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Simulation of Biogenic Amine Metabolism in the Brain

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The metabolism of a number of biogenic amines has been simulated by using data obtained from studies of the individual enzymes from pig brain. It is shown that β-hydroxylated amines such as noradrenaline and octopamine are metabolized primarily to the alcoholic metabolite whereas amines lacking this group [e.g. dopamine (3,4-dihydroxyphenethylamine) and 5-hydroxytryptamine] are metabolized at low concentrations to give the corresponding acid. Increase in the amine concentration results in an increase in the proportion of the alcoholic metabolite formed and this may in part account for the effects of the drug reserpine on amine metabolism. The effects of disulfiram (Antabuse) and ethanol (acting through its metabolite acetaldehyde) on amine metabolism may be understood in terms of this simulated model. It is shown that drugs that affect this system also cause alterations in the steady-state concentrations of the intermediate aldehydes and the possible implications of this are discussed.

The breakdown of the biogenic amines in the brain involves their deamination by monoamine oxidase to produce the corresponding aldehydes which are then either oxidized by aldehyde dehydrogenase or reduced by aldehyde reductase to yield the corresponding acids or alcohols respectively. These metabolites are then excreted as such or after conjugation (Breese *et al.*, 1969*a*,*b*; Eccleston *et al.*, 1966; Rutledge & Jonason, 1967). In brain the metabolic products formed have been found to depend in a variety of species on the structure of the substrate involved both *in vivo* and *in vitro*. Amines containing a β-hydroxyl group (e.g. octopamine and noradrenaline) have been shown to be metabolized primarily to the alcoholic products whereas those that do not possess this group are converted largely into the acid metabolites (Breese *et al.*, 1969*a*,*b*; Rutledge & Jonason, 1967; Jonason & Rutledge, 1968; Eccleston *et al.*, 1969). It has been suggested that this may simply be due to the specificities of the enzymes involved since the introduction of a β-hydroxyl group into an aldehyde causes a considerable decrease in the K_m values of the aldehyde reductases with comparatively little effect on the kinetic parameters of aldehyde dehydrogenase (Turner & Tipton, 1972*a*,*b*; Tabakoff *et al.*, 1973).

The metabolism of amines has also been found to be affected by the drugs reserpine, disulfiram and ethanol, all of which cause a relative increase in the production of the alcoholic metabolites (Smith & Wortis, 1960; Sandler & Youdim, 1968; Tacker *et al.*, 1970). Since a major effect of reserpine is to release bound amines causing an increase in the intraneuronal concentration of amines available for metabolism (see e.g. Iversen, 1967) it has been suggested that this will result in increased concentrations of aldehydes which will saturate the aldehyde dehydrogenase whereas the activity of the aldehyde reductases which have higher K_m values for aldehydes will continue to increase (Turner & Tipton, 1972*a*; Duncan & Sourkes, 1974; Tipton & Turner, 1974). Such an effect would result in an increase in proportion of the alcoholic metabolites formed as the concentration of the amine rises. The effect of disulfiram on this system may be understood in terms of its inhibitory effect on aldehyde dehydrogenase (Deitrich & Erwin, 1971) whereas the effect of ethanol may be caused by its metabolite acetaldehyde acting as a competing substrate for aldehyde dehydrogenase without having any significant effect on the activities of the aldehyde reductases (Lahti & Majchrowicz, 1969; Turner & Tipton, 1972*a*; Duncan & Sourkes, 1974; Tipton & Turner, 1974). Tipton & Turner (1974) have shown that it is possible to reconstruct the metabolism of tyramine in pig brain in terms of the properties of the individual enzymes involved by using a computer simulation approach. The results from these studies indicated that it was indeed possible to understand the qualitative effects of the above mentioned drugs solely in terms of the properties of the individual enzymes. In the present paper this approach is extended to cover a variety of biogenic amines and it is shown that the behaviour of the simulated system parallels results obtained by direct observations.

