is associated with higher progesterone levels, progesterone may contribute to the attenuation of cocaine's subjective effects during the luteal phase. To test this hypothesis, we first investigated the direct effects of progesterone on cocaine responses in two human laboratory studies (Sofuoglu, Babb, & Hatsukami, 2002; Sofuoglu, Mitchell, & Kosten, 2004). In our 2004 study, progesterone treatment, in comparison to placebo, attenuated the rating of a cocaine-induced high in male and female cocaine users (Sofuoglu et al., 2004). A subsequent study systematically

examined progesterone and cocaine interactions in both male and female cocaine users (Evans & Foltin, 2006). In that study, progesterone treatment attenuated the positive subjective effects of cocaine but only in female cocaine users. These results indicate that progesterone may attenuate the rewarding effects of stimulant drugs. Progesterone is currently being examined as a treatment for cocaine addiction in several human laboratory studies, as well as in three different clinical trials (see clinicaltrials.gov; NCT00632099, NCT00585520, and NCT00535002).

Cognitive Function

Results from preclinical studies indicate that cognitive functioning varies at different hormone transition phases and following treatment with progesterone. Female rats in natural states associated with higher progesterone/estradiol levels (during proestrus and pregnancy; Knobil & Neill, 2006; Rosenblatt et al., 1988) perform better on object placement and recognition tasks compared with female rats in natural states associated with low progesterone/estradiol levels (during diestrus; Knobil & Neill, 2006). Cognitive strategies also appear to be regulated by circulating levels of ovarian hormones with recent findings showing that during proestrus (when progesterone and estradiol levels are high) rats were more likely to use place strategies, whereas, during estrus, rats were biased toward response strategies (Frye & Walf, 2008a). Progesterone treatment in aged male and female ovariectomized mice has been reported to enhance learning and memory in hippocampal and prefrontal cortex-based tasks (Frye & Walf, 2008b). Progesterone's cognitive enhancing effects were selective for the task and dependent on the timing of injection in relation to the tasks. In a more recent study, progesterone enhanced object recognition, but not performance on a spatial recognition task in female mice (Harburger, Pechenino, Saadi, & Frick, 2008).

In contrast, progesterone's effects on cognitive functioning have been less consistent in humans. In normally cycling women, selective cognitive functions including verbal memory, attention, and visual memory were enhanced during the luteal phase of the menstrual cycle and performance in these functions were positively correlated with endogenous progesterone levels (Phillips & Sherwin, 1992; Solis-Ortiz & Corsi-Cabrera, 2008). In a recent study, women who were in the luteal phase had greater inhibitory control (assessed with the stop-signal test) than women who were in the follicular phase of their menstrual cycle (Colzato, Hertsig, van den Wildenberg, & Hommel, 2010). These findings suggest modulation of multiple cognitive functions with gonadal hormones. However, when administered directly, progesterone did not affect or reduced cognitive performance in healthy males (Gron et al., 1997), normally cycling females (van Wingen et al., 2007) or postmenopausal females (Schussler et al., 2008). Moreover, the Women's Health Initiative reported little or no benefit of estradiol plus progestins (medroxyprogesterone acetate) on global cognitive function and memory function in postmenopausal women (Rapp et al., 2003; Resnick et al., 2006). These findings clearly raise further questions regarding the specific effects of progesterone on cognitive function and how these effects are moderated by variables such as age, baseline cognitive functioning, concomitant estradiol treatment and type of progestin (progesterone vs. medroxyprogesterone; Henderson, 2008; Maki, 2005; Pazol, Northcutt, Patisaul, Wallen, & Wilson, 2009).

