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Evidence that the accumulation of 5-hydroxytryptamine in the liver but not in the brain may cause the hypoglycaemia induced by 5-hydroxytryptophan

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1 Experiments were undertaken to determine whether the site of the hypoglycaemic action of 5-hydroxytryptophan (5-HTP), a direct precursor of 5-hydroxytryptamine (5-HT), was in the central nervous system or in the liver.

2 The fall in blood glucose followed the rapid increase in the amount of 5-HT both in the brain and liver after 5-HTP injection into pargyline-treated and non-treated mice.

3 Carbidopa, an inhibitor of peripheral aromatic amino acid decarboxylase, prevented the elevation of 5-HT levels in the liver of both pargyline-treated and non-treated mice. In contrast, carbidopa did not prevent but rather enhanced the elevation of 5-HT levels in the brain of both groups of mice.

4 Corresponding to the prevention of 5-HT elevation in the liver, the fall in blood glucose was prevented by carbidopa.

5 These results support the idea that the accumulation of 5-HT in the liver but not in the brain causes the hypoglycaemia induced by 5-HTP.

Introduction

The precursor of 5-hydroxytryptamine (5-HT), 5-hydroxytryptophan (5-HTP), in large doses, produces hypoglycaemia in normal mice (Furman & Wilson, 1980). In mice pretreated with a monoamine oxidase inhibitor (MAOI), small doses of 5-HTP can also produce hypoglycaemia (Lundquist *et al.*, 1971; Furman, 1974). The hypoglycaemia induced by 5-HTP in MAOI-treated mice has been shown to be prevented by a decarboxylase inhibitor (Lundquist *et al.*, 1971; Furman, 1974) and 5-HT antagonists (Furman, 1974). In MAOI-treated mice, agents known to inhibit 5-HT uptake has been also shown to produce hypoglycaemia without administration of 5-HTP (Wilson & Furman, 1982). In addition, the 5-HT-uptake inhibitors augment the hypoglycaemic effect of 5-HTP in normal mice (Wilson & Furman, 1982). These observations suggest that the hypoglycaemic action of 5-HTP in both normal and MAOI-treated mice is mediated by 5-HT. Since marked effects of 5-HT on central nervous system (CNS), head twitching and tremor, occur in hypoglycaemic mice given 5-HTP and intracerebroventricular injection of 5-HT and 5-HTP produced hypoglycaemia, it has been suggested that the hypoglycaemia induced by 5-HTP may be due to the accumulation of 5-HT in the CNS (Darwish & Furman, 1974; Wilson & Furman, 1982).

On the other hand, a large dose of tryptophan, a precursor of 5-HTP, can also produce hypoglycaemia in rats and pharmacological studies suggest that this hypoglycaemia is also mediated by 5-HT (Smith & Pogson, 1977). Evidence indicates that the trytophan-induced hypoglycaemia may be due to the inhibition of hepatic gluconeogenesis. Although 5-HT can inhibit the gluconeogenesis in isolated hepatic cells as can other tryptophan metabolites (Smith *et al.*, 1979), quinolinate, rather than 5-HT, was suggested as the intracellular agent responsible for the inhibition of the gluconeogenesis (Smith *et al.*, 1980; Lloyd *et al.*, 1982a,b), because the ability of hepatic cells to form 5-HT from tryptophan was poor (Smith *et al.*, 1980).

Lipopolysaccharides or endotoxin are well known to produce hypoglycaemia in experimental animals. It has been suggested that a major mechanism underlying the hypoglycaemia may be an impaired hepatic gluconeogenesis (McCallum & Berry, 1973; Filkins & Cornell, 1974). Recently, I found that various mitogenic substances, as well as lipopolysaccharide, induced hypoglycaemia and produced the accumulation of 5-HT predominantly in the liver of mice (Endo, 1983; 1984). Development of hypoglycaemia and 5-HT accumulation correlated well with each other in terms of the time course and the dose-response.

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Lipopolysaccharide can also produce accumulation of 5-HT in the liver of Wistar rats (Endo, 1983). These observations led to the idea that the increase in 5-HT in the liver rather than in the brain might cause the hypoglycaemia, possibly through the inhibition of hepatic gluconeogenesis. The administration of 5-HTP can produce accumulation of 5-HT in the liver as well as in the brain (Udenfriend *et al.*, 1957). In the present study, therefore, I examined the above hypothesis by measuring the formation of 5-HT after the injection of 5-HTP into mice.