Materials and Methods

The pathway of metabolism of amines in pig brain is shown in Scheme 1. The kinetic parameters for these enzymes are summarized in Table 1. The data

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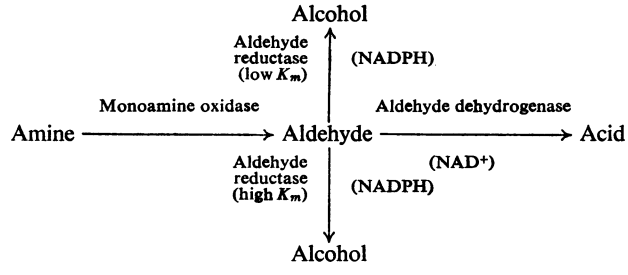
Table 1. *Kinetic constants for the enzymes of biogenic amine catabolism in pig brain*

$V_{max.}$ values are expressed as μmol of product formed/min per kg of brain tissue and refer to whole brain except for the values for 3,4-dihydroxyphenylglycolaldehyde which were obtained from caudate nucleus (Duncan & Sourkes, 1974). The constants for monoamine oxidase were determined at air-saturating oxygen concentrations and were taken from published results (Tipton, 1972) or were determined as stated in the text. The data for the aldehyde-metabolizing enzymes was taken from published results (Duncan & Tipton, 1971; Turner & Tipton, 1972*a*,*b*; Duncan & Sourkes, 1974).

	Monoamine oxidase		Aldehyde dehydrogenase		Aldehyde reductase (low K_m)		Aldehyde reductase (high K_m)	
	K_m (μM)	$V_{max.}$	K_m (μM)	$V_{max.}$	K_m (μM)	$V_{max.}$	K_m (μM)	$V_{max.}$
Tryptamine	115	74	—	—	—	—	—	—
Indoleacetaldehyde	—	—	1.2	25	5.9	12	2000	74
5-Hydroxytryptamine	28	43	—	—	—	—	—	—
5-Hydroxyindolylacetaldehyde	—	—	0.2	3.9	3.8	65	∞	—
Dopamine	376	104	—	—	—	—	—	—
3,4-Dihydroxyphenylacetaldehyde	—	—	0.3	81.8	8.7	10	40	2.6
Noradrenaline	75	51.5	—	—	—	—	—	—
3,4-Dihydroxyphenylglycolaldehyde	—	—	2.8	10.7	1.0	27.5	7.8	71
Octopamine	170	82	—	—	—	—	—	—
4-Hydroxyphenylglycolaldehyde	—	—	0.6	6.3	0.7	15.6	14	119.5

Scheme 1. *Metabolic pathway of biogenic amines in the brain as used for the simulation study*

The enzymes involved are monoamine oxidase, aldehyde dehydrogenase, which uses NAD^+ as the coenzyme, and two NADPH-dependent aldehyde reductases one of which has a lower K_m value for aldehydes than the other.



for pig brain aldehyde dehydrogenase and the two aldehyde reductases in pig brain were taken from published work (Duncan & Tipton 1971; Turner & Tipton, 1972*a*,*b*; Duncan & Sourkes, 1974) as were most of the data for pig brain monoamine oxidase (Tipton, 1972). Other values for this enzyme were determined at an oxygen concentration of 230μM as described below.

The Michaelis parameters for the oxidation of dopamine (3,4-dihydroxyphenethylamine) were obtained from double-reciprocal plots of initial-rate data determined by using the coupled assay procedure described by Houslay & Tipton (1973*a*). A polarographic assay (Tipton, 1968) was used for determinations with octopamine as the substrate and a similar assay was used for the investigation of the inhibition of monoamine oxidase by indolylacetaldehyde in which case tyramine was used as the substrate. Acetaldehyde did not cause significant inhibition of monoamine oxidase at concentrations of up to 100μM.

