and *vice versa*. In other words, the data suggested that DOPA and 5-HTP were competing for one and the same enzyme. Experiments performed with hog brain extracts gave similar results. In Figure 2, the data from a typical experiment are given, in which an extract from the caudate and lentiform nuclei, the diencephalon and the mesencephalon was used. It will be seen that the addition of one of the amino acids caused an inhibition of the decarboxylation of the other. The inhibition was 50% when the concentrations of the L-forms of the two amino acids were equal. The inhibition does not seem to be due to lack of co-enzyme, as doubling the amount of pyridoxal-5-phosphate had no effect on the results.

A similar competition possibly also occurs *in vivo*: Repeated injections to rabbits of DOPA (600 mg/kg in total) during 2 h lowered the brain 5-HT level to 50–60% of the normal. Whether this decrease was due to inhibited biosynthesis or to release followed by oxidation, remains to be discovered, however.

In order further to elucidate this problem, DOPA and 5-HTP decarboxylase activities in various regions have been determined using the same technique as described earlier[2]. The results are given in Figure 3. A certain degree of correlation between the initial accumulation of dopamine after DOPA injection and DOPA decarboxylase activity is apparent from a comparison of Figures 1 and 3. A high order of correlation was found between the distribution of the two amino acid decarboxylases. This finding lends additional support to the assumption that the decarboxylation of the two amino acids is carried out by one and the same enzyme.

After the injection of DOPA, the animals showed increased motor activity and signs of sympathetic stimulation. The effect on motor activity appeared to be closely correlated to the accumulation of dopamine in brain: both phenomena appeared to reach their maxima in about 25 min. Motor activity then appeared to decline along with the drop in the dopamine level. About 50 min. after the injection of DOPA, there was still definite evidence of central excitation. It is interesting to note that at this interval the dopamine levels were fairly low in all parts of the brain except the corpus striatum, suggesting that this part of the brain forms an important site of action of dopamine on motor functions. Administration of 5-HTP caused an appearance quite different from that produced by DOPA. There was no motor hyperactivity, rather a decrease in voluntary movements combined with general muscle tremors.

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Å. BERTLER and E. ROSENGREN

Department of Pharmacology, University of Lund (Sweden), July 24, 1959.

Zusammenfassung

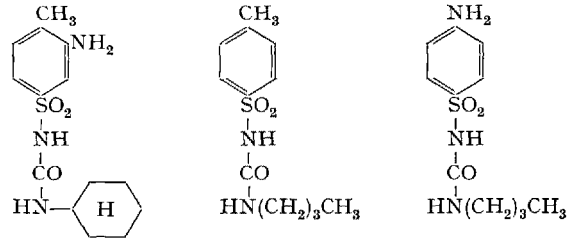
Im menschlichen Gehirn kommen grosse Mengen von 3-Hydroxytyramin im Nucleus Caudatus und dem Putamen vor.

Injektion von 3,4-Dihydroxyphenylalanin in Kaninchen bringt eine schnelle Akkumulation von 3-Hydroxytyramin in den Gehirnteilen, die reich an Katecholaminen sind, zustande. Die Fähigkeit das akkumulierte 3-Hydroxytyramin abzubauen scheint im ganzen Gehirn dieselbe zu sein.

Hemmungsversuche und Aktivitätsuntersuchungen der Fermente in verschiedenen Gehirnteilen *in vitro* sprechen dafür, dass 5-Hydroxytryptophan und 3,4-Dihydroxyphenylalanin von einem und demselben Ferment decarboxyliert werden.

On the Hypoglycemizing Effect of Metahexamide

Metahexamide (N(3-amino-4-methyl-benzenesulfonyl)-N'-cyclohexylurea) is a new oral hypoglycemizing agent[1] (see formula) having a better therapeutic index than other similar drugs.



Metahexamide D 860 BZ 55

Following the line of our previous investigations we have been interested to study the hypoglycemic action, the absorption and disappearance from blood and the effect on glucose uptake by rat diaphragm *in vitro*.

Methods. Metahexamide was always administered by stomach tube, as the reference drug *p*-tolylsulfonilbutylurea (D 860). Blood sugar levels were determined in duplicate in 0·1 ml samples by the Nelson procedure[2] in 12 h fasted Sprague-Dawley rats or rabbits of mixed breed.

Metahexamide has been evaluated in blood and kidney with a modified method of BRATTON and MARSHALL[3]. To the filtrate obtained after precipitation with 15% trichloroacetic acid and filtration through no. 1 Whatman filter paper, were added 0·1% sodium nitrite (1 ml), 0·5% ammonium sulfamate (1 ml), concentrated hydrochloric acid (1 ml) and 0·1% N (1-naphthyl)ethylenediamine dihydrochloride (1 ml). The resulting colour was read in a photoelectric colorimeter using a filter having a maximum transmission at 520 mμ. Glucose uptake tests were performed on rat hemidiaphragms in Krebs-Ringer bicarbonate buffer as described elsewhere[4–6].

