were utilized. The experiments were initiated between 08.15–09.15 h. The anterior pituitaries, from which the posterior and intermediary lobes were removed, were separated into identical halves. 3 pituitary halves were used in each group and there were 4–6 groups in each determination.

The tissues were incubated, with shaking, for 60 min at 37 °C in an atmosphere of 5% CO_2–95% O_2 in 1.0 ml of Krebs Ringer bicarbonate buffer containing 11 m*M* D-glucose[17]. The incubation medium was then replaced by fresh buffer and glucose and the somatostatin analogue was added as indicated in the Table. In the present studies, after a further 2 min incubation, 20 µl vehicle or PGE_2 (1×10^{-6} *M*) was added for the incubation period of 4 min. The vehicle employed for the PGE_2 was 0.1 ml ethanol, 0.1 ml sodium carbonate (1.8 mg/ml) and 0.8 ml water.

For the assay of the cyclic AMP, the cyclic AMP was extracted from the tissues with 5% trichloroacetic acid and measured by the receptor-binding assay of GILMAN[19] utilizing 10 µg of protein of the inhibitor and 1 µg of receptor preparation (P-5511, Sigma Chemical Co.). [8-^{3}H]-cyclic AMP (Schwarz-Mann Co.; 28 Ci/mole) was employed at a final concentration of 40 n*M*. Unlabelled cyclic AMP was obtained from Calbiochem Co. Assays were performed in triplicate. After filtration, the filters were dried and 10 ml toluene-phosphor [0.4% 2,5-diphenyloxazole and 0.005%, 1,4-*bis* (5-phenyloxazole-2-yl)benzene] employed for scintillation counting.

Results and discussion. Somatostatin, 1×10^{-7} *M*, inhibited by 50% the adenohypophyseal cyclic AMP accumulation induced by PGE_2; at the lower level of 0.2×10^{-7} *M* the inhibition was decreased (Table). Similar inhibitory activities at these concentrations were observed with the [desamino[1]]-, [desamino[1]][descarboxy[14]]- and [D-Lys[4]]-somatostatin analogues; the [descarboxy[14]]-somatostatin was effective at 5×10^{-7} *M*. The [D-Lys[9]]-somatostatin analogue did not cause an alteration in the cyclic AMP accumulation even at 5×10^{-7} *M*.

Somatostatin at 1×10^{-7} *M* did not cause any appreciable change in the basal cyclic AMP accumulation nor did any of the above analogues at 5×10^{-7} *M* (e.g., control: 5.7 ± 0.7; somatostatin: 5.0 ± 0.8; D-Lys[4]-somatostatin: 5.2 ± 0.3 pmoles cyclic AMP/anterior pituitary ± SE).

These results indicate that, in regard to the structure-activity relationship of the analogues, the terminal amino group does not appear to be of importance for the inhibitory activity on the PGE_2-induced cyclic AMP accumulation; elimination of the terminal carboxyl group results in an analogue exhibiting reduced activity. Both groups may be eliminated without altering the inhibitory activity. Further, the configuration at the asymmetric center of the lysyl moiety at position 4 is irrelevant since the [D-Lys[4]]-analogue exhibited a similar activity. In contrast, the configuration at the asymmetric center of the lysyl moiety at position 9 is of importance since the [D-Lys[9]]-analogue did not exhibit the inhibitory activity even at a higher level.

Somatostatin exhibits a wide spectrum of suppressor action on hormonal release in various species. In addition to an effect on growth hormone and thyrotropin, somatostatin also shows extrapituitary actions in inhibiting the release of insulin, glucagon and gastrin[20]. In view of the present findings, the effects of the somatostatin analogues on the release of growth hormone, and other hormones, are of interest. In this regard generally similar relative activities as found in the present study have been observed with the analogues with respect to their abilities to inhibit basal gastric acid secretion in the unanesthetized rat[21].

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The Sedative Effects of Nicotinamide on Gerbil Wheel-Running Activity[1]

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Summary. The activity of 5 groups of gerbils was monitored over 22 days. 3 of the groups received daily injections of nicotinamide (125, 250 or 500 mg/kg) and a 4th group received saline. The 5th group was untreated. The results indicated that both the 250 and 500 mg/kg nicotinamide administrations greatly reduced the activity levels of the gerbils.

BEATON et al.[2] have previously reported that the administration of 250 mg/kg nicotinamide to mice resulted in a significant increase in the amount of paradoxical or rapid eye movement sleep. WOOLLEY[3] had observed that nicotinamide administration appeared to induce sedation in mice. This was later confirmed[4] in rats using the Animex motilitymeter, however the dosage used in these studies was 1 g/kg. The present study describes the effects of lower doses of nicotinamide on gerbil activity.

