# Effect of Corticosterone and Paroxetine on Masculine Mating Behavior: Possible Involvement of Neurogenesis

Benson Wui-Man Lau, PhD,*†‡ Suk-Yu Yau, PhD,*†‡ Tatia M.C. Lee, PhD,†§ Yick-Pang Ching, PhD,*†‡ Siu-Wa Tang, PhD,* and Kwok-Fai So, PhD*†‡¶**

*Department of Anatomy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong SAR, China; †The State Key Laboratory of Brain and Cognitive Sciences, The University of Hong Kong, Pokfulam, Hong Kong SAR, China; ‡Research Centre of Heart, Brain, Hormone and Healthy Aging, Faculty of Medicine, The University of Hong Kong, Pokfulam, Hong Kong SAR, China; §Laboratory of Neuropsychology, The University of Hong Kong, Pokfulam Road, Hong Kong SAR, China; ¶Joint Laboratory for Brain Function and Health (BFAH), Jinan University, GuangZhou, China; **The University of Hong Kong, GuangZhou, China

DOI: 10.1111/j.1743-6109.2010.02081.x

**ABSTRACT**

***Introduction.*** Corticosterone inhibits male rodent sexual behavior while the mechanism remains obscured. Recent studies have disclosed that neurogenesis in the subventricular zone (SVZ) can be increased by pheromone exposure from the opposite sex, and neurogenesis is essential for normal mating behavior of female mice. Together with the neurogenesis-inhibiting effect of corticosterone, we hypothesize that cell proliferation in the olfactory system is essential for male rodent sexual functioning.

***Aim.*** The current study explored the relationship between cell proliferation in the olfactory system and male sexual behavior.

***Main Outcome Measures.*** Sexual behavior performance, proliferative cell counts, and c-fos-expressing cell counts.

***Methods.*** Adult male rats were treated with corticosterone and/or paroxetine, an antidepressant, for 2 weeks. These two drugs were shown to suppress and enhance hippocampus and SVZ cell proliferation, respectively. Mating behavior was assessed after the treatment, and proliferation of new cells and c-fos-expressing cells, activated neurons in the mating-related regions in the brain, were analyzed. To further confirm the necessity of cell proliferation in mating, inhibition of cell proliferation was performed by intracerebroventricular infusion of cytostatic cytosine arabinose (Ara-c).

***Results.*** Corticosterone treatment, which inhibited cell proliferation in both the SVZ and olfactory epithelium, led to inhibited male sexual performance. In contrast, paroxetine increased cell proliferation and improved the performance in corticosterone-treated animals. When cell proliferation in the brain was inhibited by Ara-c, a suppressed sexual performance was found. However, cell proliferation in olfactory epithelium was not inhibited by Ara-c and thus the sexual inhibition is unlikely to be linked to this region. Furthermore, a decrease in c-fos expression in the mating-related regions upon female pheromone stimulation was found.

***Conclusions.*** These results suggest that cell proliferation in the SVZ and hippocampus may be involved in the reproduction of the male rodents, and pharmacological treatments may affect sexual functioning through alteration of neurogenesis. **Lau BWM, Yau S-Y, Lee TMC, Ching Y-P, Tang S-W, and So K-F. Effect of corticosterone and paroxetine on masculine mating behavior: Possible involvement of neurogenesis. J Sex Med 2011; 8:1390–1403.**

***Key Words.*** Sexual Behavior; Male Sexual Functioning; Selective Serotonin Reuptake Inhibitor; Paroxetine; SSRI; Neurogenesis; Olfactory System; Corticosterone

## Introduction

Chronic corticosterone treatment has been shown to inhibit mating behavior of male rats, which are represented by decreased ejaculation frequencies and lengthened time to achieve ejaculation [1,2]. The mechanism behind the inhibition remains obscured, and is suggested to involve alteration of serotonergic receptors expression in the central nervous system (CNS)

Benson Wui-Man Lau and Suk-Yu Yau contributed equally to this work.

