Life Sciences Vol. 15, pp. 1533-1548

MINIREVIEW

REGULATION OF SEROTONIN SYNTHESIS

Michel Hamon, and Jacques Glowinski
Groupe NB, INSERM U.114, Collège de France
11,place Marcelin Berthelot, Paris 5e, France

Summary

The regulation of serotonin synthesis in the central nervous system seems to involve mechanisms which control the intracellular concentration of tryptophan and the hydroxylation step. Numerous situations are reviewed which demonstrate that changes in the concentration of free tryptophan in plasma and/or in the uptake of the amino acid in brain may alter tryptophan concentration and 5-HT synthesis. In other cases, modifications in 5-HT synthesis were still detected after tryptophan loading, clearly indicating that the tryptophan concentration is not the only critical parameter. In particular, changes in 5-HT synthesis dependent on nerve impulse flow seem to be regulated at the hydroxylation step. In addition, long term regulations of 5-HT synthesis involving changes in tryptophan hydroxylase concentration have been recently demonstrated. How serotoninergic neurons integrate all these regulating factors to modulate 5-HT synthesis is still an open question.

Introduction

The synthesis of serotonin (5-HT) in central serotoninergic neurons is apparently a simple process. Tryptophan is taken up in serotoninergic neurons by an active mechanism. The amino acid is then hydroxylated into 5-hydroxytryptophan (5-HTP) by the action of tryptophan hydroxylase (EC 1.14.16.4), an enzyme highly specific to serotoninergic neurons. Finally, 5-HTP is decarboxylated into 5-HT by 5-hydroxytryptophan decarboxylase (EC 4.11.28). However, despite this limited number of reactions, several points remain obscure. Little is known about the factors which control the active transport of tryptophan into serotoninergic neurons. The conception of the nature of the cofactor of tryptophan hydroxylase is still quite hypothetical. Since tryptophan hydroxylase has not yet been highly purified, little information has been obtained concerning its characteristics. Finally, there is still some doubt about the specificity of 5-hydroxytryptophan decarboxylase.

Various processes seem to be involved in the regulation of 5-HT synthesis in central serotoninergic neurons. They can be arbitrarily classified into two groups : 1. It is generally accepted that tryptophan hydroxylase, the main limiting enzyme of 5-HT biosynthesis is not saturated by its substrate in physiological states. Thus, changes in the availability of tryptophan may rapidly affect the rate of 5-HT synthesis. These changes may depend on peripheral or central factors : fluctuations in the concentration of the free form of tryptophan in the plasma ; modifications in the characteristics of the transport of this essential amino-acid in cerebral tissue ; alterations in the compartimentalization of tryptophan into serotoninergic neurons.2. In various cases, changes in 5-HT synthesis were shown to be related not only to the precursor concentration at the site of hydroxylation but also to mechanisms which control the rate of hydroxylation of this amino-acid. Various factors may affect the rate of conversion of tryptophan into 5-HT : availability of oxygen, the concentration of the cofactor, the ionic environment, the physical state of the enzyme (free in the cytoplasm or bound to the membranes) and finally the enzyme concentration. Moreover, as in other monoaminergic neuronal systems, the first limiting step of 5-HT synthesis may be influenced in some cases by the intraneuronal levels of cytoplasmic 5-HT.

It is unlikely, that the regulation of 5-HT synthesis also depends upon the rate of decarboxylation of 5-HTP ; 5-hydroxytryptophan decarboxylase activity is about 75 times higher than that of tryptophan hydroxylase (1). Therefore, some of the mechanisms which occur before the decarboxylation step will be mainly discussed.

Role of Tryptophan in the Regulation of 5-HT Synthesis

a) Plasmatic tryptophan.

Tryptophan is the only essential amino-acid which is partially boundto albumin in the plasma (2). This has at least two consequences : 1) In normal states, the quantity of tryptophan which penetrates cerebral tissues is closely dependent on the small proportion of the amino-acid still free in the plasma (3,4). This is in contrast with what is observed with the precursor of the catecholamines:tyrosine, entirely free in the plasma (5) reaches the brain in high concentrations. Therefore, tyrosine hydroxylase

always appears to be saturated (6).2) Disturbances in the equilibrium which occurs between the bound and free forms of tryptophan in the plasma, rapidly modify the availability of tryptophan in the brain and thus affect the rate of 5-HT synthesis.