Progesterone and Nicotine Addiction

Preclinical Studies

Although few studies have examined the role of progesterone using animal models of nicotine addiction, the results from three studies suggests that it plays an important role in nicotine reward. For example, preliminary data in nonhuman primates show that

progesterone treatment decreases nicotine self-administration under a progressive-ratio schedule (Mello, 2010). While the gender and hormonal state of the animals was not specified, these data indicate that progesterone can decrease nicotine's reinforcing effects. We recently examined the influence of gender, estrous cycle phase, and levels of progesterone on acquisition and subsequent motivation to obtain nicotine in male and female rats (as measured under a progressive ratio schedule; Lynch, 2009). Rats were tested during adolescence (from postnatal Day 30 to 45) because this developmental period is associated with not only an apparent vulnerability to nicotine use initiation, but also because it is a hormone transition period characterized by rapid and marked changes in levels of gonadal hormones. Consistent with previous work in adults we found that a greater percent of adolescent females acquired nicotine self-administration compared with adolescent males. Of interest, a gender difference in motivation for nicotine, though not initially apparent, emerged at the end of adolescent testing period suggesting that this difference may result from changes in ovarian hormones. Consistent with this idea, we also observed the highest level of motivation for nicotine during estrus and a negative association of progesterone and motivation for nicotine. Notably, among adult females, although motivation for nicotine is higher in females compared with males, it does not appear to vary across the estrous cycle (Donny et al., 2000). These findings suggest that hormonal regulation of nicotine's reinforcing effects may be more salient during hormone transition phases, and recent work with pregnant rats further supports this idea. Specifically, Lesage, Keyler, Burroughs, and Pentel (2007) reported that nicotine self-administration under extended access conditions (23-hr access/day) was decreased in pregnant rats compared with nonpregnant rats, particularly during the third trimester, and remained decreased for the first week or two of lactation. As mentioned previously, progesterone levels are markedly higher during pregnancy compared with during nonpregnancy, and although they show a decrease in the days preceding birth, they peak again to high levels during the first few days of lactation and remain elevated for several more days (Pepe & Rothchild, 1974; Rosenblatt, Mayer, & Giordano, 1988). Together these findings suggest that females have an increased biological vulnerability to nicotine's reinforcing effects compared with males and that progesterone may counter this enhanced vulnerability, perhaps particularly during adolescence and pregnancy. It is not yet known whether the reinforcing effects of nicotine and susceptibility to nicotine addiction vary during other hormone transition phases (menopause) or if vulnerability can be modulated following treatment with progesterone in normally cycling females and in females at different hormone transition phases.

Clinical Studies

Menstrual cycle phase and tobacco addiction—The influence that naturally fluctuating levels of estrogen and progesterone across the menstrual cycle may have on smoking and relapse to smoking has been the focus of a number of studies (Allen, Mooney, Chakraborty, & Allen, 2009; Allen et al., 2008; Carpenter, Upadhyaya, LaRowe, Saladin, & Brady, 2006; Carpenter, Saladin, Leinbach, Larowe, & Upadhyaya, 2008; Franklin et al., 2008; Franklin et al., 2004). Female smokers showed increased smoking behavior around menses and during the luteal phase in some (DeBon, Klesges, & Klesges, 1995; Mello, Mendelson, & Palmieri, 1987; Pomerleau, Garcia, Pomerleau, & Cameron, 1992; Snively, Ahijevych, Bernhard, & Mary Ellen, 2000; Steinberg & Cherek, 1989) but not in other studies (Allen, Hatsukami, Christianson, & Nelson, 1996; Pomerleau, Teuscher, Goeters, & Pomerleau, 1994). Similarly, the effect of menstrual cycle phase on tobacco withdrawal symptoms has not been consistent. A number of studies have reported an increased intensity of tobacco withdrawal symptoms during the late luteal phase (4–5 days before menses; Allen, Hatsukami, Christianson, & Brown, 2000; DeBon et al., 1995; O'Hara, Portser, & Anderson, 1989; Pomerleau et al., 1992; Sofuoglu, Babb, & Hatsukami, 2001b), although other studies found no effect of menstrual cycle phase on tobacco withdrawal severity