All the data used in these studies were obtained at 30°C and at pH7.2. Aldehyde dehydrogenase and the aldehyde reductases have been shown to catalyse essentially irreversible reactions and to be insensitive to inhibition by their respective acid and alcohol products under these conditions; the effects of these products have therefore been neglected in this simulation study (Duncan & Tipton, 1971; Turner & Tipton, 1972*a*,*b*). The aldehyde reductases and the aldehyde dehydrogenase were assumed to be saturated with their coenzymes (Tipton & Turner, 1974) and thus these enzyme reactions could be considered to obey a simple single-substrate Michaelis–Menten mechanism. Inhibition of the aldehyde reductases by the concentrations of $NADP^+$ present in brain was assumed to be negligible whereas small corrections

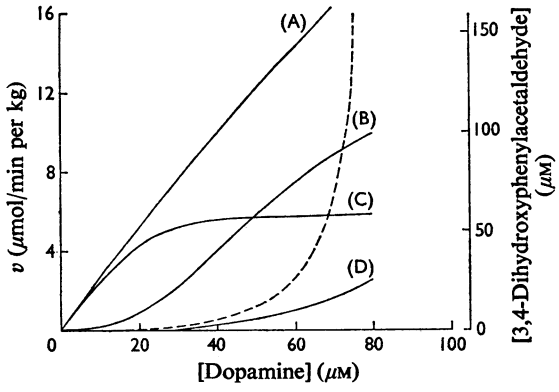


Fig. 1. *Simulation of dopamine metabolism*

The kinetic constants used are given in Table 1. ----, Concentration of 3,4-dihydroxyphenylacetaldehyde. Curve (A), monoamine oxidase; curve (B), aldehyde reductase (low K_m); curve (C) aldehyde dehydrogenase; curve (D), aldehyde reductase (high K_m).

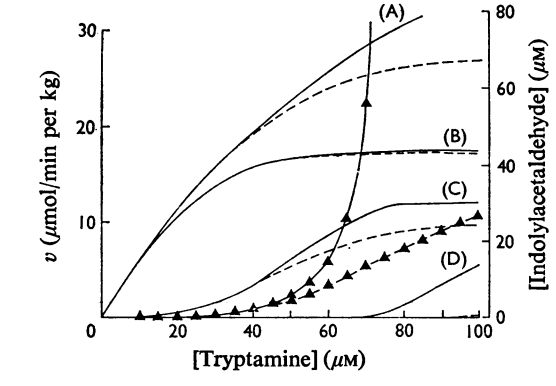


Fig. 2. *Simulation of tryptamine metabolism showing the effects of product inhibition of monoamine oxidase*

The kinetic constants used are given in Table 1 and a K_i value of 45 μM for indolylacetaldehyde as an inhibitor of monoamine oxidase was used. ——, Simulated values when product inhibition of monoamine oxidase was not taken into account; ----, situation in the presence of this inhibition. ▲, Concentrations of indolylacetaldehyde. The curves are as follows: (A) monoamine oxidase; (B) aldehyde dehydrogenase; (C) aldehyde reductase (low K_m); (D) aldehyde reductase (high K_m).

were made to the Michaelis parameters of the aldehyde dehydrogenase in order to allow for inhibition by the steady-state concentrations of NADH present in brain. This inhibition is mixed with respect to the aldehyde substrate (Tipton & Turner, 1974).

Computer simulation

The behaviour of this system was simulated by using the computer program described by Illingworth (1972*a*,*b*) with the University of Cambridge Titan computer. This program allows the individual reactions to be typed into the computer in standard chemical nomenclature. Thus for example, the reaction catalysed by monoamine oxidase (designated E) may be typed in as:

E+Amine = EAmine
EAmine = E+Amine
EAmine = E+Aldehyde

with the K_m and $V_{max.}$ values for the amine in question also being supplied. The total pathway was built up by including the reactions catalysed by aldehyde dehydrogenase and the two aldehyde reductases (which were designated F, G and H respectively for input) together with the appropriate Michaelis parameters shown in Table 1. Reversible inhibition was simulated by including the appropriate additional steps in the reaction pathway together with the K_i value.

Results

The results of these simulation studies are given in Figs. 1–7. The velocities of the aldehyde-metabolizing enzymes will of course give a direct measure of the proportions of the acid and alcoholic metabolites formed.

