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Sex differences in nicotine intravenous self-administration: A meta-analytic review

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ABSTRACT

Objective: This report reflects a meta-analysis that systematically reviewed the literature on intravenous self-administration (IVSA) of nicotine in female and male rats. The goal was to determine if sex differences in nicotine IVSA exist, estimate the magnitude of the effect, and identify potential moderators of the relationship between sex differences and nicotine consumption.

Methods: Extensive search procedures identified 20 studies that met the inclusion criteria of employing both female and male rats in nicotine IVSA procedures. The meta-analysis was conducted on effect size values that were calculated from mean total intake or nicotine deliveries using the Hedges' unbiased g^u statistic.

Results: A random effects analysis revealed that overall females self-administered more nicotine than males (weighted g^u = 0.18, 95% CI [0.003, 0.34]). Subsequent moderator variable analyses revealed that certain procedural conditions influenced the magnitude of sex differences in nicotine IVSA. Specifically, higher reinforcement requirements (> FR1) and extended-access sessions (23 h) were associated with greater nicotine IVSA in females versus males. Females also displayed higher nicotine intake than males when the experiment included a light cue that signaled nicotine delivery. Sex differences were not influenced by the diurnal phase of testing, dose of nicotine, or prior operant training.

Conclusion: Overall, the results revealed that female rats display higher levels of nicotine IVSA than males, suggesting that the strong reinforcing effects of nicotine promote tobacco use in women.

1. Introduction

The addictive nature of tobacco products is largely due to the presence of the major alkaloid compound, nicotine. Clinical studies have revealed that nicotine self-administration induces positive subjective ratings of pleasure and drug liking in human subjects [26,42,52]. Some of the early pre-clinical studies also demonstrated reliable intravenous self-administration (IVSA) of nicotine in non-human primates [15,20] and rodents [13,51]. Nicotine IVSA is based on reinforcement principles that involve strengthening a behavioral response, such as a lever press, nose poke, or licking behavior for the delivery of nicotine infusions. The frequency of self-administered infusions and the quantity of intake are used as indices of the reinforcing effects of nicotine. This review focuses on behavioral studies involving IVSA because it is the most common route of administration used in rodent studies, and it mimics the rapid distribution of nicotine to the brain via inhalation methods [4].

The National Institutes of Health currently mandate that sex be included as a biological variable in biomedical studies [37]. Indeed, epidemiological studies have shown that women are more likely to use tobacco products, and are more susceptible to the long-term negative health consequences of smoking [34,54]. In order to reduce the health disparities produced by tobacco use in women, there is a critical need to understand the biological basis for sex-based differences in nicotine addiction [22]. One possible factor that promotes tobacco use in women is the strong reinforcing effects of nicotine. This claim is based on the finding that women rate nicotine as more pleasurable [43] and report greater positive subjective effects following presentation of smoking-related stimuli [41,42] as compared to men.

To understand the biological basis of sex differences in tobacco use, pre-clinical studies have compared nicotine IVSA in female and male rats. However, these reports have yielded mixed results. Some studies report that females display higher rates of nicotine IVSA than males [21,49,59], whereas other studies report that males display higher rates of nicotine IVSA than females [25,30]. There are also studies that report no sex differences in nicotine IVSA [18,31,44,55,56]. These conflicting findings may be due to methodological differences that influence the