[1–3], but desensitization of serotonin receptors could not unambiguously explain the effect of these two drugs. In contrast with the sexual inhibitory effect of corticosterone, paroxetine was shown to resolve sexual dysfunction in patients with major depression [4], although selective serotonin reuptake inhibitor (SSRI) treatment per se may inhibit sexual behavior [5,6]. It is recently shown in rats that chronic corticosterone treatment decreased neurogenesis in the hippocampus and subventricular zone (SVZ) [7,8]. The latter is a region that continuously generates neural progenitors that are destined for the olfactory bulb [8,9]. This may provide useful clues on how corticosterone inhibits male rodent sexual behavior.

Adult neurogenesis takes place in the rodent hippocampus and several regions in the olfactory system. These regions include the olfactory bulb, subventricular zone, amygdala [10,11], and olfactory epithelium [12]. Studies that abolished adult hippocampal neurogenesis disclosed its functional significance in different behaviors, including hippocampal-dependent memory [13] and anxiolytic effect of antidepressants [14]. The functional importance of neurogenesis in the SVZ is gradually being revealed. A previous study by Mak et al. showed that female rodent sexual behavior is under the influence of adult neurogenesis [15]. When SVZ neurogenesis was abolished, female mice did not show mate preference for dominant male, which normally occurred in untreated female mice. Reciprocally, exposure to male pheromone increased SVZ neurogenesis in the female mice, which may, in turn, strengthen the mate preference. However, whether neurogenesis is involved in the male rodent sexual behavior or not is still unknown.

How SVZ neurogenesis affects sexual behavior is still unclear. Since SVZ supplies new neurons for the olfactory bulb, it is possible that new neurons in the olfactory system affect sexual behavior. The olfactory system is known to play an important role in rodent copulatory behavior [16]. Several interrelated regions of the olfactory system and other parts of the brain are involved in the initiation of male sexual behavior, including the: (i) olfactory epithelium and vomeronasal organ, where a pheromone signal is detected [17]; (ii) olfactory bulb, where the olfactory sensory neurons make the first synaptic connection; and (iii) amygdala and downstream regions involved in sexual activity, including the anterior medial amygdala (MeA), posterior medial amygdala (MeP), bed nucleus of stria terminalis (BNST), and medial preoptic areas (MPOA). Inhibition of sexual behavior, to various degrees, can be produced by damaging specific structures [18]. For instance, electrolytic lesion of the BNST in male hamsters abolishes chemoinvestigation of females, while lesion of the MPOA stops mating completely [18]. Since newly generated neurons are incorporated into neural circuitry and become functional, it is possible that they affect signal transduction in the neural circuit mentioned above and, in turn, the sexual behavior.

Given the neurogenesis-inhibiting effect of corticosterone and the importance of SVZ neurogenesis in the mating behavior of female mice, we hypothesize that corticosterone suppresses male rodent sexual behavior through inhibition of cell proliferation in the olfactory system, and that adult cell proliferation is essential for the display of the male sexual behavior. The down-regulated cell proliferation may disrupt signal transduction in the mating-related neural circuit. Previous reports showed that a chronic, high dose of corticosterone treatment suppressed hippocampal and SVZ cell proliferation, while co-treatment with paroxetine could reverse the changes [8,9]. In the present study, we adopted the same treatment paradigm to investigate the significance of neurogenesis in sexual behavior. We have demonstrated that corticosterone treatment inhibits sexual performance in male rats, which could be rescued with paroxetine. Cell proliferation in the olfactory epithelium was investigated to test whether corticosterone suppressed cell proliferation and if paroxetine could reverse the decrease. To assess whether signal transmission is affected in the rats treated with corticosterone and/or paroxetine, the levels of neuronal activation of mating-related regions (assessed using c-fos expression after exposure to female pheromones) was assessed. Finally, to study the direct relationship of cell proliferation and sexual behavior, cytostatic agent cytosine arabinoside (Ara-c) infusion was utilized to test whether inhibited cell proliferation per se can affect sexual behavior. Furthermore, an additional group of Ara-C infused animals that received paroxetine treatment was included to confirm whether paroxetine could reverse the sexual inhibition in the absence of cell proliferation.

## Materials and Methods

### *Animals*

Male Sprague-Dawley rats weighing 280 ± 10 g were used. Animals were housed at 22°C, at 12/12h light dark cycle and fed *ad libitum*. All of the animals were sexually-naïve, as disruption of