Simulation of dopamine metabolism

Fig. 1 shows the variations of the activities of the enzymes involved and the variation of the steady-state concentrations of 3,4-dihydroxyphenylacetaldehyde as the concentration of dopamine is increased from 0 to 80 μM. At low concentrations of dopamine the acid metabolite predominates, comprising some 86% of the total at 10 μM-dopamine. At higher amine concentrations the proportion of the alcoholic metabolite increases to become the predominant product at dopamine concentrations in the region of 50 μM.

Simulation of tryptamine metabolism

The reconstruction of the metabolism of tryptamine is shown in Fig. 2. In a previous study (Tipton & Turner, 1974) the possibility of inhibition of monoamine oxidase by the steady-state concentrations of its products was not considered. Of the three products of the monoamine oxidase-catalysed reaction, NH_3 appears to be a very poor inhibitor of the enzyme (Houslay & Tipton, 1973*b*) and the H_2O_2 produced would be expected to be rapidly decomposed by catalase or peroxidase activity (see e.g. Houslay & Tipton, 1973*b*). The aldehyde product of the reaction is, however, a good inhibitor of monoamine oxidase (Tipton, 1968). Indolylacetaldehyde was found to be an uncompetitive inhibitor with respect to tyramine, in

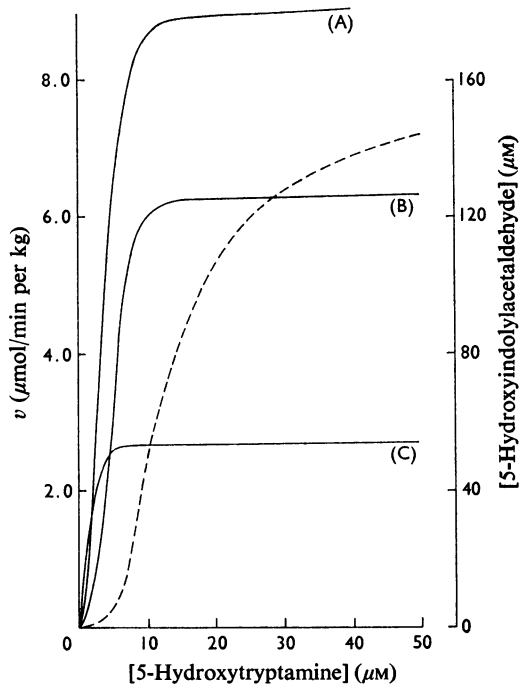


Fig. 3. *Simulation of 5-hydroxytryptamine metabolism*

The kinetic constants used are given in Table 1 and product inhibition of monoamine oxidase by 5-hydroxyindolylacetaldehyde was assumed to be uncompetitive with a K_i value of 45 μM. ----, Concentration of 5-hydroxyindolylacetaldehyde. The curves are: (A), monoamine oxidase; (B) aldehyde reductase (low K_m); (C) aldehyde dehydrogenase.

agreement with the results previously reported for phenylacetaldehyde (Tipton, 1968), and the K_i value was calculated to be 45 μM. Thus inhibition by this product could be important in systems in which the steady-state concentration of the aldehyde can reach relatively high values. The simulated curves in Fig. 2 compare the metabolism of tryptamine under conditions in which the inhibition of monoamine oxidase by the indolylacetaldehyde concentrations was and was not taken into account. A comparison of the curves shows that inhibition by indolylacetaldehyde has a negligible effect on the behaviour of the system until the activities of aldehyde dehydrogenase and the low-K_m aldehyde reductase approach saturation velocities. Above this region where the activities of these two enzymes no longer buffer the steady-state aldehyde concentrations, those of indolylacetaldehyde begin to rise rapidly and the product inhibition of monoamine oxidase becomes important.