(Allen, Hatsukami, Christianson, & Nelson, 1999; Pomerleau, Cole, Lumley, Marks, & Pomerleau, 1994). The main limitation of these studies is the use of various and sometimes imprecise terms and methods to determine the phases of the menstrual cycle. However, a very intriguing and methodologically rigorous study that stands out in the literature is one that prospectively investigated the effect of premenstrual symptoms and menstrual cycle phase on risk of relapse in over 200 women (Allen et al., 2008). Phase of the menstrual cycle was determined by progesterone, estradiol, and luteinizing hormone (LH) levels. Results showed that women who were randomly assigned to quit in the follicular phase of their menstrual cycle relapsed faster to smoking than those who quit during the luteal phase (odds ratio at 14 days point prevalence = 2.87, 95% confidence interval [CI] = 1.47–5.59; Allen et al., 2008). The majority of relapses occurred during the initial 3–5 days after quitting but despite this, the effect was robust and at 30 days the odds ratio of remaining abstinent for the luteal phase group was 3.18 (95% CI = 1.59–6.33). These findings suggest that women have more favorable outcome if they quit smoking during the luteal phase (Allen et al., 2008). What is not clear is whether similar findings would be observed if medications are used for smoking cessation. One retrospective study found that women who were using nicotine replacement had better outcomes if they made a quit attempt during the follicular phase of the menstrual cycle than those who made an attempt during the luteal phase (Franklin et al., 2008). Further studies are warranted to determine the influence of menstrual cycle phase/hormonal status on treatment outcomes using currently available pharmacotherapies (Franklin & Allen, 2009).

Although sparse, available data also suggests that factors related to smoking vulnerability vary at other hormone transition phases. For example, rates of smoking during pregnancy are much lower than those observed among similarly aged women who are not pregnant (aged 15 to 44, 16.4% vs. 27.3%; National Survey on Drug Use and Health NSDUH) with evidence to suggest that about one half of pregnant women who reported preconceptional smoking quit before or during pregnancy (Tong, England, Dietz, & Asare, 2008). Unfortunately ~50% who achieve abstinence relapse within 2 weeks, and 70% to 80% resume smoking within a year of childbirth (Colman & Joyce, 2003; Ko & Schulken, 1998; Mullen, Richardson, Quinn, & Ershoff, 1997), designating pregnancy as a period of “suspended smoking” (DiClemente, Dolan-Mullen, & Windsor, 2000). As discussed previously, progesterone reaches a very high level during pregnancy. Following childbirth, there is a significant drop in progesterone levels that coincides with relapse to smoking. In addition, the results from one study showed that the rate of nicotine metabolism, which is associated with smoking more cigarettes or smoking more intensively, is higher in women compared with men and particularly accelerated in women using oral contraceptives (possibly as a result of the increased ratio of estrogen/progesterone; Benowitz, Lessov-Schlaggar, Swan, & Jacob, 2006). Although the contribution of progesterone cannot be directly assessed in these previous studies, the results from studies administering progesterone alone (as detailed below) suggest that progesterone, at least in part, underlies the reduced vulnerability seen in women during pregnancy and not taking estrogen-based oral contraceptives.

Progesterone administration—To evaluate the potential use of progesterone in nicotine addiction, we have conducted three double-blind, placebo-controlled studies administering progesterone to smokers. In these studies, experimental procedures in women were carried out in during the early follicular phase of the menstrual cycle, which defined as the first 7 days after the onset of menses. The early follicular phase is characterized by low and stable levels of endogenous estradiol (<300 pmol/L) and progesterone (<2 nmol/L). Consequently, this timing minimizes the interaction between the endogenous sex hormones and progesterone treatment (Chabbert Buffet et al., 1998). In addition, disruption of the menstrual cycle or withdrawal bleeding is less likely to occur because endogenous estradiol