Some pharmacological treatments increase the concentration of free plasmatic tryptophan. The best example is provided by salicylate (7,8). This drug markedly increases the concentration of free tryptophan in plasma, enhancing tryptophan levels (+130%) in the brain and stimulating 5-HT synthesis (fig.1). Fatty acids easily displace bound tryptophan (9). Plasmatic levels of fatty acids are increased following food deprivation and immobilization stress (10). These procedures elevate the amount of free tryptophan in plasma and stimulate 5-HT synthesis.

An interesting situation is found in the new born rat. In our laboratory we recently observed that tryptophan is almost totally in a free state in the plasma of new born animals (8). This is not only related to the presence of high levels of fatty acids in the blood, but also to the differences in the binding properties of the new born animal's albumin. Consequently, salicylate which, as discussed previously, stimulates 5-HT synthesis in the adult by increasing free tryptophan levels, can no longer exert its effects in new born animals (fig.1).

Obviously, when rats are injected with a high dosage of tryptophan, concentrations of the bound and particularly the free form of the amino-acid increase rapidly ; resulting in an immediate increase in 5-HT synthesis (4,8,11). Conversely,the reduction of the amino-acid concentration in the blood, observed following the activation of tryptophan pyrrolase (induced by α-methyl tryptophan (12) or hydrocortisone (13)), decreases the synthesis of central 5-HT.

b) Tryptophan uptake

Fluctuations in the plasmatic concentrations of free tryptophan are not systematically associated with parallel changes in 5-HT synthesis.

For instance, injections of probenecid (14) and chlordiazepoxide (8) rapidly increase the level of free tryptophan and have no stimulating effect on 5-HT synthesis in the rat (15,16).

Insulin, which increases the proportion of tryptophan bound

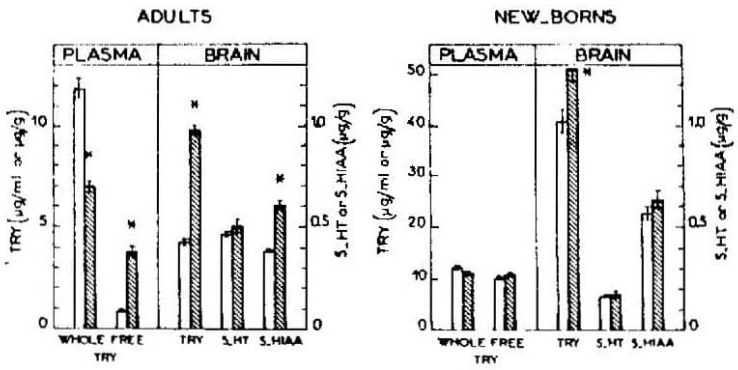

FIG.1
Effects of Salicylate (150 mg/kg) on Brain 5-HT Metabolism and Tryptophan Concentrations in Plasma of newborn and adult Rats

The drug was injected intraperitoneally one hour before death to groups of 6 newborn (1h old) or adult (3 months old) rats. Each value is the mean ± SEM of 6 determinations. Empty bars : saline treated animals ; hatched bars : salicylate treated animals. * $p < .05$ when compared with respective saline treated rats (newborns or adults).

---

to albumin by its action on plasmatic free fatty acids levels, reduce the quantities of the free form of the amino acid (17) available for 5-HT synthesis. Surprisingly, this hormonal treatment enhances tryptophan levels as well as 5-HT synthesis in the brain. According to Fernstrom and Wurtman (18) the latter effect is related to the increase ratio of tryptophan to other neutral amino acids (tyrosine, phenylalanine, leucine, isoleucine and valine) in the blood. Indeed, these authors postulate that the regulation of central 5-HT synthesis is closely dependent on the equilibrium established between tryptophan and other neutral amino acids.

Other interesting situations in which changes in central 5-HT synthesis are directly related to those of tryptophan transport in tissues have been demonstrated in our laboratory. In studies conducted by F. Hery, physiological changes in the activity of serotoninergic neurons were appreciated not only in vivo but also on brain slices immediately following the sacrifice of the animals. In rats deprived of paradoxical sleep, 5-HT synthesis is stimulated (19) ; this effect which can still be detected in vitro is

related to an increased transport of tryptophan in brain slices ; it is interesting to note that 5-hydroxytryptophan transport is not altered in this situation. In addition daily variations in 5-HT synthesis were also detected in in vitro conditions (20). Indeed, as in vivo, ^{3}H-5-HT synthesis from ^{3}H-tryptophan is higher in slices of animals sacrificed during the light period and lower in those sacrificed during the dark period. These effects are again related to parallel changes in the transport of the amino acid in the slices. Moreover, the daily changes which take place in tyrosine transport are in opposite phase to those observed in tryptophan (21). These facts suggest that the two amino acids are not transported intracellularly by the same carrier. Finally, the destruction of catecholaminergic neurons by 6-hydroxydopamine causes a reversal of the normal daily rhythm of tryptophan transport (22). All these results indicate that 5-HT synthesis is not only dependent on the concentration of tryptophan in plasma but is also regulated by changes in the activity of the amino acid carrier (table 1).

