Table III. Synergistic effects of methylbenzylamine-hydrochloride and sodium nitrite on mouse liver protein synthesis

Treatment	No. of replicates	Mean ^{3}H-leucine incorporation ± S.E.[a] (% of control values)
Control	8	53.4 ± 4.8
Sodium nitrite (100 mg/kg)	8	52.6 ± 2.3 (99%)
Methylbenzylamine-hydrochloride (1200 mg/kg)	8	56.3 ± 4.8 (105%)
Sodium nitrite and methylbenzylamine-hydrochloride	9	40.4 ± 4.2[b] (76%)

[a] Expressed as cpm/mgP; [b] Statistically significant interaction, $p < 0.01$.

The effects of DMA and $NaNO_2$ on uptake of ^{3}H-leucine into mouse liver protein are shown in Table II. Neither DMA nor $NaNO_2$ alone induced any statistically significant inhibition. However, DMA and $NaNO_2$ together produced 63 and 33% inhibition of leucine uptake at 6 and 18 h after treatment, respectively (Table II). Comparable inhibition of leucine incorporation was produced by combined administration of MBA and $NaNO_2$ (Table III).

In the present experiments, DMA or MBA when administered in combination with $NaNO_2$ produced synergistic acute inhibition of liver protein and nuclear RNA synthesis; similar inhibitory effects are also induced by dimethylnitrosamine[17] and methylbenzylnitrosamine[18]. These data confirm and extend findings of previous studies on induction of synergistic acute toxicity and hepatic nerosis in mice following oral administration of DMA or MBA together with $NaNO_2$[14] and afford strong presumptive evidence of in vivo nitrosamine synthesis from nitrite and amine precursors. The relevance of these findings to potential human hazards from continued use of nitrate and nitrite as food additives and from drinking of water with elevated nitrate merits further consideration.

Zusammenfassung. Orale Gabe von Dimethylamin oder Methylbenzylamin zusammen mit Natriumnitrit bewirkte eine synergistische Hemmung der Protein-Synthese in der Leber von Mäusen. Ausserdem hemmte die kombinierte Gabe von Dimethylamin und Nitrit synergistisch die Synthese nuklearer RNS in der Leber.

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Encephalitogenic Protein: a β-Pleated Sheet Conformation (102–120) Yields a Possible Molecular Form of a Serotonin Receptor

Carnegie[1] has recently suggested that a specified segment of the basic A1 protein composes one of the serotonin receptors in the central nervous system. The conformation suggested by Carnegie is based on a previous model of ours[2]. We wish to suggest an alternative model that accounts for the mode of action of the unusual aminoacid methyl-arginine. The model suggested by Carnegie is based on a coil conformation for the polypeptide and the role of methyl arginine is not accounted for. An α-helical conformation would be unlikely owing to the two glycine moieties in the sequence and the protein itself contains no α-helix[1]: but a β-conformation is possible. The conformation is illustrated in Figure 1 for this segment of the protein itself with 3 turns and 11 cross C=O... HN hydrogen bonds. This locates the 3 key aminoacids —Trp, Arg (Lys) and Gln—in a conformation capable of binding 5HT (in its preferred conformation)[3] in the manner shown in Figure 2. The β-structure gives a rigid molecule and the binding groups for 5HT are relatively fixed. As may be seen in Figure 2, the methyl-Arg and Phe moieties and the Gln (120), Arg (121) and Lysine (104) hydrocarbons form a lipophilic 'bed' at the bottom of which lies the indole ring of the Trp moiety, fixed by lipophilic interactions and steric hindrance. If the 5HT molecule in its preferred conformation is bound by π-π stacking to the Trp molecule, it attains the following additional contacts: 1. lipophilic: β-hydrocarbon to Trp π cloud and β-hydrocarbon and Arg γ-hydrocarbon: α-hydrocarbon to Arg

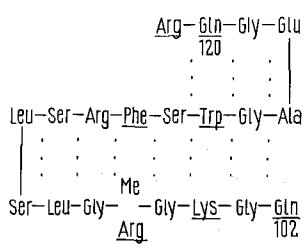

Fig. 1. The suggested conformation of the encephalitogenic polypeptide. The dots indicate CO..HN hydrogen bonds.