Methods

Determination of 5-hydroxytryptamine and blood glucose

Male ddI mice were obtained from the Mouse Centre of this university. The mice were kept under fixed conditions of light and dark (19 h 00 min to 07 h 00 min) and fed *ad libitum*. All injections were made to fed mice (6 to 7 weeks old, 24 to 27 g body weight) between 09 h 00 min and 12 h 00 min. Mice were decapitated and blood was collected in a glass tube, which was weighed before use, weighed and stored in a dry ice box. Livers and brains were removed rapidly and also stored in a dry ice box. 5-HT and blood glucose were determined as described previously (Tadano *et al.*, 1980: Endo, 1984).

Agents

5-HTP (5-hydroxy-L-tryptophan) and pargyline hydrochloride were purchased from Sigma Chemical Company (St Louis, MO, U.S.A.). Carbidopa (L-α-(3,4-dihydroxybenzyl)-α-hydrazinopropionic acid monohydrate) was a gift from Sankyo Seiyaku (Tokyo, Japan). Others agents were from Wako Pure Chemical Ind. (Osaka Japan). Agents were dissolved or suspended in saline and injected intraperitoneally into mice. In combined injections of these agents, the total volume was limited to less than 0.4 ml/mouse.

Results

Time course of the development of hypoglycaemia and the increase in the amount of 5-hydroxytryptamine in the liver and brain

In pargyline-treated mice (75 mg kg^{-1}), hypoglycaemia was produced by 5-HTP in doses of more than 5 mg kg^{-1}. The time course of the decrease in blood glucose and the increase in 5-HT in the liver and brain after the injection of 15 mg kg^{-1} of 5-HTP into pargyline-treated and non-treated mice are shown in Figure 1a. In such a dose, 5-HTP alone did not produce hypoglycaemia, but, in combination with pargyline, the 5-HTP produced profound hypoglycaemia. A rapid decline in blood glucose occurred just after the increase in 5-HT in both tissues. In pargyline-treated mice, the increase in 5-HT in both tissues was markedly higher and decline of the elevated 5-HT levels was very much slower than in those of mice not treated with pargyline, indicating that pargyline strongly inhibited the degradation of 5-HT in both tissues. Pargyline alone produced a 2 to 2.5 fold increase in 5-HT in the brain but not in the liver and did not produce hypoglycaemia.

In normal mice, i.e., mice not treated with pargyline, hypoglycaemia was not produced by doses of 5-HTP less than 100 mg kg^{-1}. Figure 1b shows the time course of the decrease in blood glucose and the increase in 5-HT in the liver and brain after injection of 5-HTP 300 mg kg^{-1}. In this case also a rapid decline in blood glucose followed the increase in 5-HT in both tissues. It should be noticed that, in spite of a great elevation of 5-HT in the liver, the elevated level of 5-HT in the brain induced by such a large dose of 5-HTP was similar to that induced by a smaller dose of 5-HTP in pargyline-treated mice (Figure 1a). This indicates that in the brain pargyline is remarkably effective in producing accumulation of 5-HT.

In pargyline-treated mice, 5-HTP injection in doses to induce hypoglycaemia produced marked effects on CNS, i.e., head twitching, tremor, and, in doses of more than 30 mg kg^{-1}, convulsion resulting in death within 1 to 3 h after 5-HTP injection. Head twitching and tremor appeared within 20 min after 5-HTP injection and continued more than 2 h. On the other hand, with 5-HTP in untreated mice even with doses as high as 300 mg kg^{-1}, these manifestations were not so severe as in pargyline-treated mice, i.e., slight and transient head twitching disappeared within 1.5 h and without tremor.

Correlation between the hypoglycaemia and the increase in 5-HT produced by 5-HTP

The hypoglycaemic responses and the increased levels of 5-HT in response to various doses of 5-HTP are shown in Figure 2. In pargyline-treated mice, 15 to 20 mg kg^{-1} of 5-HTP gave a minimum level of blood glucose at 2 h after 5-HTP injection without killing any mice. A fall of similar magnitude in blood glucose was obtained 1 h after the injection of more than 200 mg kg^{-1} of 5-HTP in normal mice.

ED_{50} values of 5-HTP to produce hypoglycaemia were about 10 mg kg^{-1} in pargyline-treated mice and about 150 mg kg^{-1} in normal mice. At these doses, the elevated levels of 5-HT in the brain in both groups of mice were in a similar range of 10 to 13 nmol g^{-1} However, in the liver there was a marked difference