Table 1

Effect of various Treatments on 5-HT Synthesis and Tryptophan Uptake

Treatments	TRY Uptake	5-HT Synthesis
Paradoxical sleep deprivation*	↗ (19)	↗ (19)
Circadian rhythm : light/dark*	↗ (20)	↗ (20)
In vivo drug administration :		
Circadian rhythm after 6-OH-DA light/dark*	↘ (22)	↘ (22)
LSD*	↘ (31)	↘ (30,31)
Reserpine**	↗ (34)	↗ (32)
Li+**	↗ (33)	↗ (33)
In vitro drug addition :		
Dibutyryl cyclic AMP*	↗ (28,29)	↗ (28,29)
Imipramine*,**	↘ (23,24)	↘ (23,24,25)
Chlorimipramine**	↘ (26)	↘ (25)
Cocaine**	↘ (27)	↘ (27)

The uptake of amino acid was estimated in brain slices (*) or synaptosomes (**). Numbers in brackets correspond to references listed in the review. ↗: increase ; ↘: decrease.

The transport of tryptophan can also be affected directly or indirectly by drugs. This was shown in slices or in synaptosomal preparations (table 1). Imipramine (23,24) chlorimipramine (25,26) and cocaine (27) inhibit both 5-HT synthesis and amino acid transport. Dibutyryl cyclic AMP induces the opposite effects in slices (28,29). The synthesis of 5-HT is inhibited by LSD administration in vivo (30). This effect has been attributed to an interneuronal regulatory process resulting from the stimulation of serotoninergic receptors by the drug. This inhibition is also observed in brain slices of rats pretreated with the drug and is associated with a decrease transport of tryptophan (31). Similarly, reserpine (32) or Li^+ (33) administration which have been shown by some authors to stimulate 5-HT synthesis activates the transport of tryptophan in synaptosomal preparations (33,34).

Following the recent discovery of a high affinity transport system for tryptophan in synaptosomal preparations (26,27,35), it could be postulated that this system is a unique process of serotoninergic neurons similar to the high affinity transport system of choline in cholinergic neurons (36). However, this is not the case since a high affinity transport of tryptophan has been demonstrated in synaptosomal preparations free of serotoninergic terminals(37)or as shown in table 2 in various cultured cells such as glial cells, fibroblasts and neuroblastoma clones (35).

Table 2

Km and Vmax Values for the high Affinity Tryptophan Uptake in Cell Lines and cortical Synaptosomes

	Apparent Km (μM)	Vmax (nmoles/mg protein/30 sec)
Synaptosomes (fraction B)	52.0	2.76
Cell lines		
C_6 glial cells	7.0	1.48
3T3 fibroblasts	6.9	1.20
N1E-115 noradrenergic neuroblastoma	15.3	3.40
S.20 cholinergic neuroblastoma	11.9	5.60

Various preparations were incubated at 37°C for 30 sec in presence of tryptophan concentrations ranging from 5μM to 0.1mM. Kinetic parameters were determined by linear regression analysis of double reciprocal plots. Each value is the mean of 3 experiments.

Therefore, the changes in tryptophan transport, observed at the same time as those of 5-HT synthesis, do not occur solely in serotoninergic neurons. More precise information concerning the role of tryptophan transport in the regulation of 5-HT will be obtained when its characteristics are examined in a pure serotoninergic preparation.

