Structure-activity relationships of bradykinin potentiating peptides

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In order to establish the nature of the active group(s) or structural characteristics of certain bradykinin potentiating pentapeptides, a number of A-VI-5 (Val-Glu-Ser-Ser-Lys) analogues and fragments were synthetized and tested for bradykinin potentiating activity (Ufkes *et al.*, 1978). It was concluded that (1) the polar groups of the side-chains are not essential; (2) the chain-length (at least 5 amino acids) and the lipophilicity are of much more importance; (3) the free N-terminal NH_2-group is not essential; (4) aromatic amino acids in position 3 result in highly active peptides.

A further study was made using peptides with a more 'neutral' character (Ala-Ala-Ala-Ala-Ala or Val-Ala-Ala-Ala-Ala) and substituted with Tyr or Trp in position 3. In order to increase the hydrophilicity of these highly insoluble peptides Lys was introduced. To confirm the importance of the presence of an aromatic amino acid in position 3, Trp was also substituted in position 2 and 4.

Several BPP_{5a}-(Pyr-Lys-Trp-Ala-Pro) analogues were synthetized and tested for bradykinin potentiating activity. Trp was replaced by Phe or (D)-Trp in position 3. To determine the importance of position 1 and 2 Pyr and Lys were replaced as well.

The synthesis, the purification as well as the determination of the bradykinin potentiating were performed as previously described (Ufkes *et al.*, 1978).

From these findings it can be concluded that (1) a certain balance between lipophilicity and hydrophilicity is required; (2) an (L)-aromatic amino acid exclusively in position 3 is essential for a high activity; (3) among the aromatic amino acids (L)-tryptophan is the best choice; (4) the amino acids in positions 1 and 2 in BPP_{5a} are responsible for additional activity; (5) Pyr-Lys-Trp-Ala-Pro seems to be the optimal configuration for a bradykinin potentiating pentapeptide.

Reference

UFKES, J.G.R., VISSER, B.J., HEUVER, G. & VAN DER MEER, C. (1978). Structure-activity relationships of bradykinin potentiating peptides. *Eur. J. Pharmac.*, **50**, 119.

Antioestrogenic derivatives of nafoxidine stimulate progesterone receptor synthesis *in vivo*

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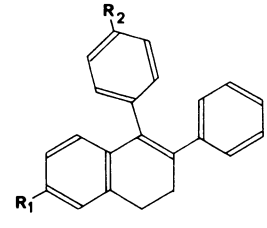
Nafoxidine (U 11,100A) is a non-steroidal antioestrogen that has been used to treat breast cancer (Legha, Slavik & Carter, 1976), and in the laboratory has been used for the investigation of antioestrogenic mechanisms. Both *in vivo* and *in vitro* oestradiol and the antioestrogen tamoxifen, which is a partial oestrogen agonist, stimulate progesterone receptor synthesis, whilst *in vitro*, nafoxidine is ineffective (Horwitz, Koseki & McGuire, 1978; Koseki, Zava, Chamness & McGuire, 1977). It is possible that the progesterone receptor synthesis promoted by tamoxifen requires conversion into the fully oestrogenic *cis* geometrical isomer, whereas the rigid structure of nafoxidine will not permit this isomerisation. We have therefore determined whether nafoxidine-like antioestrogens (U 22410A and U 10,520, Figure 1) can stimulate progesterone receptor synthesis *in vivo*.

U 22410A and U 10,520 are both partial oestrogen agonists with antioestrogenic properties in the 3d immature rat (Alderley Park strain) uterine weight test, and both increase the uterine binding of the synthetic progestogen [^{3}H]-R5020 (17α,21-Dimethyl-19 norpregna-4,9 diene-3,20-dione [17αMe^{3}H]) using the method described by Vu Hai & Milgrom (1977).



	R_1	R_2	
U-11,100A (nafoxidine)	OCH_3	OCH_2CH_2N	hydrochloride
U-22,410A	H	OCH_2CH_2N	hydrochloride
U-10,520	OCH_3	$OCH_2CH_2N(C_2H_5)_2$	

Figure 1