Results

a) *Hypoglycemic activity in vivo.* Metahexamide and D 860 (as reference drug) have been found to be active oral hypoglycemizing drugs both in rats and rabbits. In rats Metahexamide induces maximum blood glucose falls of 20, 35, and 50% respectively after 10, 40, and 100 mg/kg[7], while D 860 is without activity at 10 mg/kg and at 50 and 100 mg/kg, produces falls of blood sugar level to 35 and 50% respectively.

The maximum effect is achieved for both drugs about 2 h after administration, but Metahexamide hypoglycemia

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[7] The LD_{50} of Metahexamide by oral route in rat is about 2 g/kg.

Table

No experiment	Control glucose uptake mg/g/h	Metahexamide		D 860		% Variation	Average
		γ/ml	Glucose uptake mg/g/h	γ/ml	Glucose uptake mg/g/h		
1	7·2	5	8·5	–	–	+22	22
2	5·4	5	6·7	–	–	+24	
3	7·0	5	8·4	–	–	+20	
4	5·6	10	6·9	–	–	+23·5	26
5	6·0	10	7·7	–	–	+28·4	
6	4·5	10	5·4	–	–	+20·0	
7	6·5	10	8·9	–	–	+36·9	
8	7·8	10	9·8	–	–	+25·7	
9	4·9	10	6·2	–	–	+26·5	
10	5·6	–	–	10	6·03	+ 7·7	1·7
11	6·9	–	–	10	7·20	+ 4·3	
12	4·3	–	–	10	4·00	− 7·0	
13	5·2	–	–	20	6·30	+21	24·8
14	6	–	–	20	7·60	+26·7	
15	7·2	–	–	20	8·95	+24·5	
16	6·6	–	–	20	8·20	+26·6	

is longer lasting than that of D 860, the first being present up to 8 h after administration. Similar results have been obtained in rabbits.

b) *absorption and excretion.* After a single dose of 40 mg/kg intraperitoneally in rat, the maximum blood concentration of Metahexamide was detected after 4 h (average 7·9 mg/100 ml), but also after 12 h a concentration of 6·4 mg/100 ml was present. The kidney Metahexamide concentration closely parallels that of blood, being 5·2 mg/100 g after 4 h and 4 mg/100 g, after 12 h.

The rapid absorption and the slow desappearance from blood of Metahexamide may account for the rapid onset of hypoglycemia and the long lasting effect.

c) *glucose uptake.* In the Table are reported the effects of Meta hexamide and D 860 on glucose uptake by rat hemidiaphragm *in vitro*.

As already shown for sulfanilylbutylurea (BZ 55) and D 860, Metahexamide also increases glucose uptake by isolated rat diaphragm. In this test Metahexamide is considerably more active than D 860.

From our findings we may conclude that the remarkable hypoglycemizing action of Metahexamide is justified by two properties: the slow metabolism and the strongly enhanced peripheral glucose utilization. These two effects could explain the higher hypoglycemic activity of Metahexamide in comparison with related compounds.

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S. GARATTINI, A. JORI, V. PALMA, and L. TESSARI

Institute of Pharmacology, University of Milan (Italy), April 17, 1959.

Riassunto

La Metahexamide, N(3amino-4-metilbenzenesulfonil)N'-cicloesilurea, possiede nel ratto e nel coniglio un effetto ipoglicemizzante più narcato rispetto al *p*-tolilsulfanilbutilurea (D 860). Il nuovo farmaco si dimostra più attivo del D 860 nell'accelerare la scomparsa di glucosio da parte del diaframma isolato di ratto. La Metahexamide si distribuisce rapidamente in tutti gli organi e scompare dal sangue molto lentamente. Il maggiore effetto della Metahexamide, rispetto a composti similari, viene interpretato sulla base di un lento metabolismo e in rapporto all'intenso effetto favorente la metabolizzazione del glucosio a livello periferico.

Les glycoprotéines sériques dans le granulome expérimental provoqué par la carrageenine

Les travaux de CATCHPOLE *et al.*[1] ont déjà établi une liaison entre la prolifération du tissu conjonctif dans les états inflammatoires et l'augmentation des mucoïdes sériques et urinaires. On sait d'autre part que l'haptoglobine constitue la fraction des globulines α_2 dont l'augmentation chez l'homme est parallèle à celle des mucoïdes perchloro- ou sulfosalicylosolubles dans de nombreux états pathologiques[2] (exception faite pour la plupart des tumeurs malignes[3] et certaines affections hépatiques[4]. Dans une revue générale l'un de nous et BOUSSIER ont exposé les arguments en faveur de la production par le tissu cojonctif proliferé des mucoïdes α_1 et α_2 qui augmentent dans les états inflammatoires[5]. Cette augmentation constitue le reflet humoral de l'importance de la réaction inflammatoire de la substance fondamentale.

Nous avons entrepris une série d'études afin d'obtenir des renseignements d'ordre quantitatifs sur la teneur en mucopolysaccharides «neutres» du tissu conjonctif et sur les rapports qui existent entre ces mucopolysaccharides neutres et les glycoprotéines sériques. Dans ce travail nous étudierons le comportement des glycoprotéines sériques et en particulier celui de la fraction sulfosalicylosoluble et de l'haptoglobine au cours du développement du granulome expérimental.

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