c) Compartmentalization

It has been recently demonstrated in our laboratory that choline newly taken up into cholinergic neurons does not mix with the endogenous stores in tissues and is solely involved in Ach synthesis (38). Some of our studies on 5-HT suggest similarly that tryptophan newly taken up into serotoninergic neurons is preferentially used in 5-HT synthesis. For example, the results of experiments on the daily variations of 5-HT synthesis support this assumption. The increased formation of ^{3}H-5-HT from ^{3}H-tryptophan observed during the light period *in vivo* as well as *in vitro* depends only on changes in the specific activity of tryptophan in the tissues. These changes are a result of the increased transport of the labelled amino acid. From this observation, and according to the usual interpretation of isotopic studies, it should be concluded that 5-HT synthesis is not modified since the conversion index (^{3}H-5-HT/Tryptophan specific activity or ^{3}H-5-HT + ^{3}H-5-HIAA/Tryptophan specific activity) of tryptophan into 5-HT remains unchanged (20). This interpretation is not valid, however, since the increased 5-HT synthesis which occured during the light period was also revealed by measuring the initial rate of 5-HT accumulation following MAO inhibition. These results suggest that tryptophan is not localized in an homogenous pool in tissues. Consequently, it can be postulated that in some cases changes in 5-HT synthesis may also be dependent on the compartimentalization of tryptophan. More precisely these changes may be related in some ways to the size and turnover of the tryptophan pool contributing mainly to the synthesis of 5-HT. If this were the case, the global estimation of tryptophan specific activity in tissues made in isotopic studies in order to calculate the rate of 5-HT synthesis would be of limited value. Indeed, in recent studies made in mice in order to compare the different methods available for estimating the rate of 5-HT synthesis we were surprised to find that the rate of 5-HT synthesis estimated by the isotopic method was less than that obtained by measu-

ring the initial rate of 5-HT accumulation or 5-HIAA decline following MAO inhibition (39). These findings are contrary to previous reports (40,41).

Rate of Tryptophan Hydroxylation : A second regulatory Factor of 5-HT Synthesis

a) Changes in the Rate of Tryptophan Hydroxylation in short-term regulatory Processes of 5-HT Synthesis

In some isotopic studies, we observed that the increased formation of ^{3}H-5-HT from ^{3}H-tryptophan was not only related to the acceleration of the transport of the labelled amino acid but also to the higher rate of conversion of tryptophan into 5-HT (as suggested by the rise in the conversion index (^{3}H-5-HT + ^{3}H-5-HIAA/ tryptophan specific activity)). Such events occur in the brains of mice, slightly anaesthetized with diethyl ether (42) or placed for one hour in a hot environment (43).They are also observed in the spinal cords of rats deprived of paradoxical sleep for 96 hours by the swimming pool method (19).Although these effects could only be related to a preferential increase in the specific activity of tryptophan in the amino acid pool involved in 5-HT synthesis (an hypothesis yet to be proven),they could also be attributed to an acceleration in the hydroxylation rate of the amino acid. Other experimental evidence is in favor of this mechanism.

Stimulation of 5-HT synthesis is still observed when tryptophan hydroxylase is saturated by the peripheral administration of large quantities of tryptophan (table 3). Thus, the acceleration of 5-HT synthesis noted in rats and mice kept in a hot environment still occurs following the systemic injection of the amino acid precursor (44).

Short term regulatory processes of 5-HT synthesis have been examined more directly in studies carried out on the effect of nerve activity in transmitter formation. Thatdepolarization stimulates 5-HT synthesis was originally demonstrated by Andén et al. (45) who observed an increase in the formation of the transmitter in the isolated spinal cords of mice, subjected to electrical field stimulation. 5-HT synthesis is also accelerated *in vivo* by the electrical stimulation of raphe nuclei (46,47). Conversely, the interruption of nerve impulse flow in serotoninergic neurons induced by transection of the spinal cord in the rat, is rapidly followed by a decrease in the rate of tryptophan hydroxylation(48).

Table 3

Persistent Effects of various Treatments on 5-HT Synthesis after Tryptophan Loading

Treatments	5-HT Synthesis	5-HT Synthesis after TRY loading (Vmax of TRY.OH)
. Hot environment	↗(43,44)	↗(44)
. Stimulation of the mid brain raphe	↗(46)	↗(47)
. Acute transection of the spinal cord (below the lesion)	↘(48)	↘(48)
. MAOI (end-product inhibition)	↘(29,51,52)	↘(52)

In all cases 300-800 mg/kg of the amino acid were injected intraperitoneally. Although tryptophan hydroxylase (TRY.OH) was saturated by the amino acid, changes were still observed. In these situations, the intracellular concentration of tryptophan is not the critical parameter. ↗: increase ; ↘: decrease.
Numbers in brackets correspond to references listed in the review.

