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VASOPRESSIN ANALOGS WITH STRONG AGONISTIC - ANTAGONISTIC PROPERTIES

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Introduction

Some 20 years ago we demonstrated that both the quantity and quality of the biological effects of vasopressins were strongly dependent on the properties of the amino acid in position 8 of the C-terminal peptide side chain of these hormones. By simple changes of its properties such as the change of configuration, homologous change, functionalization and derivatization, it is possible to modify the biological activities of vasopressins almost at will. We have demonstrated the value of this piece of information on the preparation of the first "superactive" vasopressin analog, 1-desamino-8-D-arginine vasopressin (DDAVP). DDAVP has rapidly found its way into medical practice and it has been designated as belonging among the 15 most important drugs produced so far in this century. Our previour work has recently been summarized (1).

The change of configuration in position 2 has been frequently used for the preparation of potent vasopressin inhibitors (2). However, our previous studies indicated that the structural changes formed a kind of hierarchical succession, according to their influence on the biological activities of vasopressins (1). The change of configuration in position 8 seems to play a dominant role in this succession. The idea on the hierarchy of structural changes encouraged us to an attempt at introducing two changes of configuration into a vasopressin molecule simultaneously, namely into position 8 and 2. We assumed that the change of configuration in the first mentioned position would outweigh that in the latter, and by combining these changes we hoped to obtain a favorable combination of the relevant biological properties.

Results

The solid phase synthesis, purification and assay for biological activities of the double-D-substituted vasopressin analogs was carried out as usual (1). The biological activities of two representative compounds are shown in Table 1. The data in the table

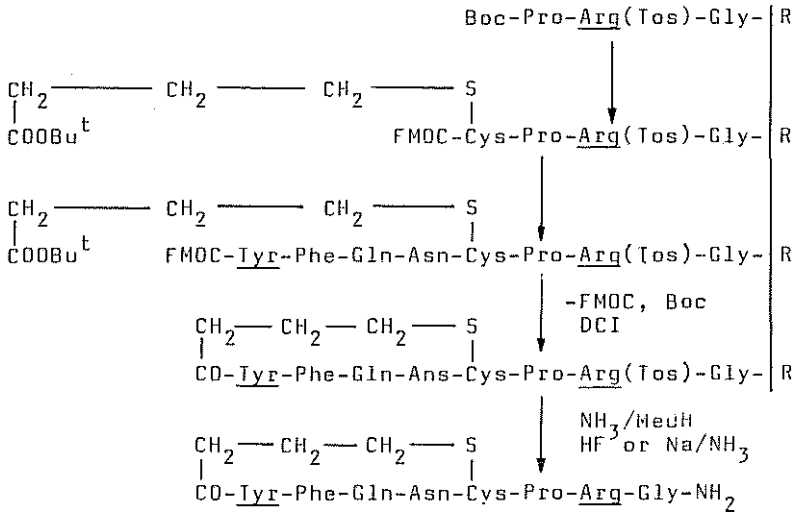
Table 1. Biological Activities of Double-D-Substituted Vasopressin Analogs

[X,Y] VP	AD	BP	UT	G
[Mpr^1, D-Tyr^2, D-Arg^8]	120-150%	0.1	inh.[a]	0.1 part.agon.
[Mpr^1, D-Tyr^2, Abu^4, D-Arg^8]	40-60%	inh.[b]	inh.[c]	inh.[d]
DDAVP	100%	0.96	5.1	

VP vasopressin, AD antidiuretic activity, BP pressor activity, UT uterotonic activity, G galactogogous activity.
[a] pA_2 6.3, 7.9 (in situ, in vitro), [b] pA_2 6.8, [c] pA_2 7.1, 8.2 (in situ, in vitro), [d] pA_2 6.6.

are in accordance with the working idea. The compounds combine the properties of 2-D- and 8-D-substituted analogs in the desired way. The first compound has markedly higher antidiuretic activity than DDAVP, it has very low pressor effect and is a potent inhibitor of the uterotonic activity. The second compound has only approximately 50% of the antidiuretic activity of DDAVP; however, it is a potent inhibitor of all of the side effects studied. The compounds represent a new type of vasopressin analogs with strong agonistic - antagonistic properties

After completing the study of a group of compounds of the type shown in Table 1 we were faced with a similar problem as two decades ago, during the development of DDAVP. The compounds in Table 1 are highly and selectively active as antidiuretics but they are not active enough to compete effectively with DDAVP. To improve their competitive ability we made an attempt to increase their antidiuretic potency.



Scheme 1. Synthesis of double-D-substituted carba-vasopressin analogs. The underlined amino acids are of D-configuration.

As has been shown by Jošt et al. (3), oxytocin and vasopressin carba-analogs frequently have higher biological activities than their disulfide bridge counterparts. We took advantage of this valuable piece of knowledge and we prepared such analogs of selected members of our double-D-substituted group of vasopressins. The compounds were obtained by a somewhat modified solid phase procedure as compared to that which is usually employed for this purpose in our laboratories. Its principle is shown in Scheme 1. The 7-9 sequence is prepared by means of Boc-amino acids. The bridge amino acid is attached as FMOC-tert-butyl ester. The synthesis is then continued with FMOC-amino acids. In the penultimate step the Boc and FMOC groups are removed, the cycle is closed and the peptide is split off from the resin by ammonolysis. The Tos residue, protecting the guanido group of D-Arg^{8}, is removed with liquid HF or with Na/NH_3. The synthesis is then completed in the usual manner. The biological properties of the compounds prepared are shown in Table 2. From the data in the table it is evident that the carba-substitution caused an unexpectedly high increase of the antidiuretic effect. Two of the compounds have a 7x and 10x higher antidiuretic effect than DDAVP. The carba-substitution does not have a negative effect on the inhibitory properties of the analogs. It is evident that the carba^{6}-analog has much lower antidiuretic activity.

Table 2. Biological Activities of Double-D-Substituted Carba-Vasopressin Analogs

[X,Y]VP	AD	BP	UT[x]	G
[dCar^1, D-Tyr^2, D-Arg^8]	7.9	pA_2 7.2	pA_2 7.5	3.6
[dCar^1, D-Tyr^2, Val^4, D-Arg^8]	10.0	pA_2 6.8	pA_2 7.9	0.4
[Mpr^1, D-Tyr^2, Car^6, D-Arg^8]	1-2	pA_2 6.8	pA_2 7.8	1.0
DDAVP	1	0.96	5.1	

[x]in vitro. dCar desamino-carba, Mpr 3-mercaptopropionic acid. Other abbreviations have the same meaning as in Table 1.

The carba analogs under consideration are very stable compounds. Their N- and C-terminal part is protected against the attack of proteolytic enzymes and they do not contain the labile disulfide bridge. Evidently, they are suitable for application per os. Indeed, in tests on experimental animals (rats) they showed a strong antidiuretic effect when applied per os. The double-D-substituted carba-vasopressin analogs certainly deserve serious consideration as possible successors to DDAVP. Perhaps it should also be mentioned that these compounds are not easily obtainable by methods of genetical engineering.

References

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