Simulation of 5-hydroxytryptamine metabolism

The simulation of 5-hydroxytryptamine metabolism is simplified because only one of the two aldehyde reductases has appreciable activity towards 5-hydroxyindolylacetaldehyde. The simulated results obtained in the amine range from 0 to 40 μM are shown in Fig. 3. The buffering power of the two aldehyde-metabolizing enzymes is relatively poor and in the absence of product inhibition of monoamine oxidase the steady-state concentrations of 5-hydroxyindolylacetaldehyde would rise rapidly at applied amine concentrations above 10 μM. Unfortunately no data are available on the inhibition of monoamine oxidase by 5-hydroxyindolylacetaldehyde and it was not found possible to prepare a sufficiently pure sample of this compound. However, an indication of the effects that might be expected if the product K_i value for this aldehyde were similar to that for indolylacetaldehyde is shown in Fig. 3.

Simulation of noradrenaline and octopamine metabolism

The results of the simulations of noradrenaline and octopamine metabolism are shown in Figs. 4 and 5 respectively. In both cases the metabolic patterns differ considerably from those given by amines that lack the β-hydroxyl group. The considerably lower activities and the relatively higher K_m values of the aldehyde dehydrogenase towards the aldehydes derived from noradrenaline and octopamine result in the rate of acid formation never exceeding 10% of the total metabolism. In addition the activities of the aldehyde-metabolizing enzymes act to form a buffer against rising aldehyde concentrations which is much

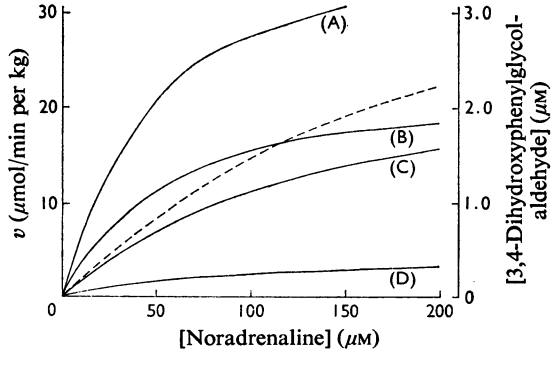


Fig. 4. *Simulation of noradrenaline metabolism*

The kinetic constants used are given in Table 1. ----, Concentration of 3,4-dihydroxyphenylglycolaldehyde. The curves are: (A) monoamine oxidase; (B) aldehyde reductase (low K_m); (C) aldehyde reductase (high K_m); (D) aldehyde dehydrogenase.

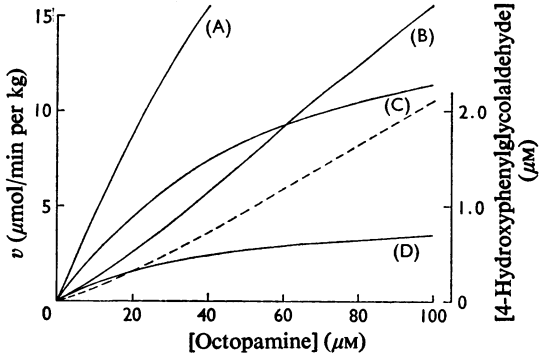


Fig. 5. *Simulation of octopamine metabolism*

The kinetic constants used are as given in Table 1. ----, Concentration of 4-hydroxyphenylglycolaldehyde. The curves are: (A) monoamine oxidase; (B) aldehyde reductase (high K_m); (C) aldehyde reductase (low K_m); (D) aldehyde dehydrogenase.

more efficient than is observed with amines which do not contain a β-hydroxyl group. In the case of noradrenaline this buffering effect results in the free 3,4-dihydroxyphenylglycolaldehyde concentration remaining below 2.5μM up to amine concentrations as high as 200μM. Such an effect may be of importance in the metabolism of this amine since it may be calculated that the free concentration of noradrenaline in the nerve ending may be as high as 100μM [see Tipton (1973) for discussion].

Simulation of the effects of acetaldehyde

The effects of increasing concentrations of acetaldehyde on the metabolism of dopamine and 5-hydroxytryptamine are shown in Figs. 6 and 7. Since it has been shown that the acetaldehyde concentrations may reach 75μM in rat brain after ethanol administration (Ridge, 1963) the concentration range used in these studies was 0–80μM. The K_i value for acetaldehyde acting as a competitive substrate of aldehyde dehydrogenase was taken as 2.6μM (Lahti & Majchrowicz, 1969).