This was determined by measuring the rate of 5-hydroxytryptophan accumulation immediately following the blocade of 5-hydroxytryptophan decarboxylase. These rapid changes in 5-HT synthesis, which are linked to fluctuations in transmitter release, are also independent of the peripheral metabolism of tryptophan. Furthermore, they seem to be unrelated to changes in the tryptophan transport in brain tissue. Indeed, as mentioned in table 3, the effects on 5-HT synthesis induced by nerve stimulation (46) or by interruption of firing (48) are still observed in rats injected with large quantities of tryptophan (47,48).

b) End-Product Regulation of 5-HT Synthesis

Although other mechanisms are involved in the short term regulatory processes of catecholamines synthesis, there is little doubt that the intraneuronal concentrations of the amines play an important role. Cytoplasmic dopamine or norepinephrine partially controls the rate of the conversion of tyrosine into DOPA by end-product inhibition (49). In contrast to catecholamines, which inhibit the activity of soluble tyrosine hydroxylase, 5-HT has no effect on the activity of soluble tryptophan hydroxylase (50). This is why the hypothesis of an *in vivo* end-product regulation of 5-HT synthesis was not retained for many years. However, re-

sults from our laboratory suggest that this hypothesis cannot be completely ruled out. Indeed, 5-HT synthesis is reduced when intra neuronal levels of the amine reach 2.5 times normal levels following MAO inhibition. This effect, first observed in vivo (51) can still be detected in brain slices of animals pretreated with MAO inhibitors (29). Inhibition of 5-HT synthesis is also observed in slices when intraneuronal stores of 5-HT in serotoninergic terminals are increased with exogenous 5-HT. This inhibitory process occurs during the first step of the amine synthesis. No reduction in ^{3}H-5-HT synthesis can be seen in rats injected with MAO inhibitors when ^{3}H-5-hydroxytryptophan is substituted for ^{3}H-tryptophan. As shown in slices, the rate of 5-hydroxytryptophan formation is reduced when intraneuronal stores of 5-HT are elevated. Similar conclusions were made by Carlsson and his colleagues in recent studies (52). These authors observed a decrease in the rate of 5-HTP accumulation in the brains of mice injected with MAO inhibitors following the blocade of 5-hydroxytryptophan decarboxylase.

As to the reduction in 5-HT synthesis resulting from the interruption of nerve impulses, the inhibition of the transmitter synthesis induced by the presence of large intraneuronal quantities of 5-HT does not appear to be related to changes in the transport of tryptophan (table 3). The inhibition of 5-HT synthesis observed two to three hours following MAO inhibition still appears in the brains of mice injected with large quantities of tryptophan (52). In addition, the inhibition of the amine synthesis seen in brain slices after loading serotoninergic terminals with exogenous 5-HT, persists in the presence of dibutyrylcyclic AMP, a potent activator of tryptophan transport (29).

The existence of an end-product regulation of 5-HT synthesis in pharmacological circumstances is now well established. Whether or not this mechanism plays a part in controlling the rate of tryptophan hydroxylation under physiological stimulation or inhibition of serotoninergic neuron activity remains to be demonstrated.

c) Other Factors possibly involved in the rapid Control of the Rate of Tryptophan Hydroxylation.

The rapid changes in the rate of tryptophan hydroxylation cannot be attributed to modifications in the concentration of tryptophan hydroxylase. They may be related to transient fluctuations in the concentration of the pteridine cofactor at the hydroxyla-

ting site of the enzyme. 5-HT or ionic changes could be involved in this effect.

Despite numerous efforts made to identify the natural cofactor, the structure of this molecule is still unknown (53). It is thought to be analogous to tetrahydrobiopterin (54). The activity of the soluble form of the enzyme appears to be very dependent upon the nature of the cofactor used. For example, tetrahydrobiopterin (54) and 6-methyltetrahydropteridine(55) are much more active than dimethyltetrahydropteridine. Consequently, the identification of the natural cofactor is prerequisite to the understanding of the role of the intraneuronal concentration of the cofactor in the regulatory process of hydroxylation.

As revealed in in vivo studies, changes in the availability of oxygen, the second substrate of tryptophan hydroxylase, rapidly influences the rate of 5-HT synthesis (56,57). Local modifications in O_2 pressure which may occur during nerve activity may also be involved in the short term regulation of 5-HT synthesis.

It has been postulated that two forms of tryptophan hydroxylase (58,59) may exist since the enzyme has not yet been completely solubilized. As in the case of tyrosine hydroxylase (60) one form of tryptophan hydroxylase could be bound to neuronal membranes and its characteristics could be different from the soluble form. It is conceivable that this form is particularly sensitive to changes in the ionic environment which occur during nerve activity. However, the estimation of the activity of the particulate form of the enzyme may correspond to an enzymatic activity distinct from that of the soluble form or only to the overall measurement of the activity of the enzyme still localized in synaptosomes.