Methods. 25 adult, male gerbils weighing between 55 and 65 g were used. The gerbils were housed singly in a sound-attenuated room which had a reverse 12 h light/dark cycle. The lights were off from 06.00–18.00 h. Each animal was given access to a Lafayette Instrument Company Running Wheel, with a circumference of 1.1 meters, for 30 min on 2 consecutive habituation sessions on which no data were recorded. The animals were given a further 6 pre-study sessions to determine a baseline level of running wheel activity. These sessions were on the Monday, Wednesday and Friday of the 2 weeks preceeding the study. The number of wheel revolutions per animal per session was noted each day. The total number of wheel revolutions per animal was calculated over all 6 pre-study sessions. On the basis of these data the gerbils were divided into 5 equal groups which were matched on the level of wheel running activity.

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Table I. The mean and standard deviation for the number of wheel turns per group of gerbils per session

	Baseline	Saline	Nicotinamide		
			125 mg/kg	250 mg/kg	500 mg/kg
Pre-study	361.9 ± 107	363.9 ± 114	360.5 ± 121	355.0 ± 109	361.0 ± 104
Day 1	408.3 ± 117	427.1 ± 98	269.9 ± 80	280.6 ± 139	280.0 ± 104
Day 3	445.7 ± 138	503.9 ± 83	305.1 ± 170	356.6 ± 191	386.3 ± 113
Day 8	446.1 ± 109	492.2 ± 65	438.9 ± 161	360.3 ± 175	302.2 ± 134
Day 10	431.4 ± 133	462.2 ± 78	499.8 ± 112	387.1 ± 152	281.4 ± 119
Day 15	522.6 ± 130	525.4 ± 51	550.3 ± 118	472.2 ± 116	285.4 ± 113
Day 17	428.2 ± 126	452.0 ± 84	497.0 ± 160	369.5 ± 144	343.6 ± 134
Day 22	550.6 ± 138	506.2 ± 93	531.9 ± 170	366.6 ± 140	322.4 ± 122

Table II. The percentage change from the untreated baseline for the saline and nicotinamide groups

	Saline	Nicotinamide		
		125 mg/kg	250 mg/kg	500 mg/kg
Pre-study	100	100	99	100
Day 1	105	66	69	69
Day 3	113	68	80	87
Day 8	110	98	81	68
Day 10	107	116	90	65
Day 15	101	105	90	55
Day 17	106	116	86	80
Day 22	92	97	67	59

Table III. The percentage difference between the nicotinamide treatments and the saline control

	125 mg/kg	250 mg/kg	500 mg/kg
Day 1	− 39	− 36	− 36
Day 3	− 45	− 33	− 26
Day 8	− 12	− 29	− 42
Day 10	+ 9	− 17	− 42
Day 15	+ 4	− 11	− 46
Day 17	+ 10	− 20	− 26
Day 22	+ 5	− 25	− 33

Because earlier studies with gerbils (unpublished data) have shown that the baseline level of activity shifts even after 20 sessions, it was decided to include 1 group of gerbils to which no treatments were to be administered (baseline group). The 4 other groups consisted of a saline injected group and 3 nicotinamide groups (treated with 125, 250 and 500 mg/kg nicotinamide). The pH of all nicotinamide solutions was adjusted to approximately 7.4. All injections were in a volume of 0.1 ml/20 g and were given i.p. 30 min before the animals were placed in the wheel. The baseline group was handled at this time.

The animals were run in the wheel on days 1, 3, 8, 10, 15, 17 and 22, but were injected daily. The total number of wheel revolutions per 30 min session was noted for each animal.

Results. The mean and standard deviation were calculated for each group for each data collection day and these data are shown in Table I. The standard deviations are relatively large because of the small number of subjects in each group. As was noted in the Methods section we have previously observed that the baseline shifts over time with this measurement. The data were therefore recalculated and expressed as percentages of the untreated baseline group. These data are shown in Table II. Table III shows the percentage difference between the saline and nicotinamide treated groups.

It is quite obvious from Tables II and III that the administration of 250 and 500 mg/kg nicotinamide resulted in decreased wheel-running rates. The lowest dosage of nicotinamide, although inducing an initial decrease in activity, was inactive.

Discussion. Much controversy surrounds the use of niacin in the treatment of schizophrenia. HOFFER[5] and his associates have repeatedly reported the effectiveness of nicotinic acid in the treatment of schizophrenia; however, many other investigators have failed to do so (these studies are reviewed by WYATT et al.[6]). Nicotinamide was used therapeutically because of its alleged role as a methyl group acceptor. However, it has not been shown that nicotinic acid can reverse the exacerbations observed in schizophrenics after the administration of methionine[7], nor is there any reported evidence that it impairs the methylation capacity of the body. Furthermore, BALDESSARINI[8] reported that nicotinamide is not a good methyl group acceptor in the rat and does not lower levels of S-adenosyl methionine.

We have previously observed that nicotinamide alters the sleepwake cycles of mice such that the percentage of rapid eye movement sleep increased significantly. Also WOOLLEY[3] and others[4] have noted a sedative effect in mice and rats after the administration of nicotinamide. This present study shows quite clearly a marked decrease in wheel-running activity in gerbils after 250 and 500 mg/kg of nicotinamide. Therefore, nicotinamide must have central effects unrelated to its role as a vitamin. The degree to which the therapeutic effects of niacin are related to the observed sedative effects are worthy of further investigation.

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