CHARACTERIZATION OF SEX DIFFERENCES IN THE REINFORCING EFFECTS OF NICOTINE

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Lovingly dedicated to my beautiful wife, Monica Flores, for all the love and support she has provided me with throughout graduate school.

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Abstract

It is presently unclear whether ovarian hormones, such as estradiol (E2) promote the reinforcing effects of nicotine in females. Thus, we compared extended access to nicotine intravenous self-administration (IVSA) in intact male, intact female, and OVX female rats (Study 1) as well as OVX females that received vehicle or E2 supplementation (Study 2). The E2 supplementation procedure involved a 4-day procedure involving 2 days of vehicle administration and 2 days of E2 administration. Two doses of E2 (25 or 250 ug) were assessed in separate groups of OVX females in order to examine the dose-dependent effects of this hormone on the reinforcing effects of nicotine. The rats were given 23-hour access to nicotine IVSA using an escalating dose regimen (0.015, 0.03, and 0.06 mg/kg/0.1 ml). Each dose was self-administered for 4 days with 3 intervening days of nicotine abstinence. The results revealed that intact females displayed higher levels of nicotine intake as compared to males. Also, intact females displayed higher levels of nicotine intake versus OVX females. Lastly, our results revealed that OVX rats that received E2 supplementation displayed a dose-dependent increase in nicotine intake as compared to OVX rats that received vehicle. Together, our results suggest that the reinforcing effects of nicotine are enhanced in female rats via the presence of the ovarian hormone, E2.

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Introduction

Nicotine and tobacco use: Tobacco products contain nicotine, which has been identified as the main compound that motivates smoking behavior (Pogocki et al., 2007; Pontieri et al., 1996). For example, acute self-administration of nicotine in nonsmoking human subjects is associated with pleasurable subjective responses (Perkins et al., 2001). Similarly, nicotine increases ratings of drug high and liking in experienced smokers (Kalman et al., 2005). Humans also show a preference for nicotine versus saline in studies involving intravenous (IV; Henningfield et al., 1983; Harvey et al., 2004) and nasal (Perkins et al., 1996) administration. Taken together, these studies show that people use tobacco products largely to experience the pleasurable/reinforcing effects of nicotine

Neurobiological effects of nicotine: Nicotine exerts behavioral effects via activation of nicotinic acetylcholine receptors (nAChRs) in the brain. nAChRs belong to a family of ligand-gated ion channel receptors that are made up of five polypeptide subunits (Albuquerque et al., 1997; Lindstorm et al., 1996; Dani, 2001; Dani et al., 2001). The different combinations of these polypeptide subunits define the various nAChR subtypes (Cooper et al., 1991). nAChRs can be homo-oligomeric or hetero-oligomeric. Homo-oligomeric nAChRs are formed from α7, α8, or α9 subunits. However, hetero-oligomeric nAChRs reflect a combination of αβ, α2, α6, or β2-β4 subunits (Markou, 2008).

Previous studies have established that the reinforcing effects of nicotine are mediated via the dopaminergic pathway that projects from the ventral tegmental area (VTA) to several forebrain structures including the nucleus accumbens, amygdala, and frontal cortex (Corrigall et al., 1994; Pidoplichko et al., 1997; Sziráki et al., 2002). In the VTA, dopamine neurons are under excitatory