efflux should have been more prominent in midbrain slices than in cortical slices if the effect of halothane on GOT efflux is related to its anesthetic action.

The observed changes in GOT efflux in cerebral cortical slices exposed to halothane are best explained on the basis of increased cell membrane permeability. Which nerve cells are affected, how they are affected and the significance of the effect warrant further investigation.

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Indole-2-carboxylic acids, a new class of hypoglycemic compounds

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IN THE COURSE of screening for hypoglycemic agents, 5-methoxyindole-2-carboxylic acid (MICA) was found to consistently lower blood sugar in the fasted rat. Many similar compounds were tested and the results of these experiments are herein reported.

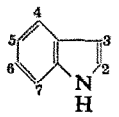
Alloxan monohydrate was obtained from Eastman Organic Chemicals; sodium tolbutamide was a gift of the Upjohn Company. Test compounds were obtained from commercial sources or were synthesized in these laboratories, as indicated in the tables. Commercially obtained compounds were used without further purification. High viscosity sodium carboxymethylcellulose (7HF) was obtained from the Hercules Powder Company and dissolved in water by prolonged boiling. Other chemicals were Merck, reagent grade. Rats were of the Sherman (Wistar) strain, raised in these laboratories; mice were either of the ICR or MF-1 strain from Manor Farms, New York.

Test compounds were homogenized in 0·5% sodium carboxy-methylcellulose at an appropriate concentration so that the desired dose could be administered in 1 ml/100 g of body weight. They were injected i.p. into unanesthetized animals or injected intragastrically by stomach tube under light ether anesthesia. Blood samples (0·1 ml) were obtained from rats from the tail, diluted 10-fold in 0·25% sodium oxalate, and analyzed for reducing sugar content by the alkaline ferricyanide method[1] as modified for the Technicon autoanalyzer.[2] Mice were alloxanized by the rapid i.v. injection of 0·1 ml of 2% alloxan monohydrate. Mice were tested for glycosuria by use of a glucose oxidase paper.* The occasional mice which did not develop glycosuria were discarded, and the remaining diabetic mice were used within 1–3 weeks of alloxanization. Blood was obtained from decapitated mice from the cervical stump, diluted 20-fold and analyzed for reducing sugar as above.

Results of testing in the rat are given in the tables. Compounds in the indole series are shown in Table 1. The following structurally related non-indoles were tested at 200 mg/kg and were not hypoglycemic: benzofuran-2-carboxylic acid, benzoxazole-2-carboxylic acid, benzimidazole-2-

* Available under the trademark Tes-Tape (Eli Lilly & Co.).

TABLE 1. RESULTS OF HYPOGLYCEMIC TESTING ON INDOLES IN RATS



	Source*	Effect (% lowering at 3 hr)†		
		dose (mg/kg)	i.p.	oral
2-Carboxy-	A	100	37	33
2-Carboxy-5-methoxy-	A	100	42	29
2-Carboxy-5-methyl	A	200		58
		50	44	
2-Carboxy-5-methyl-,ethyl ester	A	200	35	23
2-Hydroxymethyl-	L	200	28	12
2-Carboxy-5-bromo-	A	200	24	22
2-Carboxy-3-methoxy-	L	100	20	NS‡
2-Carboxy-4-chloro-	L	250	26	21
2-Carboxy-5-benzyloxy	L	100	18	NS
2-Carboxy-5-chloro-	A	250	NS	
2-Carboxy-6-methoxy-	L	200	NS	
Unsubstituted		200	NS	
5-Methoxy-	L	200	NS	
5-Benzyloxy-	L	250	NS	
3-Carboxy-	A	300	NS	
3-Acetic acid	A	200	NS	
3-(3′-Aminopropyl)-, hydrochloride	A	50	NS	
2-Methyl-	A	200	NS	
2-Hydroxy-	L	200	NS	
2-Carboxy-5-methoxy-, ethyl ester	L	250	NS	
2-Carboxy, ethyl ester	A	200	NS	
2-Carbamoyl-	L	200	NS	
2-Carboxyl-l-methyl-	L	200	NS	
2-Carboxy-5-hydroxy-	L	200	NS	
2-Carboxy-5-nitro-	L	200	NS	
2-Carboxy-5-methoxy-6-methyl-	L	250	NS	
2-Carboxy-6-chloro-	L	200	NS	
2-Carboxy-6-benzyloxy-5-methoxy-	R	200	NS	
2-Carboxy-5,6-dibenzyloxy-	R	200	NS	
2-Carboxy-7-methoxy-	L	200	NS	
2,3-Diphenyl-	A	200	NS	

