Cardiomodulating Actions of Low-Molecular Peptides from Various Groups

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A total of 61 low-molecular peptides belonging to various groups was tested and compared for their cardiomodulating potentials using *in situ* isolated frog hearts, and some neuropeptides among them showed marked cardiomodulating activity, as was evidenced by the substantial alterations they caused in the recorded parameters of strophanthin K cardiotoxicity.

Key Words: *heart; strophanthin K; peptides; functional modulation*

Cardiac glycosides remain the major therapeutic agents in many acute and chronic human diseases. Their use is, however, accompanied by toxic effects in 7.7% to 60% of patients [3,9]. The risk of intoxication is increased in patients (especially elderly ones) with impaired renal, hepatic, or endocrine functions or with acid-base disorders. Optimal means of preventing or minimizing the toxic effects of cardiac glycosides need therefore to be developed.

Recent studies have demonstrated adaptogenic, antiarrhythmic, and cardioprotective actions of certain neuropeptides including, among others, derivatives of enkephalins and delta sleep-inducing peptide [1,5,7,8]. We have examined and compared protective cardiomodulating properties of low-molecular peptides from various groups.

MATERIALS AND METHODS

The tests were conducted on male frogs (body weight 30-35 g) using the standard pharmacopeial procedure [2]. Briefly, groups of 15 frogs in each were fixed on their backs with plastic pins to foam plastic plates and their hearts were isolated *in situ* with dissection of the pericardium; a standard cardiotoxic dose of 0.005% strophanthin K was then injected under the skin of one thigh in a volume of 0.30 to 0.35 ml (depending on body weight), while the test peptide was injected at 0.15 mg/kg body weight in 0.1 mg of physiological saline under the skin of the other thigh (control frogs received only saline), and the time of onset and duration of two strophanthin K toxic effects — depressed cardiac automaticity and cardiac standstill in systole — were recorded; these effects usually occurred between minutes 45 and 60 post-injection.

Cardiomodulating activities of the following 61 peptides were estimated and compared: delta sleep-inducing peptide (DSIP) of the formula:
H-Trp-Ala-Gly-Gly-Asp-Ala-Ser-Gly-Glu OH (1)
1 2 3 4 5 6 7 8 9
and its analogs DSIP[DTrp^1] (2), DSIP[Phe(NO_2)^1] (3), DSIP[Phe^1] (4), DSIP[DPhe^1] (5), DSIP[Trp^1] (6), DSIP[Glu^3] (7), DSIP[Asn^5] (8), DSIP[Glu^5] (9), DSIP[DAla^2] (10), retro DSIP (11), DSIP 1-6[Phe^1] (12), DSIP[Phe^1,DAla^2] (13), DSIP[Phe^1, DAla^3] (14), DSIP[retro Phe^9] (15), DSIP[Phe^1, DAla^2] (16), DSIP[Phe^1,Gln^3] (17), tuftsin-DSIP 1-6 (18), DSIP 1-6[DTrp^1](19), DSIP 6-9[retro Phe^9] (20), DSIP[retro 5-7] (21), cyclo DSIP[Gly^3-Gly^9] (22); ACTH 4-7 (23), ACTH-DPhe 4-7 (24), ACTH 5-10 (25); substance P (SP) 6-11 (26), SP 8-11 [NLeu^{11}] (27), SP 10-11[NLeu^{11}] (28), SP 4-11 (29), SP 7-11[NLeu^{11}] (30); β-chain of MSH fragment 8-

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10 (31); neurotensin (NT) (32), NT[DTrp^{11}] (33), NT 9-13[DTrp^{11}] (34), NT 6-13[DTrp^{11}] (35), NT 11-13 (36), NT 10-13 (37), NT 9-13[Trp^{11}(NH_2)] (38), NT 9-13[DTrp^{11}(NH_2)] (39); tuftsin (40), tuftsyl-aminoadamantane-1 (41), tuftsyl-aminoadamantane-2 (42); dermorphin (D) (43) and its analogs D-2 (44), D-3 (45), D-4 (46), D-5 (47); kyotorphin (48), DArg kyotorphin (49); angiotensin-I (50), angiotensin-II (51); angiotensin-converting enzyme inhibitor (52); N-terminal fragment of fibrin α-chain (53); oxytocin 7-9 (MIF) (54); arginine vasopressin (55), lysyl vasopressin (56); oxytocin (57); pituitrin (58); mammophysine (59); hyphotocin (60); Glu-Trp dipeptide (thymogen) (61).

RESULTS

While most of the neuropeptides tested altered the latent period of strophanthin's cardiotoxic action to a small extent and only for a short time, the following neuropeptides exerted very marked modulating (protective or potentiating) effects:

- DSIP and its analogues 2, 4, 6, 10, and 21, tuftsin, neurotensin analogs 36 and 37, and fibrin α-chain fragment 53 prolonged the latent period by factors of 1.5 to 2.12 and decreased the time of cardiac systolic standstill ($p<0.05$);
- neurotensin analog 33, D-Arg kyotorphin, and angiotensin I shortened the latent period by factors of 1.44 to 1.86 and increased the time of systolic standstill ($p<0.05$-0.01).

Of interest are not only the demonstrated effects of peptides from different groups on cardiac function under toxic stress, but also, and especially, the recorded differences in the duration and magnitude of these effects between peptides from the same group. Although this phenomenon requires further study on hearts of warm-blooded animals and on isolated cardiac muscle cells, it may be assumed that low-molecular peptides can modulate the well-known mechanism via which cardiac glycosides such as strophanthin K exercise their pharmacological activity. Thus, the primary effect of glycosides is inhibition of the membrane enzyme Na^+, K^+-ATPase which mediates the ATP hydrolysis coupled with active ion transfer across membranes [4, 6]. As a result, Na^+ and K^+ transport and water binding change, with a consequent severalfold rise in the concentration of Ca^{2+} ions that will now activate actomyosin contraction and thus induce a systolic contraction of the cardiac muscle, which can be recorded experimentally [2].

Neuropeptides probably modulate the above process both via neurohumoral regulatory systems and by direct action on the membranes of cardiac muscle cells, thus leading to alterations in the properties of receptor areas of these cells and in the mechanisms by which ions are deposited and liberated. Unraveling the mechanisms by which neuropeptides are metabolized may demonstrate more complex relationships between the regulatory mechanisms involved in stress and antistress, in the maintenance of homeostasis, and in producing the variability of functions performed by neuropeptide metabolites.

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