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PEPTIDES INDUCING PSYCHOSIS

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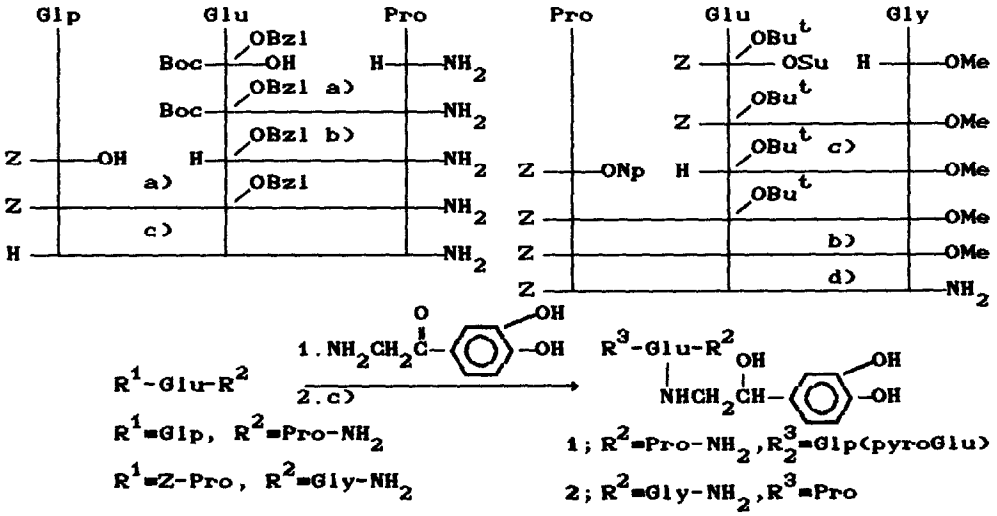
TRH and MIF analogues pyroglutamyl-N$^{\gamma}$[2-(3',4'-dihydroxyphenyl)-2-hydroxyethyl]glutaminyl-prolinamide (1) and prolyl-N$^{\gamma}$[2-(3',4'-dihydroxyphenyl)-2-hydroxyethyl]glutaminyl-glycinamide (2) were synthesized. Prolonged effects on higher nervous activity and behavioral effects in cats were caused by peptides 1 and 2 after intraperitoneal injection.

Since both catecholamines and neuroactive peptides thyrotropin-releasing hormone (TRH) and melanocyte-stimulating hormone-release inhibiting factor (MIF) coexist in synaptic terminals and have an interdependent influence on each other, hybridizing catecholamines with either TRH or MIF might provoke an aggravation of psychotropic effects, because hybrid molecules could be bound to both TRH (or MIF) and catecholamine receptors. Such compounds might display alternating activity from either of its components. We supposed that TRH- and MIF-modified norepinephrine could bind to both TRH or MIF and noradrenaline receptors, and thus change the normal functioning of catecholamine neurotransmitter systems. Such a result might be expressed as behavioral disorders in experimental animals.

For this purpose, TRH and MIF analogues 1 and 2 have been prepa-



Scheme: a) DCCI, 1-hydroxybenzotriazole; b) 4N HCl/dioxane;
c) H_2, 10% Pd/C; d) NH_3/MeOH

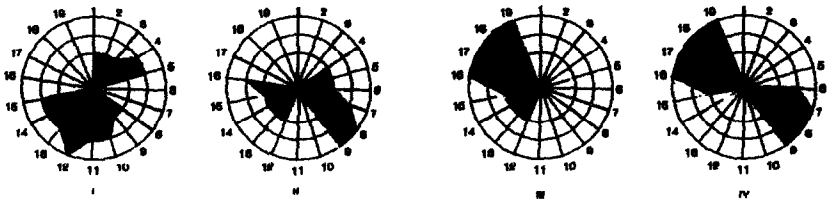


Fig. Lesion of original spectrum of emotional reactivity of cats after administration of peptides 1 and 2. I - the original spectrum of emotional reactivity before administration of peptides. II - the spectrum of emotional reactivity for first two days after administration of peptide 1. III - the spectrum of emotional reactivity in four days after administration of peptide 1. IV - the spectrum of emotional reactivity for first four days after administration of peptide 2. 1-19 - components of the spectrum of emotional reactivity: 1-play, 2-curiosity, 3-pleasure, 4-neatness, 5-guarded reaction, 6-anxiety, 7-fear, 8-fury, 9-clashing reaction, 10-sensation of pain, 11-sexuality, 12-sense of direction, 13-attitude to food, 14-attitude to drink, 15-locomotor activity, 16-stereotyped behavior, 17-catatonia, 18-catalepsy, 19-negativism

red by stepwise solution peptide chemistry starting with either prolinamide or glycine methyl ester (Scheme). Peptides Glp-Glu-Pro-NH_2 and Pro-Leu-Gly-NH_2 were coupled with α-amino-3,4-dihydroxyacetophenone [1], followed by catalytic hydrogenolysis and coupling of the norepinephrine moiety.

Peptides 1 and 2 (effective dose 1.6 mg/kg) were tested on cats in chronic experiments. The prolonged effects on higher nervous system activity and behavioral effects in cats last 51 days for peptide 1 and 11-13 days for peptide 2 after a single intraperitoneal dose in 10% aqueous ethanol. The spectrum of emotional reactivity (Fig.) was described using modified Valdman's approach [2]. The picture of prolonged behavioral disorder with an associated sequence of syndromes caused by peptide 1 can be regarded as a pattern of animal psychosis. The combination of affective disorder (fear and others) with catatonia was shown by peptide 2 as distinct from compound 1. Note that prolonged behavioral effects were observed only after injection of the peptide solution in the presence of ethanol. This is further evidence that alcohol exerts effects or neuropeptides and on specific neurotransmitter systems in different areas of brain [3] and affects the release of endogenous catecholamines from specific regions of brain [4].

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