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ORIGINAL RESEARCH—BASIC SCIENCE

Effects of Adenosine Monophosphate Used in Combination with L-Arginine on Female Rabbit Corpus Cavernosum Tissue

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ABSTRACT

Introduction. Sexual dysfunction is significantly more prevalent in women than in men. However, to date, no satisfactory oral treatment is yet available.
Aim. The aim of this study was to study the effects of adenosine monophosphate (AMP) alone or its combination with L-Arginine on the relaxation of the female rabbit corpus cavernosum.
Methods. Cylinder strips from the corporal body of the excised clitoris from female New Zealand White rabbits were incubated in Krebs solution. Phenylephrine (PE) precontraction was achieved, then the drugs AMP and L-Arginine were administered either independently or in sequential combinations to the strips under precontracted conditions.
Main Outcome Measures. Contraction percentages were compared.
Results. When precontraction was induced by PE 8 μM or 20 μM, AMP was shown to induce relaxation up to 25% in a dose-dependent manner. The relaxation induced by L-Arginine reached 15.6% at 5.10^{-4} M vs. 16.5% at AMP 5.10^{-4} M under the same experimental conditions. Nitric oxide (NO) synthase inhibitor N-nitro-L-arginine strongly inhibited the relaxing effect provoked by AMP, suggesting that the action mechanism of this nucleotide is related to the NO pathway. The combination of L-Arginine at 5.10^{-4} M with AMP at different doses ranging from 5.10^{-4} M to 10^{-3} M significantly amplified the relaxing response up to 40.7% and 58%, respectively.
Conclusions. Our results demonstrate that AMP induces a relaxing effect on the female rabbit corpora. They also show that L-Arginine and AMP can potentiate each other and that a synergistic effect can be obtained by their combined use. Because only slight differences exist between both sexes in response to NO donors and/or nucleotide purines or in their use together, it is very likely that close biochemical mechanisms, although not to the same degree and not quite similar, are involved in the engorgement of the penis and the clitoris of New Zealand White rabbits.
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Key Words. Purines; AMP; ATP; L-Arginine; Female Corpus Cavernosum Relaxation; Nitric Oxide

Introduction

Over the past two decades, greater attention has been paid to male impotence than sexual disorders in women. Scientific investigation has primarily focused on male sexual dysfunction. In comparison, however, there has been a dearth of research concerning the physiology and the functional mechanisms underlying female sexual dysfunction (FSD). In many respects, the epide-

miological study published in 1999 by the National Health and Social Survey [1] was the first major study to address this problem. It confirmed that women not only suffer from sexual dysfunction, but it also revealed that the prevalence of this disorder is even more significant in women than in men (43% vs. 31%, respectively). Since then, FSD has been identified as being of widespread public health concern driven by many possible underlying causes responsible for desire, arousal, orgasm, or pain disorders and in some cases, a combination of these conditions. It is now accepted that these disorders deserve a specific therapeutic approach that should not be limited to psychosocial and relationship aspects alone but sometimes extended to the use of specific drugs as in the case of female sexual arousal disorders (FSAD) and hypoactive sexual desire. This has given rise to several scientific projects to assess the problem of FSD. However, to date, no reported study, to our knowledge, has emerged as a satisfactory therapeutic solution. Further studies are required to broaden our knowledge in the field of FSD. Therefore, we were prompted to conduct a study based on a program dedicated to the search of vasoactive drugs, which would exclusively focus on the treatment of FSAD.

In a previously reported study, we evaluated the effect of adenosine monophosphate (AMP) combined with L-Arginine on the mechanism of erection in the male rabbit penis [2]. We were able to show a synergistic effect because of these combinations on strips of smooth muscle corpus cavernosum (CC). The present study was designed to evaluate the effect of the same compounds alone, or in combination, on the female New Zealand rabbit clitoral CC. The existence of close similarities between the rabbit and the male human erectile tissues, which are greater than that between men and other mammal erectile specimens, has been widely documented [3–6]. Morphological and physiological similarities between male and female New Zealand rabbit CC have also been described [7,8]. Therefore, the female New Zealand White rabbit was selected, for this preliminary approach, as it was considered the most suitable animal model.

Materials and Methods

Strip Preparation

Healthy female New Zealand White rabbits weighing 2–2.4 kg and 10–12 weeks of age were sacrificed by an overdose of sodium pentobarbital injected into the marginal vein of the ear. The clitoris was excised from surrounding external genitalia and placed in Krebs solution equilibrated with 95% O^2 and 5% CO^2 at 4°C. The corporal body was dissected free from the tunica and then sliced into four cylinder strips (two proximal, two distal) of approximately 4–5 mm each as previously described by other authors [9].

Tissue Bath Setup

Longitudinal strips were attached to force transducers using silk sutures. They were incubated in Krebs solution in 25 mL organ baths, equilibrated with 95% O^2 and 5% CO^2 and maintained at 37.5°C. Isometric strip tension was recorded through an acquisition unit (MP30, BioPac, Goleta, CA, USA) connected to a computer database. After mounting, each strip was allowed to equilibrate with a basal tension between 0.20 g and 0.25 g for at least 2 to 3 hours. During this time, the harvested segments were washed regularly.

Drug Administration

Phenylephrine (PE) (Sigma, Saint-Louis, MO, USA) precontraction was achieved by the addition of 8 or 20 μM (as indicated by the manufacturer) to each bath in order to reach a stable strip contracting effect. Although 8 μM PE was generally considered sufficient with no detectable change at 20 μM PE, we preferred to use the 20 μM dosage in order to obtain the highest possible precontraction effect. Drugs AMP (Interchemica S.r.l., Strambino, Italy) and L-Arginine (Sigma-Aldrich, Saint-Quentin-Fallavier, France) were administered either independently or in sequential combinations (AMP at different doses, then L-Arginine at different doses, then the combination AMP–L-Arginine) to the strips under precontracted conditions. The final bath concentrations were between 10^{-4} M and 10^{-3} M. Nitric oxide (NO) synthase inhibitor N-nitro-L-arginine (L-NNA) at the dose of 5.10^{-4} M was also administered to the strips before treatment with AMP.

Statistical Analysis

Contraction percentages were compared between groups by a variance analysis in repeated measurements. A value of $P < 0.05$ was considered significant in all tests. All results are expressed as mean ± standard error of the mean.

Results

The maximal relaxing effect after addition of active substances was measured at each stage (for