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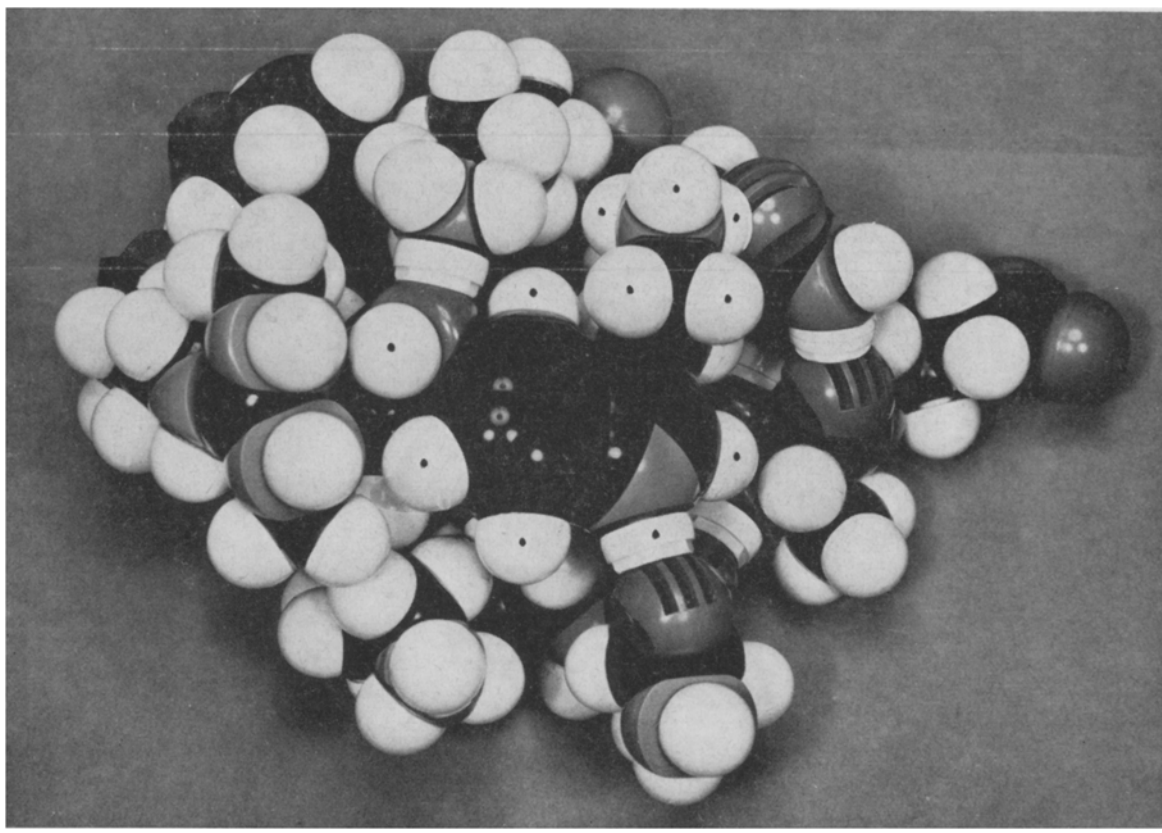

Fig. 2. CPK molecular model of the polypeptide forming a possible receptor site for 5HT shown bound. Aminoacids 107–112 are left out. They form a simple β-turn.

δ-hydrocarbon: ring hydrocarbons to Methyl-Arg, 2. *Polar*: $-NH_3+$ to Gln O: hydroxyl O from Arg $= NH_2^+$ and ring NH to Gln (102) O. Note that the Gln-Arg carbon-carbon bond (120–221) is twisted by a break in the β-conformation. The β CO = NH hydrogen bond is replaced by a hydrogen bond from Ser (114) OH to peptide O (Pro – 122) and possibly a second from Arg (112) to the next peptide O (123). This twist is necessary for the Arg-5HT interaction described. Gln (120) binds by a hydrogen bond to the carbonyl O of Ala (117).

The complex (Trp-Gln-Arg) somewhat resembles in size, form and charge distribution the molecule of strychnine. This may explain the convulsant activity of the basic protein when injected intraventricularly[1]. The function of 5HT in this position might be to maintain this segment of the protein molecule in its β-conformation or to disrupt it by a charge transfer operation (to Trp). This hypothesis can be tested by direct physical investigations using NMR, ORD and CD techniques of the conformation of these polypeptides[4].

Zusammenfassung. Es besteht die Annahme (CARNEGIE 1970), dass das basische Gehirnprotein als Rezeptor für Serotonin wirkt, und es wird der Vorschlag für molekularbiologische Reaktionen von Serotonin-Rezeptoren gemacht.

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[5] Acknowledgments. We are most grateful to Dr. D. URRY for advice on protein conformation, to Dr. P. R. CARNEGIE for helpful discussions and the Ealing Corporation for the generous loan of molecular models.

The Linear Amino Acid Sequence of-α_1Acid Glycoprotein

Although α_1-acid glycoprotein (orosomucoid), a human plasma globulin (for review see ref. [1]), is probably the most extensively studied protein with regard to the structure[2] and biosynthesis[3] of its carbohydrate moiety, it is only very recent that significant information concerning its amino acid sequence has been reported[4,5]. The complete elucidation of its primary structure has been hampered by the inability of investigators to establish the amino-terminal sequence, since digestion of α_1-acid glycoprotein by specific (chymotrypsin and trypsin) and nonspecific (pronase) proteases does not yield overlapping peptides, but affords the same pyrrolidone carboxylic acid, PCA-