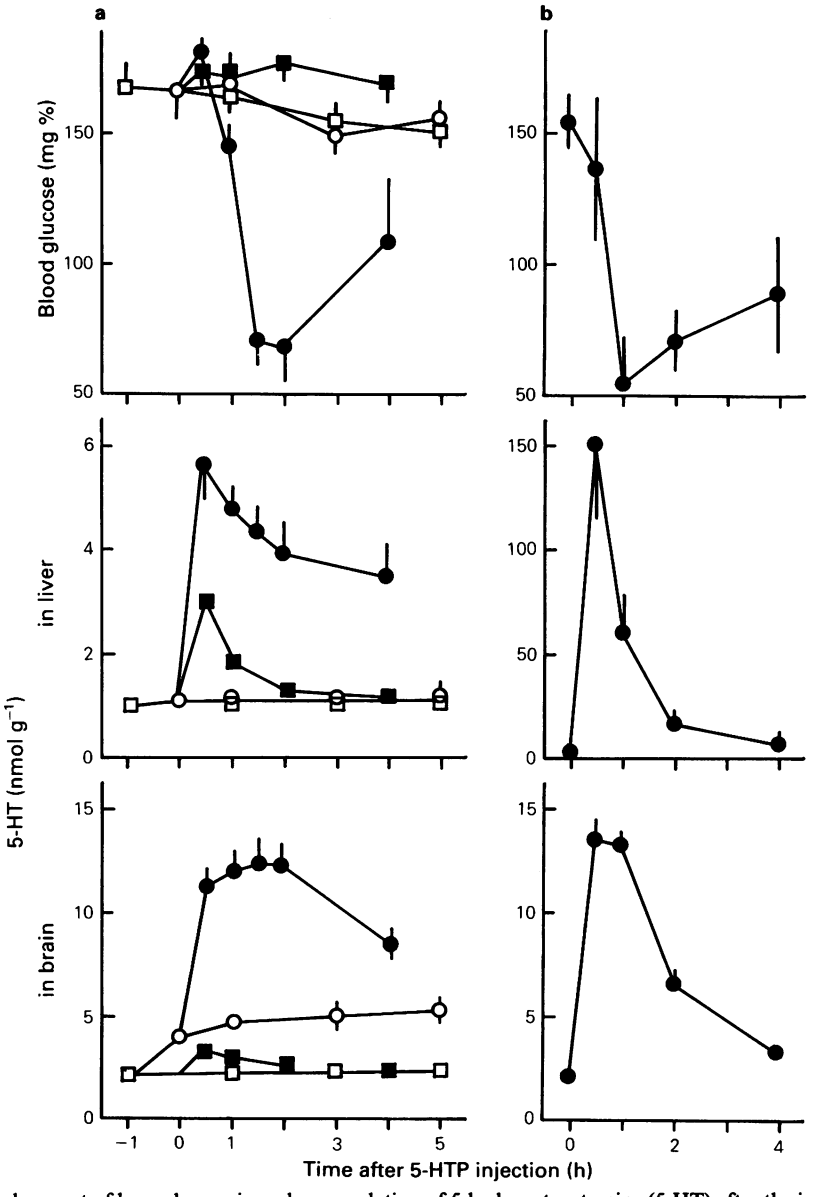

Figure 1 Development of hypoglycaemia and accumulation of 5-hydroxytryptamine (5-HT) after the injection of 5-hydroxytryptophan (5-HTP) into mice. (a) The responses induced by the injection of 5-HTP 15 mg kg^{-1} into normal or pargyline-treated mice (75 mg kg^{-1}); (□) saline alone injected at − 1 h; (○) pargyline alone at − 1 h; (■) 5-HTP alone at time 0; (●) pargyline at − 1 h and 5-HTP at time 0. (b) The responses induced by the injection of 5-HTP 300 mg kg^{-1} into normal mice. Each value is the mean from 3 mice; s.d. shown by vertical lines.

between the levels of 5-HT in the pargyline-treated and non-treated mice.

The increase in 5-HT in the blood was not observed in pargyline-treated mice in the experiments shown in Figure 1a and Figure 2a. In normal mice, blood 5-HT increased with doses of 5-HTP of more than 100 mg kg^{-1} (Figure 2b). However, the increase in 5-HT in the blood was very low when compared with increases in the brain and liver.

