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# COMMENTARY

# Neutral endopeptidase inhibition: could it have a role in the treatment of female sexual arousal disorder?

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Female sexual arousal disorder (FSAD) is the inability to attain or maintain an adequate lubrication-swelling response of sexual excitement. The potentiation of vascular responses leading to increased blood flow in clitoris and vagina has represented the main focus in the pharmacological treatment of FSAD, including the evaluation of the type 5 phosphodiesterase (PDE5) inhibitors. However, due to a lack of clear efficacy, there is no approved pharmacotherapy for FSAD to date. In the present issue of the *British Journal of Pharmacology*, Wayman *et al.* show that the administration by intravenous or intravaginal routes of a novel neutral endopeptidase inhibitor, UK-414,445, results in enhanced genital blood flow responses to pelvic nerve stimulation in female rabbits, without significantly affecting blood pressure. Neutral endopeptidase inhibition, by preserving vasoactive peptides such as vasoactive intestinal polypeptide, raises the possibility of a new pharmacological approach to the treatment of FSAD.
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**Keywords:** female sexual arousal disorder (FSAD); genital blood flow responses; neutral endopeptidase (NEP); UK-414,495; vasoactive intestinal polypeptide (VIP)

**Abbreviations:** FSAD, female sexual arousal disorder; NEP, neutral endopeptidase; PDE5, type 5 phosphodiesterase; VIP, vasoactive intestinal polypeptide

Female sexual dysfunction is a largely unresolved medical problem. Female sexual arousal disorder (FSAD) is the second most prevalent manifestation of female sexual dysfunction after hypoactive sexual desire disorder. Arousal phase of female sexual response involves an increase in genital blood flow for allowing lubrication and swelling, a process that can be altered by vascular insufficiency or reduced vasodilation of arteries supplying female genitalia. Thus, pharmacological strategies for potentiating blood flow responses to sexual stimulation seem to be a reasonable approach for treating FSAD. Most molecules evaluated for treating FSAD had previously shown efficacy in the treatment of erectile function. In this way, alprostadil (prostaglandin $E_1$), the α-adrenoceptor antagonist, phentolamine, and the type 5 phosphodiesterase (PDE5) inhibitor, sildenafil, which potentiates NO/cGMP pathways have been evaluated for the treatment of women with FSAD. Although positive results have been sometimes obtained, the inconsistency of outcomes and the lack of clear efficacy have prevented their approval for the treatment of FSAD. In fact, in the report from the third International Consultation on Sexual Medicine, no recommendation for pharmacotherapy for FSAD could be made because of lack of efficacy and/or unwanted side effects (Brotto *et al.*, 2010). Thus, the need of other therapeutic approaches for the treatment of FSAD is obvious.

In this context, Wayman *et al.* (2010), in the present issue of the *British Journal of Pharmacology*, propose the inhibition of neutral endopeptidase (NEP) as a way to enhance genital blood flow responses in order to positively modulate female sexual arousal. NEP cleaves a variety of vasoactive peptides, causing their biological inactivation. Several peptides that have been suggested to participate in the female sexual arousal process are included among the substrates for NEP, including vasoactive intestinal polypeptide (VIP), natriuretic peptides, bradykinin, endothelins, calcitonin gene-related peptide and substance P, and their actions are thus potentiated or prolonged by NEP inhibition. Wayman *et al.* showed

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that the NEP inhibitor, UK-414,495, had the capacity to increase blood flow responses to pelvic nerve stimulation in vagina and clitoris from female rabbits and also potentiated blood flow increases in vagina induced by exogenously added VIP. NEP inhibition with UK-414,495 did not result in significant alteration of blood pressure, in contrast to the systemic haemodynamic effects of giving VIP.