* L = Lederle Laboratories, Organic Chemical Research Section; A = Aldrich Chemical Co., Inc.; R = Regis Chemical Co., Inc.

† Lowering = [(mean blood sugar of controls − mean blood sugar of test rats) × 100]/mean blood sugar of controls.

‡ NS = not significant. Significance was estimated from a 2-stage sequential test using a historical population variance based on tests of sodium tolbutamide, 50 mg/kg, i.p. Each datum is a mean based on at least four rats compared with six controls; the estimated 95 per cent confidence limits are ± 8 per cent lowering.

carboxylic acid, quinoline-2-carboxylic acid, 4,8-dihydroxyquinoline-2-carboxylic acid, pyrrole-2-carboxylic acid, L-proline and pyrrocoline-2-carboxylic acid. The doses employed were all nontoxic in the crude sense that they caused no deaths in 24 hr.

The results of several experiments in alloxan diabetic mice are shown in Table 2. It is apparent that the mice were sufficiently alloxanized to be refractory to tolbutamide, and yet were still responsive to MICA.

Several indoles have been previously reported by others as hypoglycemic in the rat: L-tryptophan in large doses[3] and a series of homologues of indole-3-acetic acid.[4, 5] The indole-2-carboxylic acids herein reported as active are far more active than L-tryptophan. They presumably differ also from indole-3-acetic acid because the latter is reported ineffective in the alloxanized rat[6] and human juvenile diabetic,[7] while MICA is active in the alloxan diabetic mouse. The structural requirements for hypoglycemic activity are rather stringent, even minor modifications of the compounds causing loss of activity. The requirements may be summarized as follows: (1) indole nucleus; (2) carboxyl group

TABLE 2. EFFECT OF 5-METHOXYINDOLE-2-CARBOXYLIC ACID ON ALLOXANIZED MICE*

Expt.	No. of mice/group	Median blood sugar (mg/100 ml)		
		Control	Tolbutamide (50 mg/kg, i.p.)	5-Methoxyindole-2-carboxylic acid (100 mg/kg, i.p.)
1	3	478	483	330
2	6	504	530	378
3	10	412	479	354

* Alloxanized male mice, dosed as indicated, were bled 60 min after dosing. Medians are used to avoid large changes in mean from occasional "tolbutamide-responders" and occasional hypoglycemic moribund mice. However, analysis of variance, without correcting for or discarding outlying values, shows 5-methoxyindole-2-carboxylic acid to lower blood sugar significantly ($P = 0{\cdot}02$), while tolbutamide does not.

at the 2-position or a potential carboxyl group at the 2-position; (3) the 1-position must be unsubstituted, as must be the 6- and 7-positions. A variety of electron-releasing groups seem to be suitable for the 5-position.

Studies on the mechanism of action of these compounds suggest that they inhibit gluconeogenesis.[8–10]

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The effect of γ-hydroxybutyric acid on amino acid levels in brain

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γ-HYDROXYBUTYRIC acid (GHB), a general anesthetic with certain unusual properties, has recently been extensively studied in experimental animals and in man.[1–4] The chemical structure of GHB is quite similar to that of γ-aminobutyric acid (GABA), which is a normal constituent of brain with