levels are minimal. In our first study (Sofuoglu, Babb, & Hatsukami, 2001a), we examined the effects of 200 mg oral progesterone treatment, compared with placebo, on smoking behavior in 12 female smokers, who were in the early follicular phase of their menstrual cycle. Following overnight abstinence from smoking, women received either progesterone or placebo in two experimental sessions. Progesterone, compared with placebo, attenuated craving for and the subjective effects from smoking. Under progesterone treatment, there was a trend for decreased smoking behavior even though the modest sample size could not adequately test this. These findings were replicated and extended our earlier findings in a recent study, in which 30 female and 34 male smokers were randomly assigned to either 200 or 400 mg/day of progesterone or placebo, given in two separate doses (Sofuoglu et al., in press). Smokers abstained from smoking for the first 3 days of the treatment period. Progesterone treatment, 400 mg/day, reduced urges to smoke in both male and female abstinent smokers. Although 200 mg/day of progesterone treatment improved cognitive performance in the Digit Symbol Substitution Test in both male and female abstinent smokers, only females showed improvement in the Stroop task performance. These findings suggested that progesterone may reduce urges to smoke and improve cognitive function in abstinent smokers.

In our third study, we examined the effects of progesterone, on acute physiological and subjective responses to pure nicotine administered via intravenous (IV) route (Sofuoglu, Mitchell, Mooney, et al., 2009). Twelve smokers, six males and six females, participated in two experimental sessions, where they were treated orally with a single dose of either 200 mg progesterone or placebo. Progesterone treatment, compared with placebo, enhanced the ratings of “bad effects,” from IV nicotine and attenuated the rating of “drug liking.” Progesterone also enhanced suppression of smoking urges by nicotine as assessed by the Brief Questionnaire on Smoking Urges (BQSU) further supporting the notion that progesterone may be useful as a treatment for nicotine addiction. The studies summarized above point to several treatment implications for progesterone in women trying to quit smoking (Table 1).

Future Research

Much more work is needed to examine the role of progesterone in initiation of smoking and as a potential treatment. Some potential directions are suggested below for both phases.

Role of Progesterone in Initiation to Smoking

Although sparse, the available data on the effects of progesterone on initiation of smoking suggests that it may reduce vulnerability to nicotine use initiation. More work is needed to: (1) determine the exact role of progesterone and estradiol in the development of nicotine addiction, (2) determine whether the roles of progesterone and estradiol in vulnerability to nicotine addiction change across the life span (i.e., during adolescence, during the transition from adolescence to adulthood, during pregnancy and postdelivery, and at menopause), and in females taking hormone supplements, (3) to understand the underlying neurobiology for progesterone’s protective effects on vulnerability to smoking (i.e., interactions with GABA and nicotinic receptors), particularly during adolescence and pregnancy, and (4) identify possible pharmacological interventions, including the use of progesterone alone or in combination with another medication, that may reduce vulnerability to nicotine addiction. These questions are important to address given that adolescents that begin smoking today are likely to continue smoking for many years, particularly females.

Progesterone as a Treatment for Tobacco Addiction

Progesterone may have therapeutic utility for smoking cessation in women. More work is needed to: (1) determine whether progesterone's efficacy at reducing cigarette craving and smoking behavior in the human laboratory translates to the "real-world," (2) determine whether its efficacy varies across the life span (i.e., is it useful during adolescence, during pregnancy, in postmenopausal women?), and (3) what is the underlying mechanism's for progesterone's efficacy? To address these questions, systematic future studies are needed. Clinical research studies in this area have many challenges including the difficulty of conducting the study during a certain phase of the menstrual cycle. In addition, women of reproductive age have multiple commitments and participation in a research study with a demanding schedule may not be an easy task. Nevertheless, clinical research in this area is crucial to develop more effective treatments for nicotine addiction that will tailor to the needs of women.