The so-called "particulate form" exhibits properties different from those of the soluble one. For example, differences in sensitivity to heat inactivation or to ultrasonic oscillation could be observed (Fig.2, (61)). Moreover, the two forms do not react in a similar way to specific inhibitors such as parachlorophenylalanine (59) and their affinity constants toward tryptophan seem to be different (58). Whether or not these apparent differences are related, not only to the enzyme environment, but to new properties resulting from the enzyme binding to neuronal membranes, remains to be clearly demonstrated.

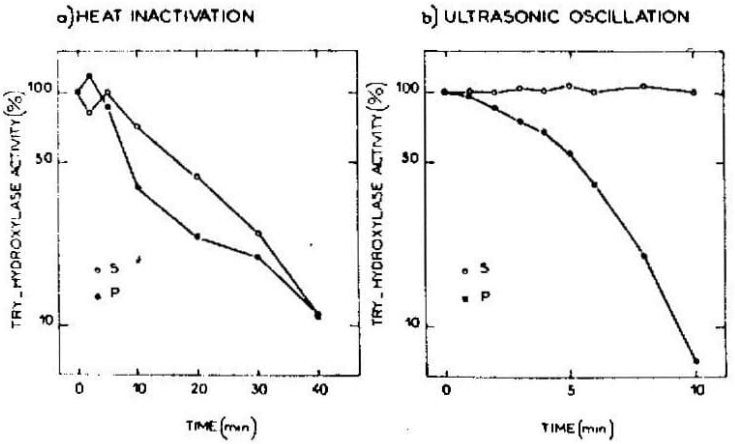

FIG. 2

a) Effect of heat inactivation on tryptophan hydroxylase activity. Pig brain stems were homogenized in 0.32 M sucrose, and tryptophan hydroxylase activity estimated on the crude mitochondrial fraction (P) and the corresponding supernatant (S). In the latter case, 1mM $DMPH_4$ was used as the cofactor. Both enzyme preparations were heated at 45°C in a water bath for times up to 40 min. Each value is the mean of 4 determinations. The activity was measured with 3µM ^{3}H-tryptophan ; 100% for the S enzyme corresponds to 3.86 picomoles ^{3}H-5-HT/mg protein/h. For the P enzyme, this value is 10.41 picomoles ^{3}H-5-HT/mg protein/h.

b) Effect of ultrasonic oscillation on tryptophan hydroxylase activity. The same preparations (as in -a-) were used. Ultrasonication (20 kHz, 100 W) was performed for times up to 10 min. Each value is the mean of 4 determinations. Note the rapid decay of particulate tryptophan hydroxylase activity which could not be reactivated with 1mM $DMPH_4$.

d) Long-term Regulatory Processes in the Rate of Tryptophan Hydroxylation

In contrast to the rapid regulatory processes, the sustained changes in the rate of 5-HT synthesis can be related to modifications in the concentration of tryptophan hydroxylase in serotoninergic neurons. Increased activity of the enzyme has been clearly demonstrated in the brain stem and spinal cord of rats 12 hours following reserpine injection (62). A similar effect is observed in the brain stem of adrenalectomized rats treated with corticosterone (63).

Discussion

Various independent factors or processes seem to play a role in the modulation of 5-HT synthesis. Changes in the synthesis of the transmitter may occur without modifying the rate of tryptophan's conversion into 5-HT. Indeed, in some cases fluctuations in the availability of tryptophan alone may be responsible for the effects observed. These fluctuations may depend on the concentration of the free form of tryptophan or on the equilibrium between tryptophan and other neutral amino acids in the plasma. They could also be simply attributed to modifications in the rate of transport of the amino acid precursor in neuronal tissues or to modifications in its intraneuronal compartimentalization.

Under certain circumstances, both the availability of tryptophan and its rate of hydroxylation are involved in the regulation of 5-HT synthesis. But, as we have seen, the synthesis of the transmitter can be accelerated or slowed by mechanisms apparently independent of the substrate availability. The rate of the conversion of tryptophan into 5-HTP may be influenced by nerve activity whatever the concentration of tryptophan in the tissues.

The synthesis of 5-HT is undoubtedly partly affected by the peripheral metabolism of tryptophan. This type of influence may be a unique characteristic of serotoninergic neurons. However, more subtile processes may integrate the numerous apparent independent factors involved in the control of the transmitter formation. In other words, some well-defined relationships may exist between the processes controlling the arrival of tryptophan at the hydroxylation site and the processes which influence the rate of amino acid's conversion into 5-HTP. Synthesis and release are, in most cases, closely related processes in neurons. In contrast to catecholaminergic and cholinergic neurons, we still have only limited information concerning the characteristics of 5-HT release in serotoninergic neurons. In our opinion, the development of a unifying model of the mechanisms regulating 5-HT synthesis is contingent to a better understanding of the release mechanisms of the transmitter.

