Structure-Activity Investigation of Unusual Analogues of the Potent Vasoconstrictor Angiotensin II

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Despite the huge amount of derivatives studied to date, a clear consensus regarding the mode of action of vasoactive angiotensin II (DRVYIHPF, AngII) is not achieved yet. In addition to classical pharmacological experiments, the tachyphylaxis phenomenon, defined as the acute loss of response of some smooth muscles upon repeated stimulation with AngII continues to be also a source of controversy. Previous studies have shown that the presence of protonated α-amine group associated with free Arg^2 and Tyr^4 residues are all essentials for tachyphylaxis. To following with previous investigation AngII analogues were synthesized but mainly containing modifications at these three positions. The unusual analogues bearing the bulky and very lipophilic 9-fluorenylmethyloxycarbonyl (Fmoc) group at N^{α}-terminus of Asp^1-, Glu^1- and sarcosine^1-AngII were all tachyphylatic, thus suggesting that the presence of a protoned amino group is not essential in some circumstances for the manifestation of tachyphylaxis. In contrast, analogues containing succinil or isomers of aminobenzoic acid (o-, m- and p-Abz) at position 1 were all devoid of tachyphylatic property. In terms of biological property, these compounds still maintained partially the AngII potency. In complement, analogues containing modification at either position 2 (His, Glu, Lys, α-Fmoc-Lys and N^G-NO_2-Arg) or 4 (Asp, Phe, 2,6-dimethyl-Tyr or DMT) were not tachyphylatic, thus confirming the importance of the presence of free Arg^2 and Tyr^4 residues for tachyphylaxis. Most of these derivatives were also devoid of contractile property, excepting the His^2-AII and DMT^4-AII that maintained partially the AII activity in the ileum. Conformation of these and several other synthesized analogues have been currently examined in CD experiments for further correlation with their biological properties.