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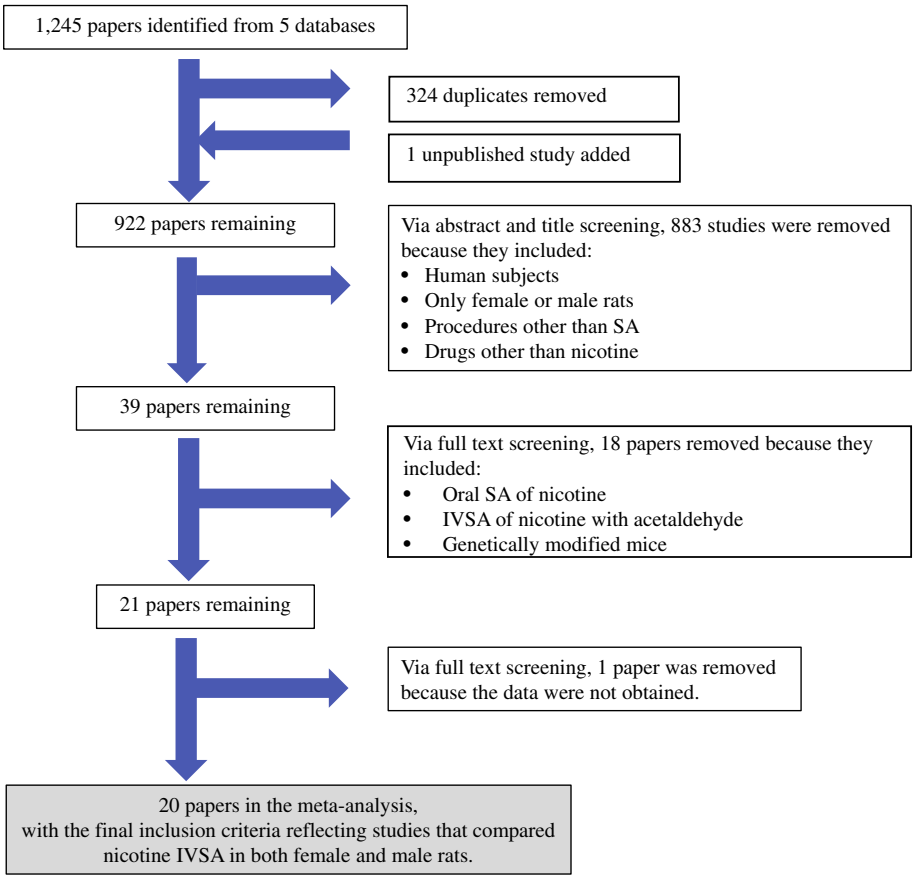
Fig. 1.



magnitude of sex differences, such as the presence of cues [6] or differences in social context [40]. The absence of sex differences in some studies may also be due to small sample sizes that reduce statistical power, thereby decreasing the likelihood of detecting sex differences in IVSA when such differences exist in the population.

Several narrative reviews of pre-clinical studies have shed light on the various factors that may promote tobacco use in females [3,14,35,58]. These reviews have been useful in suggesting patterns of sex differences in the litany of pre-clinical studies, and thereby generating hypotheses for further scientific investigation. Recently, Pogun et al. [45] presented an extensive narrative review of sex differences in the behavioral effects of nicotine. These authors suggested that sex is an important factor that influences nicotine IVSA, a hypothesis that is statistically tested in the current meta-analytical review. Despite the strengths of narrative reviews, they cannot statistically integrate findings from a large body of conflicting evidence, such as the existing studies of sex differences in nicotine IVSA. Also, narrative reviews cannot estimate the magnitude of sex differences in IVSA, identify moderator variables, or overcome problems arising from low statistical power among individual studies [5].

Meta-analytic reviews offer an alternative approach for summarizing IVSA findings, allowing for an empirical synthesis of effect sizes to help resolve uncertainties among a large pool of mixed reports [17,60]. Specifically, meta-analysis combines studies in a manner that increases statistical power and the likelihood of detecting sex differences in a set of studies even when the individual studies themselves may fail to reveal an effect [12]. Meta-analytical approaches can also be useful towards identifying the degree to which certain procedural variables influence sex differences in nicotine IVSA. The results of these moderator variable analyses are useful for generating hypotheses regarding the parameters under which sex differences are more likely to be detected, and these parametric variables need to be tested in future empirical studies. For example, Bardo et al. [1] published a meta-analysis of rodent studies that assessed the magnitude of conditioned place preference (CPP) produced by stimulant and opiate drugs. Their analysis revealed that certain experimental features, such as dose, housing conditions, and route of administration influenced the magnitude of drug-induced CPP. Based on their analysis, the authors provided recommendations regarding the optimal experimental features for studying CPP produced by drugs of abuse in rodents. Indeed, a subsequent empirical study found that the magnitude of CPP produced by cocaine was influenced by dose and route of administration [39], as suggested by Bardo and colleagues. A similar approach may help to advance our understanding of sex differences in nicotine IVSA. Thus, the current review presents a meta-analytic review of studies investigating sex differences in nicotine IVSA in female and male rats. The overall goal of this review was to estimate the magnitude of sex differences in nicotine IVSA and identify potential moderator variables.

2. Methods

2.1. Literature search

A comprehensive literature review was conducted via a computer search of the following databases: Web of Science, PubMed, JSTOR, and Google Scholar. A search for unpublished findings was also conducted via Proquest. The following terms were used for all searches: nicotine, reward, reinforcement, sex difference(s), gender difference(s), male(s), female(s), rat(s), rodent(s), intravenous self-administration, IVSA, SA, and operant procedure(s). The title and abstract of each paper were both searched for these terms. The search was limited to documents in English. The search period included January 1, 1955 to June 22, 2017. An unpublished study was also added from our laboratory. Additional