Summary and Conclusions

Although little information is available on the effect of progesterone on acquisition of nicotine use, the preliminary results summarized for nicotine in combination with findings from other drugs of abuse suggest that it may have potential utility. Results from other drugs of abuse reveal that initiation of drug use is slower and subsequent motivation for drug is lower in females assessed during high progesterone states (during pregnancy and in OVX and intact rats treated with progesterone) compared with during low progesterone states. Preclinical findings show that females are more sensitive to the reinforcing effects of nicotine with preliminary evidence to suggest that progesterone can attenuate sensitivity in females. During adolescence motivation for nicotine increases over time and is positively associated with progesterone levels. These findings were observed during adolescence, but not during adulthood, suggesting that hormone transition phases may be a particularly sensitive periods for hormone-drug interactions, an idea further supported by work in pregnant rats.

Although more work is needed to address its potential utility at hormone transition phases, the available data suggests that progesterone may facilitate smoking cessation in normally cycling women. Its efficacy in improving cognitive performance in both animals and human, its ability to attenuate smoking urges in abstinent smokers as well as its efficacy in attenuating subjective effects from smoking and nicotine point to potential therapeutic value for smoking cessation. Smokers trying to quit experience reduced cognitive function and improvement of cognitive function has been proposed as one of the treatment targets for more effective smoking cessation pharmacotherapies. Furthermore, the first few cigarette puffs following abstinence is regarded to be highly rewarding and linked to relapse in smokers trying to quit (Brandon, Tiffany, Obremski, & Baker, 1990; Kenford et al., 1994). Attenuation of the subjective effects of the first cigarette with progesterone supports its potential use in preventing relapse in abstinent smokers. Of importance, the cognitive-enhancing effects of progesterone were much more prominent in female smokers than males, supporting its potential use as a treatment agent for smoking cessation in women.

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Figure 1.

(a) Changes in levels of progesterone and estradiol across the human menstrual cycle. A. was adapted from *Cocaine's effects on neuroendocrine systems: clinical and preclinical studies*, by N. K. Mello and J. H. Mendelson (1997). *Pharmacology, Biochemistry & Behavior*, 57(3), 571–599. (b) Changes in levels of progesterone and estradiol across the different phases of the rat estrous cycle. B. was adapted from *The neuroendocrine control of the ovarian cycle of the rat*, by M. E. Freeman (1994). In: E. Knobil and J. D. Neill (Eds.) *The physiology of reproduction*, 2nd ed. Raven Press, New York, pp. 613–658.

Table 1
Summary of the Clinical Findings for the Effects of Progesterone on Measures of Smoking

Subjects	Study type	Treatment	Results	Authors
Female smokers ($N = 12$)	Double-blind, placebo-controlled, crossover study	PRO 200 mg vs. PLA	PRO 200 mg attenuated craving for cigarettes in overnight abstinent smokers	Sofuoglu et al., 2001
Female ($N = 30$) and male smokers ($N = 34$)	Double-blind, placebo-controlled study	PRO 200 or 400 mg/day or PLA for 4 days	PRO 400 mg/day reduced craving for cigarettes, PRO 200 mg/day improved cognitive performance in the Stroop and DSST in abstinent smokers	Sofuoglu et al., 2010
Female ($N = 6$) and male smokers ($N = 6$)	Double-blind, placebo-controlled, crossover study	PRO 200 mg vs. PLA IV Nicotine (PLA, 0.5, 1.0 mg/70 kg)	PRO 200 mg attenuated some of the subjective effects from IV nicotine	Sofuoglu et al., 2009
Female smokers ($N = 202$)	Randomized, clinical trial	Behavioral intervention for smoking cessation	Women who quit during the FP has shorter days to smoking relapse than those who quit during the LP	Allen et al., 2008
Female smokers ($N = 37$)	Open-label clinical trial, retrospective analysis	NRT plus behavioral intervention	Women who were in the FP at quit date ($N = 16$) responded better to NRT than those who were in the LP ($N = 21$)	Franklin et al., 2008

Note. PRO = progesterone; PLA = placebo; DSST = Digital Symbol Substitution Test; IV = intravenous; FP = follicular phase; LP = luteal phase; NRT = nicotine replacement therapy.