The results show that the competitive inhibition of aldehyde dehydrogenase results in an elevation of the steady-state concentration of the 'biogenic aldehydes' 3,4-dihydroxyphenylacetaldehyde (Fig. 6) and 5-hydroxyindolylacetaldehyde (Fig. 7) which causes an increase in the activities of the aldehyde reductases. A qualitatively similar behaviour was seen in simulation of the effects of acetaldehyde on tryptamine metabolism which gave results which were also similar to those previously reported for the metabolism of tyramine (Tipton & Turner, 1974). The effects of acetaldehyde on the metabolism of octopamine and noradrenaline followed a similar general pattern but the changes observed were smaller because of the relatively minor role of aldehyde dehydrogenase in the metabolism of these aldehydes.

Discussion

The results obtained in this study confirm and extend those previously reported for the simulation of tyramine metabolism (Tipton & Turner, 1974). A comparison of the metabolism of octopamine and noradrenaline with tyramine and dopamine indicates that the presence of a β-hydroxyl group in the parent amine causes a significant decrease in the metabolism of the aldehyde by the oxidative pathway and an increased metabolism to the alcoholic product. In

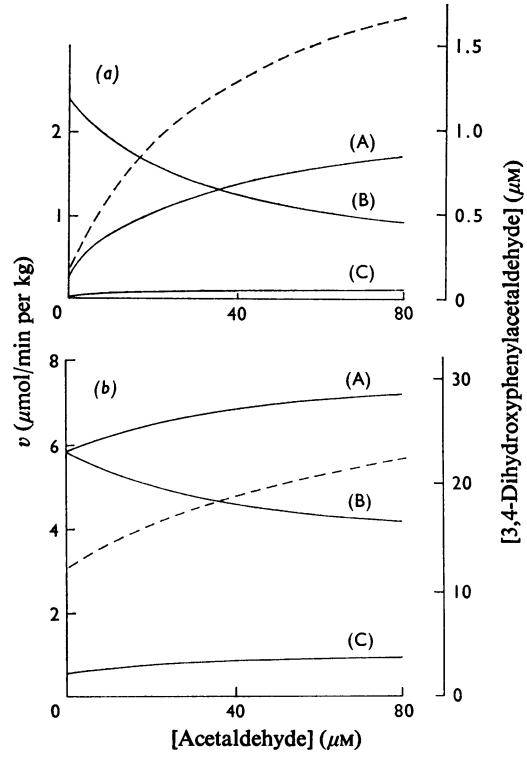


Fig. 6. *Simulation of the effect of acetaldehyde on the metabolism of dopamine*

The kinetic constants for dopamine metabolism were taken from Fig. 1 and the K_i value for acetaldehyde as a competitive substrate for aldehyde dehydrogenase was 2.6μM. ----, Concentrations of 3,4-dihydroxyphenylacetaldehyde. (*a*) Simulation at a dopamine concentration of 10μM; (*b*) simulation at a dopamine concentration of 50μM. The curves are: (A) aldehyde reductase (low K_m); (B) aldehyde dehydrogenase; (C) aldehyde reductase (high K_m).