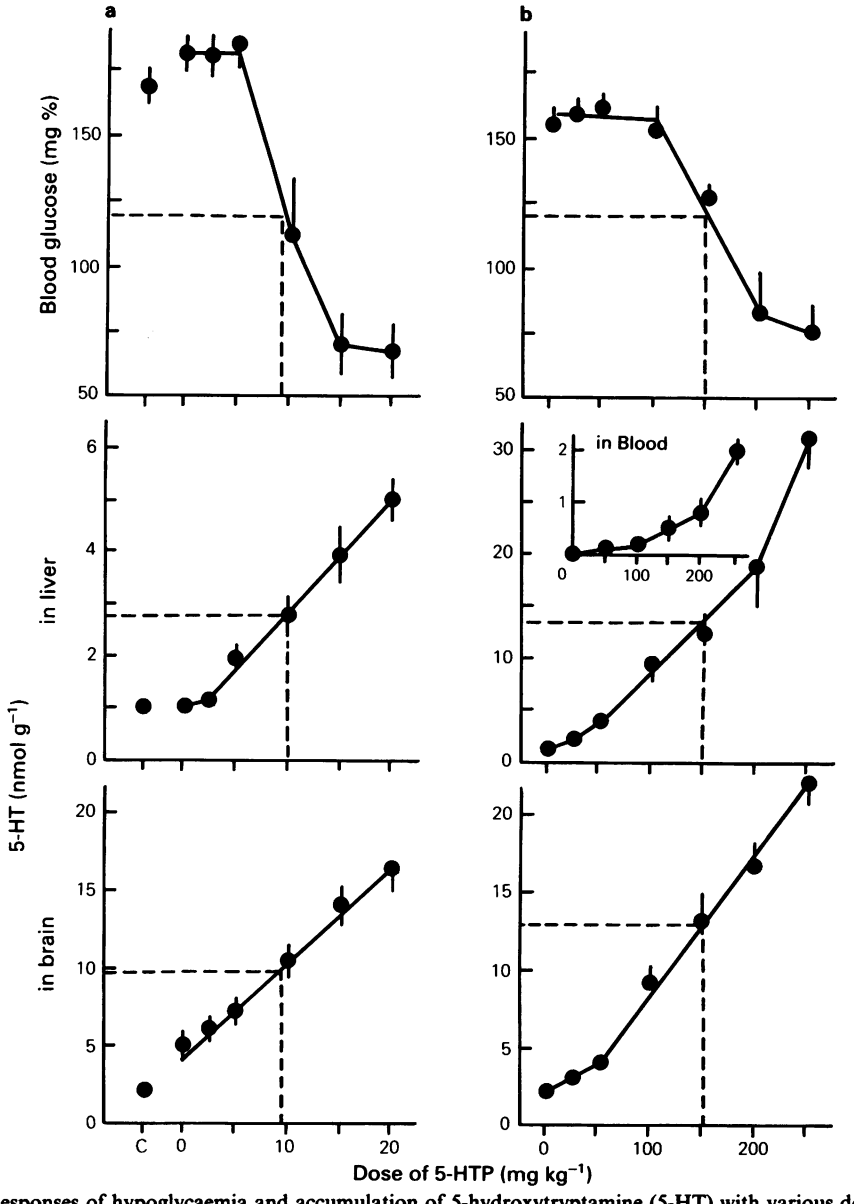

Figure 2 Responses of hypoglycaemia and accumulation of 5-hydroxytryptamine (5-HT) with various doses of 5-hydroxytryptophan (5-HTP) in (a) pargyline-treated and (b) normal mice. Pargyline (75 mg kg^{-1}) was injected at 1 h before 5-HTP injection. In (a) mice were killed at 2 h and in (b) at 1 h after the injection of 5-HTP. C, values from normal mice. Each value is the mean from 3 mice; s.d. shown by vertical lines.

The effects of carbidopa on the 5-HTP-induced hypoglycaemia and the increased levels of 5-HT in pargyline-treated mice

Carbidopa or MK-486 has been shown to be an inhibitor of peripheral aromatic amino acid decarboxylase (Warsh & Stancer, 1976). Therefore, I first examined the effects of various doses of carbidopa on hypoglycaemia and 5-HT increase in pargyline-treated mice at 2 h after 5-HTP injection (20 mg kg^{-1}) (Figure 3). Cardidopa alone, in doses of 30 to 120 mg kg^{-1}, did not show any significant effect on either blood glucose

