se demostró incubando la mescalina radioactiva con la fracción soluble del cerebro de las ratas. Nuestros resultados indican que el cerebro de dichos animales puede acetilar mescalina, y que la acetilación ocurre predominantemente en la fracción soluble.

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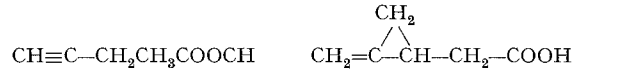
Elevation of Hepatic Tyrosine 2-Oxoglutarate Aminotransferase in Rats by 4-Pentynoic Acid, a Hypoglycemic Agent

Hardeland[1] reported that quinolinic acid and quinaldic acid, two tryptophan metabolites that are hypoglycemic, elevate tyrosine aminotransferase (TAT) in rat liver. He suggested that the enzyme change was related to the hypoglycemia caused by the two agents and possibly resulted from secretion of an anti-hypoglycemic hormone like glucagon[2]. Because of that suggestion, we are reporting studies on a structurally dissimilar hypoglycemic agent, 4-pentynoic acid, which according to unpublished studies in these laboratories has pharmacologic properties much like those of hypoglycin. Hypoglycin elevates plasma urea concentrations[4] by a mechanism thought to involve increased deamination of amino acids that serve as gluconeogenic precursors[5], providing another basis for expecting hypoglycin-like compounds to elevate amino acid catabolizing enzymes such as TAT.



4-pentynoic acid

methylenecyclopropylacetic acid (active metabolite of hypoglycin[3])

Materials and methods. Male 150 g Wistar rats were used in groups of 5. The rats received food and water ad libitum prior to the experiment but only water during the experimental period. All rats were killed at the same time (during midday), having received injections at specified times earlier, to minimize effects of diurnal variation in enzymes and metabolites[6]. 4-Pentynoic acid was synthesized in the Lilly Research Laboratories. Livers from decapitated rats were rapidly removed and frozen on dry ice. Hepatic TAT was measured spectrophotometrically[7], corticosterone was measured fluorometrically[8], and glucose and glycogen (after isolation and hydrolysis[9]) were measured using Worthington glucostat reagents[10].

Results and discussion. Figure 1 shows that the activity of hepatic TAT was elevated within 1 h after injection of 4-pentynoic acid. Highest enzyme activity, nearly 4 times the control level, was reached at 3 h. Enzyme activity had begun to return toward control values at 5 h.

Other changes induced by 4-pentynoic acid are shown in Figure 2. Plasma glucose levels were decreased, the maximum effect being at 1 h. Hepatic glycogen levels were decreased along a similar time course. Plasma corticosterone levels were markedly increased initially but had returned nearly to control levels by 5 h.

[1] R. Hardeland, Z. Naturforsch. *B 26*, 858 (1971).
[2] R. Hardeland, Comp. Biochem. Physiol. *41B*, 39 (1972).
[3] M. D. Milne, Clin. Pharmac. Ther. *9*, 484 (1968).
[4] C. H. Hassall, K. Reyle and P. C. Feng, Nature, Lond. *173*, 356 (1954).
[5] A. E. Senior and H. S. A. Sherratt, Biochem. J. *110*, 521 (1968).
[6] R. W. Fuller, in *Enzyme Synthesis and Degradation in Mammalian Systems* (Ed. M. Rechcigl; Karger, Basel 1971).
[7] E. C. C. Lin, B. M. Pitt, M. Civen and W. E. Knox, J. biol. Chem. *233*, 668 (1958).
[8] J. H. Solem and T. Brinck-Johnsen, Scand. J. clin. Lab. Invest. *17*, Suppl. *80*, 1 (1965).
[9] C. A. Good, H. Kramer and M. Somogyi, J. biol. Chem. *100*, 485 (1933).
[10] Worthington Biochemical Corporation, Freehold, N. J. 07728, USA.

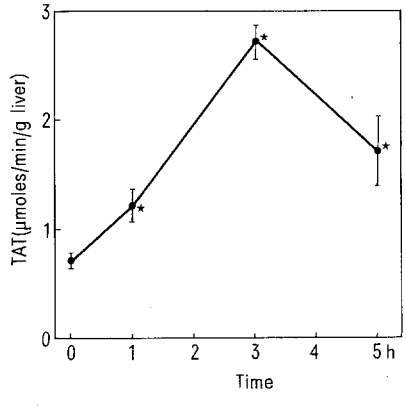


Fig. 1. Elevation of TAT by 4-pentynoic acid. 4-Pentynoic acid was injected s.c. at 10 mg/kg. Mean values with standard errors are shown for 5 rats per group. Values marked with an asterisk were significantly different ($P < 0.025$) from zero time.

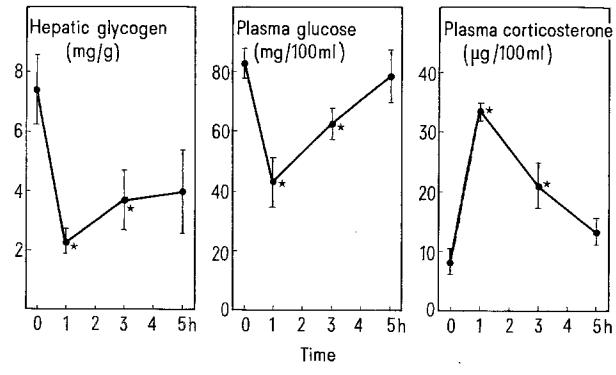


Fig. 2. Time course of changes in plasma glucose, hepatic glycogen, and plasma corticosterone levels caused by 4-pentynoic acid in rats. 4-Pentynoic acid was injected s.c. at 10 mg/kg. Mean values with standard errors are shown for 5 rats per group. Values marked with an asterisk were significantly different ($P < 0.05$) from zero time.

