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A novel hypoglycemic compound*

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THE HYPOGLYCEMIC activity of 2-piperazino-4(3H)-quinazolinone monoacetate (referred to as Compound I) on rat and rabbit has been reported.[1,2] More recently the effect of Compound I has been studied in other species of normal animals and in diabetic rats and monkeys The results obtained are presented in this paper.

Albino rats of the Central Drug Research Institute colony (120–175 g) and the Charles–Foster strain (118–135 g); albino rabbits (1·2–1·5 kg) and guinea pigs (400–600 g) of the Central Drug Research Institute colony; mongrel dogs (6–11 kg) and rhesus monkeys (*Macaca mulatta*) (4–6 kg) were used in these experiments.

Compound I was administered orally as a solution in distilled water, in doses from 10 to 100 mg/kg body wt as shown in the tables. Control animals received an equal volume of the vehicle.

Alloxan, obtained from British Drug Houses, was administered to albino rats and monkeys. Administration of 1 to 4 units of Plain and PZ insulin per animal were needed to override the initial phase of hyperglycemia and acidosis for about 3 weeks. Albino rats after fasting had a blood sugar level greater than 400 mg per cent and monkeys had levels greater than 300 mg per cent. Only animals in this range were selected. Another group of albino rats were 95 per cent pancreatectomized by the method of Scow.[3] After recovery (28 days) they received an intramuscular injection of hydrocortisone (Calbiochem) (5 mg/rat/day) in 10 per cent ethyl–alcohol for 4–6 days to produce diabetes, characterized by a fasting blood sugar level greater than 200 mg per cent on 2 successive days.

The animals were fasted overnight, water being allowed *ad lib*. Blood from a vein was collected from the animals prior to administration of Compound I and later at various intervals. Blood sugar was estimated according to Somogyi's method as modified by Nelson.[4]

It can be seen from Table 1, that Compound I has a lowering effect on the blood sugar in albino rats, rabbits and dogs. However, the blood sugar of the monkey increases slightly. The blood sugar levels of guinea pigs were not altered.

From Table 2, it is clear that Compound I is capable of lowering the blood sugar of hydrocortisone treated pancreatectomized (max = 51 per cent) rats; whereas it has just a slight effect (max = 6 per cent) on alloxan-treated rats. Compound I lowers blood sugar levels of alloxan-treated monkeys, the maximum effect being 51 per cent, as is evident from Table 2. Thus the hypoglycemic character of Compound I has been confirmed in different species of normal and diabetic animals. It can lower blood sugar considerably when given orally to hydrocortisone-treated pancreatectomized albino rats

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as well as alloxan-treated monkeys. Failure of the compound to evoke hypoglycemia in dogs and monkeys is unexplained.

Chronic toxicity of the compound and its mode of action is being currently investigated.

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TABLE 1. SHOWING THE EFFECT OF COMPOUND I IN DIFFERENT SPECIES OF NORMAL ANIMALS

	Species	No. animals	Dose (mg/kg)	Time after dosing (hr)	Change in blood sugar from initial (%)
1	Albino rat (C.F. strain)	6	75	2	(−) 57
2	Albino rat (CDRI colony)	6	0	2	0
3	Albino rat (CDRI colony)	10	75	2	(−) 63
4	Albino rat (CDRI colony)	26	50	2	(−) 52
5	Albino rat (CDRI colony)	12	35	2	(−) 54
6	Albino rat (CDRI colony)	18	25	2	(−) 46
7	Albino rabbit (CDRI colony)	4	0	2	(+) 6
8	Albino rat (CDRI colony)	7	100	2	(−) 27
9	Guinea pig	4	100	2	0
10	Dog (mongrel)	2	0	½	0
11	Dog (mongrel)	3	50	½	(−) 15
12	Dog (mongrel)	2	20	½	(−) 15
13	Dog (mongrel)	2	10	1	(−) 19
14	Rhesus monkey (*Macaca mulatta*)	2	0	2-4	(+) 6
15	Rhesus monkey (*Macaca mulatta*)	3	100	2	(+) 20
16	Rhesus monkey (*Macaca mulatta*)	2	60	2	(+) 20
17	Rhesus monkey (*Macaca mulatta*)	2	20	2	(+) 14·5

(−) Fall in blood sugar.
(+) Rise in blood sugar.

TABLE 2. SHOWING THE EFFECT OF COMPOUND I, IN HYPERGLYCEMIC ALBINO RAT AND RHESUS MONKEY

Species	Nature of diabetes	Drug	Dose (mg/kg)	Blood sugar mg/100 ml			
				Fasting	after 1 hr	after 2 hr	after 4 hr
Albino rat	Alloxan	Nil		415 ± 22·3 (4)	397 ± 40·81 (4)		390 ± 31·01 (4)
Albino rat	Alloxan	I	100	446 ± 12·88 (6)	392 ± 26·17 (6)		358 ± 31·01 (6)
Albino rat	Pancreatectomized hydrocortisone treated	I	100	218 ± 21·49 (6)	*116 ± 16·30 (6)		106 ± 24·59 (6)
Rhesus monkey	Alloxan			340 ± 20·4 (3)	333 ± 27·2 (3)	320 ± 40·3 (3)	360 ± 5·2 (3)
Rhesus monkey	Alloxan	I	50	545 ± 71·1 (3)	346 ± 45·7 (3)	*286 ± 25·0 (3)	*266 ± 26·6 (3)

Figures in parentheses indicate number of observations.
* Significant at 5 per cent level compared to fasting value.
Values indicate Mean ± S.E.