Vasoactive intestinal polypeptide stands out among the candidate peptides whose inactivation could mediate the effects of the NEP inhibitor. The presence of VIP-containing nerves has been demonstrated in human vagina, innervating vascular structures and vaginal wall (Hoyle *et al.*, 1996). Furthermore, the administration of VIP to women results in increased vaginal blood flow and lubrication (Ottesen *et al.*, 1987). As UK-414,495 potentiates VIP-induced blood flow responses and VIP has an important role in sexual arousal, the preservation of VIP through NEP inhibition seems to be a reasonable explanation for the potentiating effects on stimulated genital blood flow by UK-414,495. However, the inhibition of NEP could also enhance the biological activity of other peptides contributing to blood flow responses. In fact, some cases of persistent sexual arousal disorder in women have been suggested to be produced by an elevation of atrial natriuretic peptide levels inducing vasodilatation and increased vascular permeability (Bell *et al.*, 2007). Inhibition of NEP could lead such potentiation of the action of natriuretic peptides facilitating the enhancement of female genital blood flow responses. The relevance of NEP in the modulation of sexual function is highlighted by the existence of endogenous inhibitors of this enzyme, opiorphins, which have been shown to increase sexual responses in male animals and are down-regulated in patients with erectile dysfunction (Davies, 2009). Whether or not the levels of endogenous NEP inhibitors are reduced in FSAD is an interesting unresolved question that could reinforce the convenience of using a NEP inhibitor to treat such problem.

Female sexual arousal requires an adequate vascular response to sexual stimulation for increasing blood flow in genitalia. Altered vascular function would therefore compromise female sexual arousal. This is supported by the increased prevalence of sexual dysfunction in women with cardiovascular risk factors (Veronelli *et al.*, 2009). The presence of diabetes is associated with a high prevalence of female sexual dysfunction, including arousal and lubrication problems (Enzlin *et al.*, 2009; Fatemi and Taghavi, 2009). As conditions related to effects on vascular function favour the development of FSAD, it is reasonable to expect a beneficial effect on female sexual arousal by pharmacological interventions enhancing vascular responses. In fact, diabetic women with sexual dysfunction have been suggested to represent a population more responsive to the effects of PDE5 inhibitors (Schoen and Bachmann, 2009). In addition to a profound depression of the NO/cGMP pathway (Angulo *et al.*, 2010), diabetes also reduces VIP levels and VIP-ergic innervation (Noda *et al.*, 1990) while, at least in rabbit cavernosal tissue, the relaxation caused by exogenous VIP remains unaltered or potentiated in diabetes (Miller *et al.*, 1995). The preservation of VIP by NEP inhibition could reverse the functional impairment caused by diabetes in the VIP-ergic system and could potentially alleviate genital vascular impairment in diabetic women.

In the same way as that observed with the PDE5 inhibitors, Wayman *et al.* (2010) show that the NEP inhibitor, UK-414,495, requires stimulation, that is, neuronal activity, in order to observe its potentiating effects on genital blood flow, suggesting that could enhance the response to sexual stimulation rather than trigger a response by itself, a characteristic that presents obvious advantages in a clinical setting. Another positive feature is that UK-414,495 has pharmacological effect when given intravaginally. This would allow the delivery of therapeutic concentrations of the drug to the target organ with lower systemic concentrations, thus minimizing possible side effects that have been observed with the other NEP inhibitors that have been evaluated as cardiovascular therapeutic agents.

Considering all these facts, the article by Wayman *et al.* in addition to providing evidence of a possible role for NEP inhibition with UK-414,495 in the treatment of FSAD, has further implications and raises several questions to be answered. For instance, it should be interesting to assess the efficacy of a combined inhibition of NEP and PDE5 – would there be additive efficacy?

Although these findings are encouraging, they must be treated with caution as the effects of NEP inhibition on the therapeutic management of FSAD could be limited by different factors. The demonstrated potentiation of genital blood flow responses by PDE5 inhibitors in animal models (Angulo *et al.*, 2003) has not been translated to a clear efficacy in the treatment for FSAD in women. The lack of correlation between the measurements of objective sexual arousal to the perception of subjective sexual arousal in women has been proposed as the explanation for the variable outcomes observed in clinical trials with PDE5 inhibitors. The outcome is also influenced by the concomitant existence of impairments in other areas of female sexuality, as desire or orgasm, in women complaining of FSAD. Such situations would also affect the utility of the NEP inhibitor. However, it should be also considered that if this pharmacological approach achieves a sufficient effect on physiological arousal, it would then exert some effects on subjective arousal. Thus, based on the results obtained by Wayman *et al.* (2010) and the unmet need of pharmacological treatment, it should be worthwhile to explore further the utility of modulating NEP activity for the treatment of FSAD.

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