Table I. Dose-dependent effects of 4-pentynoic acid on hepatic TAT, hepatic glycogen, plasma glucose, and plasma corticosterone

Dose (mg/kg, s.c.)	Hepatic TAT (μmoles/min/g)	Hepatic glycogen (mg/g)	Plasma glucose (mg/100 ml)	Plasma corticosterone (μg/100 ml)
0	0.63 ± 0.10	8.00 ± 0.95	90 ± 4	19.9 ± 4.6
3.2	0.65 ± 0.10	16.82 ± 2.37[a]	117 ± 14	33.8 ± 1.0[a]
5.6	1.16 ± 0.13[a]	12.82 ± 1.12[a]	91 ± 2	47.6 ± 1.4[a]
10.0	2.19 ± 0.32[a]	3.64 ± 1.15[a]	54 ± 10[a]	41.3 ± 3.3[a]
17.8	1.90 ± 0.20[a]	1.93 ± 0.15[a]	30 ± 11[a]	51.0 ± 3.6[a]

[a] Significantly different from zero dose control, $P < 0.05$. All parameters were measured at 3 h except for plasma corticosterone levels, which were measured at 1 h. Mean values with standard errors for 5 rats per group are shown.

Several connections between the biochemical changes shown in Figure 2 and the elevation of hepatic TAT (Figure 1) are possible. First, and of primary interest to us, was the possible relation between the hypoglycemia and the elevation of enzyme activity. Second, the fall in hepatic glycogen content might also be related to the enzyme change. PERAINO et al.[11] suggested a reciprocal relationship between hepatic glycogen stores and amino acid catabolizing enzymes. They offered the teleological explanation that depletion of hepatic glycogen would create a demand for amino acid catabolism for the purpose of fulfilling existing energy requirements, and they entertained the possibility that glycogen might itself repress the synthesis of such enzymes. Third, glucocorticoids induce hepatic TAT, and the elevation of TAT after 4-pentynoic acid might have resulted from the elevation of corticosterone. Considering these possibilities, we determined whether a dose-response comparison could separate the effects of 4-pentynoic acid.

The Table shows the results with 4 different doses of 4-pentynoic acid. Surprisingly, glycogen stores were *increased* at the 2 lower doses and *decreased* at the 2 higher doses. Plasma glucose tended to increase at the low dose, and decreased at the 2 higher doses. Plasma corticosterone was elevated at all doses. Hepatic TAT was unchanged at the low dose and elevated at the 3 higher doses. These results argue against any direct relation between hepatic glycogen and TAT activity.

Hypoglycemia might lead to increased hepatic TAT levels via increased neural or hormonal input to the liver. Several lines of evidence suggest that neural control of hepatic TAT can occur[6,12–15]. Alternatively, hypoglycemia should result in increased release of hormones like glucagon, epinephrine, or glucocorticoids, and these hormones can elevate TAT. In an attempt to distinguish between the stimuli causing elevation of hepatic TAT after injection of 4-pentynoic acid, we measured its effect in adrenalectomized rats (Figure 3). Adrenalectomy completely prevented the elevation of TAT, showing that the enzyme effect was dependent on the adrenal glands and had been brought about by the secretion of adrenal hormones or by a steroid-dependent mechanism.

Zusammenfassung. 4-Pentinsäure, ein hypoglykämisches Mittel, vermehrte Leber-Tyrosinaminotransferase in intakten, nicht aber in adrenalektomierten Ratten.

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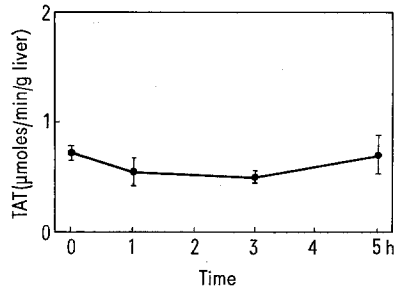

Fig. 3. Failure of 4-pentynoic acid to elevate hepatic TAT in adrenalectomized rats. All conditions as in Figure 1 except that the rats had been bilaterally adrenalectomized 8 days previously.

[11] C. PERAINO, C. LAMAR JR. and H. C. PITOT, Adv. Enzym. Regul. *4*, 199 (1966).
[12] R. W. FULLER and I. H. SLATER, Fedn. Proc. *27*, 403 (1968).
[13] I. B. BLACK and J. AXELROD, Proc. natn. Acad. Sci., USA *59*, 1231 (1968).
[14] I. B. BLACK, J. AXELROD and D. J. REIS, Nature, Lond. New Biol. *230*, 185 (1971).
[15] I. B. BLACK and D. J. REIS, J. Physiol., Lond. *219*, 267 (1971).

Hormonal Influences on Erythrocyte Catechol-*O*-Methyl Transferase Activity in Humans

Catechol-*O*-methyl transferase (COMT) catalyses the transfer of a methyl group from S-adenosylmethionine to the hydroxyl of catecholamines, such as adrenaline or noradrenaline[1]. It is a soluble enzyme of erythrocytes[2], absent from plasma and platelets, but present in trace amounts in leukocytes[3]. Its major physiological function is inactivation of catecholamines in the circulation and in tissues with sparse adrenergic innervation[4].

Women with depression (primary affective disorder) have reduced erythrocyte COMT activity which cannot