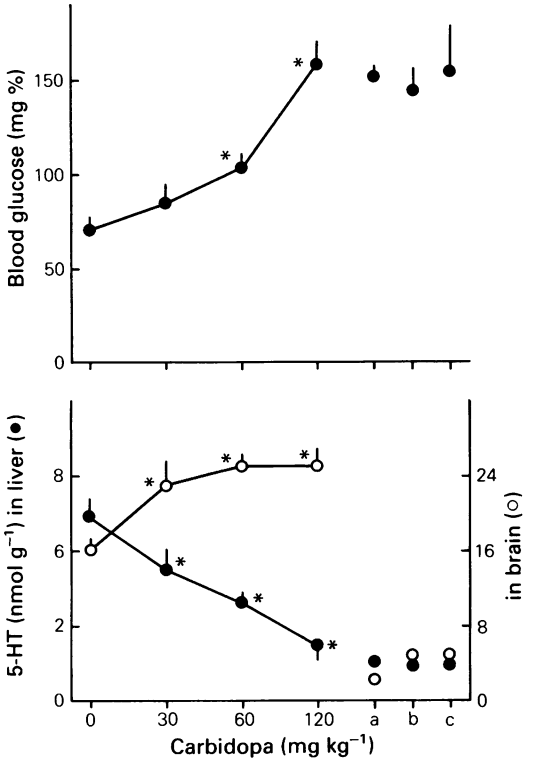

Figure 3 Effects of various doses of carbidopa in pargyline-treated mice by 5-hydroxytryptophan (5-HTP). Pargyline (75 mg kg^{-1}) and carbidopa were injected at 1 h and 0.5 h, respectively, before 5-HTP injection (20 mg kg^{-1}). Mice were killed at 2 h after the 5-HTP injection. (a) Three injections of saline; (b) pargyline + carbidopa (120 mg kg^{-1}) + saline, (c) pargyline + 2 injections of saline. Each value is the mean from 4 mice; s.d. shown by vertical lines. * $P < 0.01$ vs values of mice given 5-HTP alone (Student's t test).

or 5-HT levels in the liver and brain of the mice at 2.5 h after the injection. The agent prevented the decline in blood glucose induced by 5-HTP in a dose-dependent manner; it also suppressed dose-dependently the elevation of 5-HT in the liver. In contrast, it did not suppress but rather enhanced the elevation of 5-HT in the brain.

Next, the effects of carbidopa were examined at various time intervals after 5-HTP injection (10 mg kg^{-1}) into pargyline-treated mice (Figure 4). Carbidopa, in a dose of 90 mg kg^{-1}, prevented completely the decline in blood glucose induced by 5-HTP at an early period (within 1.5 h). The blood glucose, however, declined at a later period (after 1.5 h), but its extent was not profound.

In a manner corresponding to the prevention of hypoglycaemia, carbidopa also prevented the elevation of 5-HT in the liver almost completely at an early period, and, at a later period, 5-HT in the liver increased slightly and slowly.

In the brain, treatment with carbidopa prevented the increase in 5-HT to a small extent at an early period, but later, the 5-HT level was enhanced and exceeded the level in mice not treated with carbidopa. Although, in the latter mice, CNS effects (head twitching and tremor) appeared within 20 min after 5-HTP injection, the effects in carbidopa-treated mice appeared more than 1 h later and lasted for more than 1 h longer.

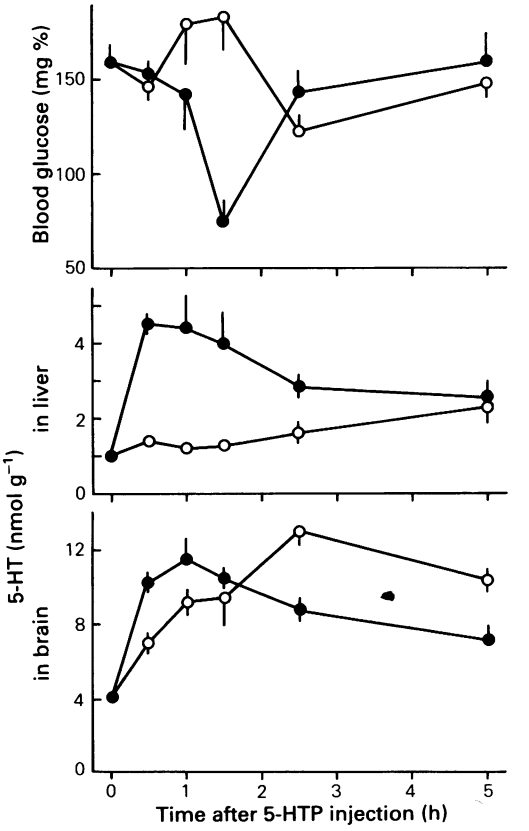

Figure 4 Effects of carbidopa on the development of hypoglycaemia and accumulation of 5-hydroxytryptamine (5-HT) induced in pargyline-treated mice by 5-hydroxytryptophan (5-HTP). Pargyline (75 mg kg^{-1}) and carbidopa (90 mg kg^{-1}) were injected at 1 h and 0.5 h, respectively, before 5-HTP injection (10 mg kg^{-1}). (○) Carbidopa-treated and (●)-non-treated mice. Each value is the mean from 3 mice; s.d. shown by vertical lines.