References

1. D.A.V. PETERS, P.L. McGEER and E.G. McGEER, J. Neurochem. 15 1431-1435, 1968.
2. R.H. McMENAMY and J.L. ONCLEY, J. Biol. Chem. 233: 1436-1447, 1958.
3. P.J. KNOTT and G. CURZON, Nature 239: 452-453, 1972.
4. A. TAGLIAMONTE, G. BIGGIO, L. VARGIU and G.L. GESSA, Life Sci. 12: 277-287, 1973.
5. R.H. McMENAMY, C.C. LUND and J.L. ONCLEY, J. Clin. Invest. 30: 1672-1679, 1957.
6. S. UDENFRIEND, Pharmacol. Rev. 18: 43, 1966.
7. A. TAGLIAMONTE, G. BIGGIO, L. VARGIU and G.L. GESSA, J. Neurochem. 20: 909-912, 1973.
8. S. BOURGOIN, A. FAIVRE-BAUMAN, P. BENDA, J. GLOWINSKI and M. HAMON, J. Neurochem. (in press)
9. G. CURZON, J. FRIEDEL and P.J. KNOTT, Nature 242:198-200, 1973.
10. G. CURZON, M.H. JOSEPH and P.J. KNOTT, J. Neurochem. 19: 1967-1974, 1972.
11. J.D. FERNSTROM and R.J. WURTMAN, Science 173: 149-152, 1971.
12. T.L. SOURKES, K. MISSALA and M. ORAVEC, J. Neurochem. 17: 111-115, 1970.
13. G. CURZON and A.R. GREEN, Br.J. Pharmacol. 43: 39-52, 1971.
14. G.L. GESSA and A. TAGLIAMONTE, in "Aromatic amino acids in the brain" Ciba Foundation Symposium Elsevier/Excerpta Medica/ North Holland, 207-216, 1974.
15. J. KORF, H.M. VANPRAAG and J.B. SEBENS, Brain Res. 42:239-242, 1972.
16. J.A. DOMINIC, in "Serotonin and behavior", ed. J. Barchas and E. Usdin, Academic Press, NY London, 149-155, 1973.
17. B.K. MADRAS, E.L. COHEN, J.D. FERNSTROM, F. LARIN, H.N. MUNRO and R.J. WURTMAN, Nature 244: 34-35, 1973.
18. J.D. FERNSTROM and R.J. WURTMAN, Science, 178: 414-416, 1972.
19. F. HERY, J.F. PUJOL, M. LOPEZ, J. MACON and J. GLOWINSKI, Brain Res. 21: 391-403, 1970.
20. F. HERY, E. ROUER and J. GLOWINSKI, Brain Res. 43:445-465, 1972.
21. F. HERY, E. ROUER, J.P. KAN and J. GLOWINSKI, in "Advances in Biochemical Psychopharmacology, Vol 11. Serotonin - New Vistas, ed. E. Costa, G.L. Gessa and M. Sandler, Raven Press, N.Y. (in press).
22. F. HERY, E. ROUER and J. GLOWINSKI, Brain Res. 58:135-146, 1973.
23. J. BRUINVELS, Eur.J.Pharmacol. 20: 231-237, 1972.
24. M. HAMON, F. JAVOY, M. JEANNE-ROSE and J. GLOWINSKI (unpublished observations).

