Sildenafil and a Compound Stimulating Endothelial NO Synthase Modify Sexual Incentive Motivation and Copulatory Behavior in Male Wistar and Fisher 344 Rats

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ABSTRACT

Introduction. Earlier studies have shown that sildenafil may modify some aspects of male rat sexual behavior and sexual incentive motivation. Stimulation of endothelial nitric oxide synthase (eNOS) has also been reported to affect sexual motivation in old rats.

Aim. To determine the effects of sildenafil and a compound stimulating eNOS on copulatory behavior and sexual incentive motivation in young adult Fisher 344 and Wistar male rats.

Methods. The rats were selected for a low intromission ratio, and then treated with Impaza (stimulator of eNOS), sildenafil, or Impaza + sildenafil for 28 days. Tests for copulatory behavior and sexual incentive motivation were performed before the beginning of treatment and at days 7, 14, and 28 of treatment.

Main Outcome Measures. Standard parameters of copulatory behavior and sexual incentive motivation. Measurements of penis length at mount, intromission, and ejaculation.

Results. The Fisher 344 rats displayed a higher level of sexual incentive motivation than the Wistar rats, while the copulatory behavior was similar in both strains. Impaza and sildenafil enhanced the sexual incentive motivation after 28 days of treatment in the Wistar rats, but failed to do so in the Fisher 344 rats. The copulatory behavior was unaffected in the Wistar strain, while the Fisher 344 males had an enhanced intromission ratio after treatment with Impaza and sildenafil for 28 days.

Conclusions. The nitric oxide-guanylyl cyclase pathway seems to be of importance for sexual incentive motivation in animals with a modest baseline level. The different drug effects in the Wistar and Fisher 344 rats can be attributed to baseline differences. The importance of eNOS for sexual functions should not be overlooked. **Chu X, Zhavbert ES, Dugina JL, Kheyfets IA, Sergeeva SA, Epstein OI, and Ågmo A. Sildenafil and a compound stimulating endothelial NO synthase modify sexual incentive motivation and copulatory behavior in male Wistar and Fisher 344 rats. J Sex Med 2008;5:2085–2099.**

Key Words. Sexual Incentive Motivation; Sexual Behavior; Endothelial NO Synthase; Sildenafil; Erection

Introduction

A common consequence of the clinical use of proerectile drugs is that the frequency of penile-vaginal intercourse is increased in the men taking such drugs (e.g., [1]). An equally common explanation for this fact is that the enhanced intercourse frequency is a result of improved erection, making this kind of sexual activity possible. It could also be maintained that proerectile drugs enhance sexual motivation, which would facilitate erection as well as the desire to use it for intercourse. However, a majority of clinical data suggest that proerectile drugs do not enhance sexual motivation. This assertion applies both to the most commonly used treatments for erectile deficiency, the phosphodiesterase type 5 (PDE5) inhibitors, as well as to the centrally acting agent apomorphine (e.g., [1,2]). To the contrary, results from experimental studies in rodents suggest that

sildenafil may enhance motivation [3–5]. Further evidence for a stimulatory action of sildenafil on male sexual motivation has been obtained in the goats [6]. Animal data with apomorphine are conflicting, but there is some evidence showing that the compound enhances sexual motivation in animals displaying an unusually low sexual activity (reviewed in [7]). One likely explanation for the discrepancy between animal and human data is that the clinical studies have focused on evaluating improvements in erectile function. In fact, the evaluation of potential actions on sexual desire (the term frequently used for sexual motivation in the human literature) has not been a major goal of any clinical study. Thus, motivational actions of proerectile drugs in humans cannot be excluded. Such actions could, in fact, contribute to the therapeutic actions of these drugs, because erectile deficiency frequently is associated with reduced motivation to engage in sexual activity [8,9].

We recently reported that sildenafil and a compound stimulating endothelial nitric oxide synthase (eNOS), Impaza, showed a tendency to stimulate the sexual incentive motivation in old Fisher 344 rats displaying a very low level of copulatory behavior [10]. Despite the incentive motivational effect of the drug treatments, the 20-month-old rats continued to display little copulatory behavior. The reason for employing the Fisher 344 strain, rarely used in studies of sexual behavior, was that it is one of the strains where old rats are commercially available.

Aims

In the present experiments, we evaluated the effects of sildenafil and Impaza on sexual incentive motivation and on copulatory behavior in young adult Fisher 344 rats. In order to determine the drug effects in a strain more commonly used, we also administered the drugs to Wistar rats. Furthermore, some clinical data suggest that a combination therapy with sildenafil and Impaza is more efficient than any of these compounds administered separately [11]. Thus, a group of animals receiving both drugs was included in the present experiments. Prior to drug treatment, animals with a low erectile capacity were selected from a larger pool.

Materials and Methods

Animals

Male (about 300 g upon arrival) Wistar and Fisher 344 rats were purchased from Scanbur, Sollentuna, Sweden. They were housed in pairs in Macrolon cages under a reversed light/dark cycle (12:12 hours, lights on 2,300) in a room with controlled temperature (21 ± 1°C) and relative humidity (55 ± 10%). Rodent pellets (RM1(E), Special Diets Services, Witham, Essex, UK) and tap water were freely available.

Female Wistar rats (about 250 g upon arrival) were obtained from the same provider and were kept under conditions identical to those of the males. They were ovariectomized under isoflurane anesthesia at least 2 weeks before the beginning of experiments. Prior to each testing session, estrus was induced by administration of estradiol benzoate, 25 μg/rat, followed by progesterone, 1 mg/rat, 48 hours later. Females were used between 4 and 8 hours after the progesterone injection. The steroids were from Sigma (St. Louis, MO, USA). They were dissolved in peanut oil and were injected subcutaneously in a volume of 0.2 mL/rat.

The experimental procedures employed were approved by the Norwegian Committee for Ethics in Research on Animals, and were in agreement with the European Union Council directive 86/609/EEC.

Apparatus

Test for Sexual Incentive Motivation

The arena used for determining the intensity of sexual incentive motivation consists of a rectangular open field (100 × 50 cm) with rounded corners. On each long side, there is an opening (25 × 25 cm), at floor level, in the 45-cm-high arena wall. The openings are diagonally opposed. Outside each opening, a cage (15 × 25 × 25-cm high) can be fitted. These outside cages are equipped with a double wire mesh wall (mesh size, 12 mm; the distance between the meshes was 10 mm) facing the arena. The arena wall, as well as the external cages, is made of sheet-steel covered with a black plastic surface. A dark gray polyvinylchloride was used for the floor. The apparatus was located in a room adjacent to the animals' room. A video camera, connected to a computer, was installed above the arena. The experimental subject's position in the arena was determined online every 200 msec with a videotrack system (Ethovision Pro, Noldus, Wageningen, the Netherlands). An incandescent light bulb provided a dim white light (about 5 lux in the arena). Detailed descriptions of the apparatus can be found in [12,13].

In front of each external cage, a virtual zone of 30 × 21 cm was defined. The videotrack system calculated the time the experimental animal spent