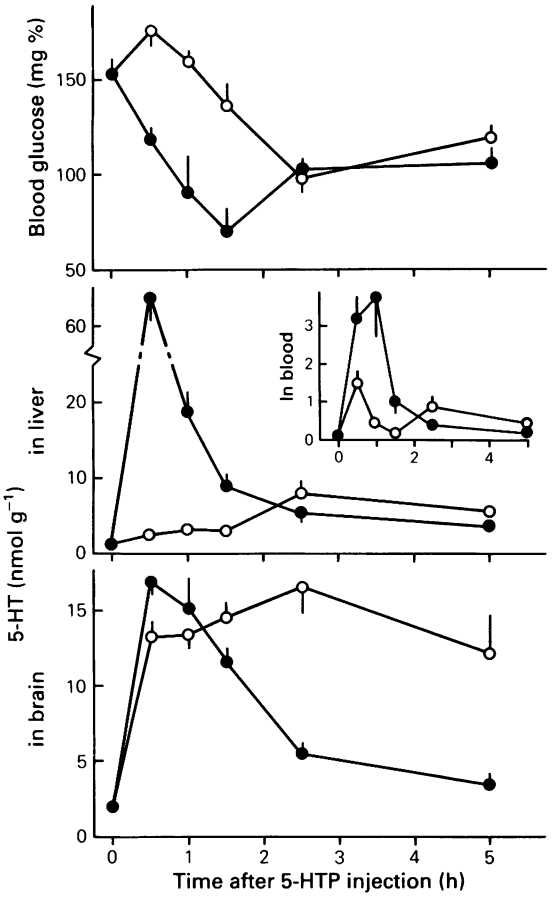

Figure 5 Effects of carbidopa on the development of hypoglycaemia and accumulation of 5-hydroxytryptamine (5-HT) induced in normal mice by a large dose of 5-hydroxytryptophan (5-HTP). Carbidopa (90 mg kg^{-1}) was injected into normal mice at 0.5 h before 5-HTP injection (200 mg kg^{-1}). (○) Carbidopa-treated and (●)-non-treated mice. Each value is the mean from 3 mice; s.d. shown by vertical lines.

The effects of cabidopa on the hypoglycaemia and the increased 5-HT levels induced in normal mice by a large dose of 5-HTP

As shown in Figure 5, the treatment with carbidopa (90 mg kg^{-1}) prevented the 5-HT increase induced in the liver by 5-HTP 200 mg kg^{-1} almost completely at an early period, but the level was elevated to 6 to 8 fold at a later period. Corresponding to the slight and delayed elevation of liver 5-HT, blood glucose declined slowly and a small degree of hypoglycaemia continued for the later period.

The variations in brain 5-HT were similar to those shown in Figure 4. As described in a previous section, large doses of 5-HTP (150–300 mg kg^{-1}) injected into normal mice produced smaller CNS effects than those in pargyline-treated mice given smaller doses of 5-HTP (10–20 mg kg^{-1}). These smaller central effects produced by 5-HTP continued for more than 2 h longer in carbidopa-treated mice than in mice not treated with carbidopa.

The increase in 5-HT in the blood was also suppressed by carbidopa. In the carbidopa-treated mice, the elevation of blood 5-HT was biphasic. The 5-HT increase in the later period may reflect the fact that carbidopa is not very long acting, i.e., in the later period, a large amount of 5-HT might be formed from 5-HTP that had been retained at a high level by the blockade of peripheral decarboxylase at an early period (Warsh & Stancer, 1976).

Discussion

Pharmacological studies suggest that the hypoglycaemic action of 5-HTP in MAOI-treated mice is mediated by 5-HT (see Introduction). However, there have been no studies to show the correlation between hypoglycaemia and 5-HT accumulation, and therefore, the site of the hypoglycaemic action of 5-HTP was uncertain. In the present study, I have examined the relationship between the formation of 5-HT in mouse tissues and hypoglycaemia.

After 5-HTP injection into normal and pargyline-treated mice, the decline in blood glucose occurred just after the rapid elevation of 5-HT in both the brain and liver.

Since marked effects of central origin (head twitching and tremor), known to be produced by 5-HT, accompanied the hypoglycaemic response, and intracerebroventricular injection of 5-HT and 5-HTP produced hypoglycaemia, it was suggested that the 5-HTP-induced hypoglycaemic response was due to the accumulation of 5-HT in the brain (Darwish & Furman, 1974; Wilson & Furman, 1982). However, the intracerebroventricular injection of such high doses as 10 μg of 5-HT and 5-HTP (25 nmol/brain of 5-HT and 45 nmol/brain of 5-HTP) to nialamide-treated mice (two injections of 80 mg kg^{-1} within 24 h before 5-HT or 5-HTP injection) are questionable when studying the site of the hypoglycaemic action of 5-HTP given peripherally (Darwish & Furman, 1974). Such a high level of 5-HT seems not to be attained by peripheral injection of 5-HTP without killing the mice. Nialamide, a hydrazine derivative, in two such injections within 24 h has been shown to be hypoglycaemic itself (Lundquist *et al.*, 1971) by its possible hydrazine-like inhibitory action on gluconeogenesis (Ray *et al.*, 1970).