25. J.SCHUBERT, H. NYBACK and G. SEDVALL, J.Pharm.Pharmacol. 22: 136-139, 1970.

26. M.F. BELIN et J.F. PUJOL, C.R. Acad.Sci. Paris, 275:3017-3020, 1972.

27. S. KNAPP and A.J. MANDELL, Science, 177: 1209-1211, 1972.

28. A. TAGLIAMONTE, P. TAGLIAMONTE, J. FORN, J. PEREZ-CRUET, G. KRISHNA and G.L. GESSA, J. Neurochem 18: 1191-1196,1971.

29. M. HAMON, S. BOURGOIN and J.GLOWINSKI, J. Neurochem. 20 : 1727-1745, 1973.

30. R.C. LIN, S.H. NGAI and E. COSTA, Science,166:237-239,1969.

31. M. HAMON, S. BOURGOIN, J. JAGGER and J. GLOWINSKI, Brain Res. 69: 265-280, 1974.

32. T.N. TOZER, N.H. NEFF and B.B. BRODIE, J. Pharmacol.exp.Ther. 153: 177-182, 1966.

33. S. KNAPP and A.J. MANDELL, Science, 180: 645-647, 1973.

34. M.F. BELIN, G. CHOUVET et J.F. PUJOL, Biochem.Pharmacol. 23: 587-597, 1974.

35. A. BAUMAN, S. BOURGOIN, P. BENDA, J. GLOWINSKI and M. HAMON, Brain Res. 66: 253-263, 1974.

36. M.J. KUHAR, V.H. SETHY, R.H. ROTH and G.K. AGHAJANIAN, J. Neurochem. 20: 581-593, 1973.

37. M.J. KUHAR, R.H. ROTH and G.K. AGHAJANIAN, J.Pharmacol.exp. Ther. 181: 36-45, 1972.

38. P. GUYENET, P. LEFRESNE, J. ROSSIER, J.C. BEAUJOUAN and J. GLOWINSKI, Mol. Pharmacol. 9: 630-639, 1973.

39. Y. MOROT-GAUDRY, M. HAMON, S. BOURGOIN, J.P. LEY and J. GLOWINSKI, Naunyn-Schmiedeberg'sArch.Pharmacol.282: 223-238, 1974.

40. N.H. NEFF, P.S. SPANO, A. GROPPETTI, C.T. WANG and E. COSTA, J.Pharmacol.exp.Ther. 176: 701-710, 1971.

41. A. CARLSSON, J.N. DAVIS, W. KEHR, M. LINDQVIST and C.V.ATACK, Naunyn Schmiedeberg's Arch.Pharmacol. 275: 153-168, 1972.

42. S. BOURGOIN, Y. MOROT-GAUDRY, J. GLOWINSKI and M. HAMON, Eur. J.Pharmacol. 22: 209-211, 1973.

43. Y. MOROT-GAUDRY, M. HAMON, S. BOURGOIN and J. GLOWINSKI (in preparation).

44. R. SQUIRES, in "Advances in Biochemical Psychopharmacology Vol.10- Serotonin-New Vistas", ed. E. Costa, G.L. Gessa, and M. SANDLER, Raven Press, N.Y. (in press).

45. N.E. ANDÉN, A. CARLSSON, N.A. HILLARP and T. MAGNUSSON, Life Sci. 3: 473-478, 1964.

46. P.J. SHIELDS and D. ECCLESTON, J. Neurochem. 19:265-272,1972.

47. D. ECCLESTON, I.M. RITCHIE and M.H.T. ROBERTS, Nature, 226: 84-85, 1970.

48. A. CARLSSON, M. LINDQVIST, T. MAGNUSSON and C. ATACK, Naunyn-Schmiedeberg's Arch.Pharmacol. 277:1-12, 1973.

49. S. SPECTOR, R. GORDON, A. SJOERDSMA and S. UDENFRIEND, Mol. Pharmacol. 3: 549-555, 1967.

50. E. JEQUIER, D.S. ROBINSON, W. LOVENBERG and A. SJOERDSMA, Biochem.Pharmacol. 18: 1071-1081, 1969.

51. J.B. MACON, L. SOKOLOFF and J. GLOWINSKI, J. Neurochem. 18: 323-331, 1971.

52. A. CARLSSON and M. LINDQVIST, J.Neural Transmission,33: 23-43, 1972.

53. E.M. GÁL and A.E. ROGGEVEEN, Science,179: 809-811,1973.

54. P.A. FRIEDMAN, A.H. KAPPELMAN and S. KAUFMAN, J.Biol.Chem. 247: 4165-4173, 1972.

55. A.J. MANDELL, S. KNAPP and L.L. HSU, Life Sci. 14: 1-17,1974.

56. P.M. DIAZ, S.H. NGAI and E. COSTA, in "Advances in Pharmacology", ed. S. Garattini and P.A. Shore, Academic Press,6B: 75-92, 1968.

57. J.N. DAVIS and A. CARLSSON, J. Neurochem. 21:783-790, 1973.

58. A. ICHIYAMA, S. NAKAMURA, Y. NISHIZUKA and O. HAYAISHI, J. Biol. Chem. 245: 1699-1709, 1970.

59. S. KNAPP and A.J. MANDELL, Life Sci. 16: 761-771, 1972.

60. R.T. KUCZENSKI and A.J. MANDELL, J. Biol. Chem. 247: 3114-3122, 1972.

61. M. HAMON, S. BOURGOIN and M.B.H. YOUDIM (in preparation)

62. B. ZIVKOVIC, A. GUIDOTTI and E. COSTA, Brain Res. 57: 522-526, 1973.

63. E.C. AZMITIA Jr and B.S. McEWEN, Science,166: 1274-1276,1969.