Carbidopa, an inhibitor of aromatic amino acid

decarboxylase, prevented almost completely the elevation of 5-HT in the liver of both pargyline-treated and non-treated mice at an early period. On the other hand, carbidopa was ineffective in suppressing the elevation of brain 5-HT but rather enhanced the elevation at a later period. These results are in good agreement with the effects of the agent as an inhibitor of peripheral aromatic amino acid decarboxylase (Warsh & Stancer, 1976). Concomitant with the prevention of 5-HT increase in the liver, the decline in blood glucose induced by 5-HTP was prevented by carbidopa. In carbidopa-treated mice, brain levels of 5-HT were elevated but this was not associated with hypoglycaemia. Additionally, an injection of L-tryptophan, in a dose ($450\,mg\,kg^{-1}$) that does not produce hypoglycaemia in pargyline-treated mice ($75\,mg\,kg^{-1}$), elevated brain 5-HT to about $10\,nmol\,g^{-1}$ after 2 h and produced central effects similar to those observed by 5-HTP injection. 5-HT in the liver was not increased at all by this tryptophan injection (unpublished observations). These results suggest that the accumulation of 5-HT in the brain, by itself, is unlikely to produce hypoglycaemia and support the idea that the accumulation of 5-HT in the liver causes the hypoglycaemia induced by 5-HTP. If this idea is correct, it is interesting that the hypoglycaemic response in normal mice was less sensitive to the increased 5-HT in the liver than in pargyline-treated mice (Figure 2a). One possible explanation for this result is that the 5-HT increased in the blood of normal mice which might have acted to enhance blood glucose, because 5-HT injection has been shown to be hyperglycaemic in normal fed mice (Lundquist *et al.*, 1971). However, the present results cannot exclude completely a component of brain 5-HT in the hypoglycaemic response to 5-HTP. The decline of blood glucose at a later period in carbidopa-treated mice might be, in part, due to a direct or indirect effect of 5-HT on the central nervous system, although it appears also to correlate with an increase in liver 5-HT. It is also possible that the 5-HT accumulation in both brain and liver might be necessary for the production of hypoglycaemia. The contribution of 5-HT accumulation in the brain may be clarified, if the 5-HT formation in the brain could be selectively suppressed.

A lipopolysaccharide and various other mitogenic substances can produce an increase in 5-HT selectively in the liver (2 to 5 fold) and produce hypoglycaemia (Endo, 1983; 1984). The development of hypoglycaemia and 5-HT accumulation correlated well with each other in terms of the time course and the dose-response relationship. A major mechanism underlying the lipopolysaccharide-induced hypoglycaemia is an impaired hepatic gluconeogenesis (McCallum & Berry, 1973; Filkins & Cornell, 1974). Gluconeogenesis in isolated hepatic cells has been shown to be inhibited by some tryptophan metabolites such as tryptamine and 5-HT at the step catalyzed by phosphoenolpyruvate carboxykinase, a key enzyme in gluconeogenesis (Smith *et al.*, 1978; 1979). These observations and the present results strongly suggest that the inhibition of gluconeogenesis in the liver by the accumulated 5-HT at the site may be the cause of the hypoglycaemia. In addition to the mechanism of the 5-HT increase, it remains to be clarified whether carbidopa can suppress the mitogen-induced elevation of liver 5-HT and can inhibit the decline in blood glucose.

Although intracellular 5-HT formation from 5-HTP in pancreatic islets has been shown to inhibit insulin secretion (Lundquist *et al.*, 1971), there are some pieces of evidence that extracellular 5-HT stimulates insulin secretion as reviewed by Lundquist *et al.* (1971) and Smith & Porte (1976). An elevation in plasma insulin occurs in normal mice after a large injection of 5-HTP (Furman & Wilson, 1980) but not in MAOI-treated mice given small doses of 5-HTP (Furman, 1974; Furman & Wilson, 1980; Wilson & Furman, 1982). In the present study, 5-HT in the blood was increased in normal mice by large doses of 5-HTP but not in pargyline-treated mice given small doses of 5-HTP. These observations, therefore, suggest that the increased 5-HT in the blood could produce a secretion of insulin. As described above, the injection of 5-HT itself, however, does not produce hypoglycaemia or rather produces hyperglycaemia as observed by Furman & Wilson (1980) and Lundquist *et al.*, (1971). On the basis of some additional observations, these workers have doubted the contribution of insulin as a major factor in producing hypoglycaemia induced by 5-HTP and have suggested additional mechanisms, i.e., stimulation of peripheral glucose utilization by intracellular 5-HT (Lundquist *et al.*, 1971) or unknown mechanism relating to neuronal function (Lundquist *et al.*, 1971; Furman, 1974; Furman & Wilson, 1980). Although the contribution of insulin cannot be excluded, present findings on the hypoglycaemia induced by 5-HTP, as well as by mitogens, support the idea that a major mechanism underlying these hypoglycaemic responses is an impaired gluconeogenesis by the accumulated 5-HT in the liver. The stimulation of peripheral glucose utilization suggested by Lundquist *et al.* (1971) but not substantiated (Furman, 1974) may also possibly facilitate the decline of blood glucose.

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References

DARWISH, S.A.E. & FURMAN, B.L. (1974). Mediation of the hypoglycaemic effect of 5-hydroxytryptophan by a central nervous system action. *Experientia*, **30**, 1306–1307.

ENDO, Y. (1983). A lipopolysaccharide and concanavalin A induce variations of serotonin levels in mouse tissues. *Eur. J. Pharmac.*, **91**, 493–499.

ENDO, Y. (1984). Induction of hypoglycaemia and accumulation of 5-hydroxytryptamine in the liver after the injection of mitogenic substances into mice. *Br. J. Pharmac.*, **81**, 645–650.

FILKINS, J.P. & CORNELL, R.P. (1974). Depression of hepatic gluconeogenesis and the hypoglycaemia of endotoxin shock. *Am. J. Physiol.*, **227**, 778–781.

FURMAN, B.L. (1974). The hypoglycaemic effect of 5-hydroxytryptophan. *Br. J. Pharmac.*, **50**, 575–580.

FURMAN, B.L. & WILSON, G.A. (1980). Further studies on the effects of 5-hydroxytryptophan on plasma glucose and insulin in the mouse. *Diabetlogia*, **19**, 386–390.

LLOYD, P., SMITH, S.A., STRIBLING, D. & POGSON, C.I. (1982a). Factors affecting tryptophan-induced hypoglycaemia in rats. *Biochem. Pharmac.*, **31**, 3563–3569.

LLOYD, P., STRIBLING, D. & POGSON, C.I. (1982b). Endotoxin and tryptophan-induced hypoglycaemia in rats. *Biochem. Pharmac.*, **31**, 3571–3576.

LUNDQUIST, I., EKHOLM, R. & ERICSON, L.E. (1971). Monoamines in the pancreatic islets of the mouse. 5-Hydroxytryptamine as an intracellular modifier of insulin secretion, and the hypoglycaemic action of monoamine oxidase inhibitors. *Daibetelogia*, **7**, 414–422.

McCALLUM, R.E. & BERRY, L.J. (1973). Effects of endotoxin on gluconeogenesis, glycogen synthesis, and liver glycogen synthase in mice. *Infect. & Immunity*, **7**, 642–654.

RAY, P.D., HANSON, R.L. & LARDY, H.A. (1970). Inhibition by hydrazine of gluconeogenesis in the rats. *J. biol. Chem.*, **245**, 690–696.

SMITH, P.H. & PORTE, D. Jr. (1976). Neuropharmacology of the pancreatic islets. *A. Rev. Pharmac. Tox.*, **16**, 269–285.

SMITH, S.A. & POGSON, C.I. (1977). Tryptophan and the control of plasma glucose concentration in the rats. *Biochem. J.*, **168**, 495–506.

SMITH, S.A., ELLIOTT, K.F. & POGSON, C.I. (1978). Differential effects of tryptophan on glucose synthesis in rats and guinea pigs. *Biochem. J.*, **176**, 817–825.

SMITH, S.A., ELLIOTT, K.F. & POGSON, C.I. (1979). Inhibition of hepatic gluconeogenesis by tryptophan metabolites in rats and guinea pig. *Biochem. Pharmac.*, **28**, 2145–2148.

SMITH, S.A., CARR, F.P.A. & POGSON, C.I. (1980). The metabolism of L-tryptophan by isolated rat liver cells. *Biochem. J.*, **192**, 673–686.

TADANO, T., ENDO, Y. & KISARA, K. (1980). A simple determination of serotonin, 5-hydroxyindoleacetic acid and 5-hydroxytryptophan decarboxylase activity in rat brain areas and parallel correlation among the levels. *Jap. J. Pharmac.*, **30**, 347–356.

UDENFRIEND, S., WEISSBACH, H. & BOGDANSKI, D.F. (1957). Increase in tissue serotonin following administration of its precursor 5-hydroxytryptophan. *J. biol. Chem.*, **224**, 803–810.

WARSH, J.J. & STANCER, H.C. (1976). Brain and peripheral metabolism of 5-hydroxytryptophan-^{14}C following peripheral decarboxylase inhibition. *J. Pharmac. exp. Ther.*, **197**, 545–555.

WILSON, G.A. & FURMAN, B.L. (1982). Effects of inhibitors of 5-hydroxytryptamine uptake on plasma glucose and their interaction with 5-hydroxytryptophan in producing hypoglycaemia in mice. *Eur. J. Pharmac.*, **78**, 263–270.

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