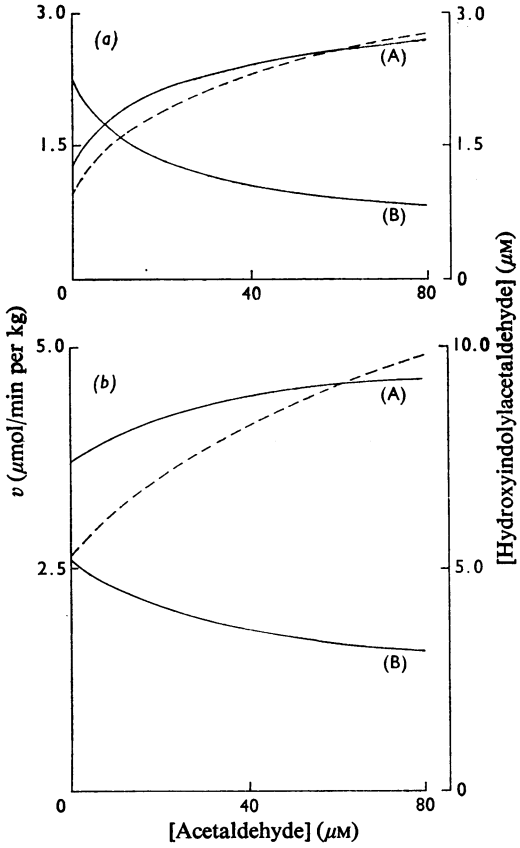


Fig. 7. *Simulation of the effect of acetaldehyde on 5-hydroxytryptamine metabolism*

The kinetic constants for 5-hydroxytryptamine metabolism were taken from Table 1 and the K_i value for acetaldehyde acting as a competitive substrate for aldehyde dehydrogenase was 2.6μM. ----, Concentrations of 5-hydroxyindolylacetaldehyde. (*a*) Simulation at a 5-hydroxytryptamine concentration of 2.5μM; (*b*) simulation at a 5-hydroxytryptamine concentration of 5μM. The curves are: (A) aldehyde reductase (low K_m); (B) aldehyde dehydrogenase.

addition the activities of the aldehyde-metabolizing enzymes combine to provide a much more efficient buffer against rising amine concentrations than they do when the parent amines lack the β-hydroxyl group. In the case of the latter amines, elevated concentrations can lead to steady-state concentrations of aldehydes such that product inhibition of monoamine oxidase may become important.

A large number of studies on the metabolic fate of biogenic amines which have used either brain slices (Breese *et al.*, 1969*a*,*b*; Kellogg *et al.*, 1971; Rutledge & Jonason, 1967) or brain homogenates (Feldstein & Williamson, 1968; Eccleston *et al.*, 1966) have indicated that the effects of amine structure on the pattern of product formation show little species variation. Similar results have been obtained by analysing the radioactive products in the brain of animals that had been killed at time-intervals after radioactive amines had been injected directly into the brain (Maas & Landis, 1968; Breese *et al.*, 1969*a*; Taylor & Laverty, 1969). Perhaps the only exception that has yet been found to this general species similarity is that reported for amine metabolism in the dog (Chase *et al.*, 1971). However, these latter investigations involved the determination of the amine metabolites in urine after administration of the amine and hence the results do not simply reflect the metabolism in brain.

It is not easy to compare quantitatively the results of a simulation study such as this with those observed in the studies mentioned above since it is not possible to estimate the concentrations of amines available to monoamine oxidase in the direct studies. In most cases very low concentrations of the radioactive amines being studied were used (see Table 2) but of course the total concentration of amines available to monoamine oxidase in these systems will be greater owing to the endogenous amines already present. In addition, although relatively low concentrations of amines were used in most of the direct studies the local concentrations of these amines in the vicinity of monoamine oxidase are unknown and some degree of concentration may be expected because of active up-

Table 2. *Pattern of metabolism of the biogenic amines*

The simulated values for tyramine were taken from Tipton & Turner (1974). The literature values cited were obtained with rat, guinea-pig, chick or rabbit brain slices or homogenates (Breese *et al.*, 1969*a*,*b*; Eccleston *et al.*, 1966; Feldstein & Williamson, 1968; Kellogg *et al.*, 1971; Rutledge & Jonason, 1967).

		Ratio of acid product/neutral product				
			Simulated values			
Amine	Supplied amine concentration (μM)	Literature values	At 2.5μM-amine	At 5μM-amine	At 10μM-amine	At 50μM-amine
Tyramine	0.4	8	25	18	13	0.8
Dopamine	about 0.1	25–110	100	64	12.5	0.89
5-Hydroxytryptamine	25 and 200	0.85–4.3	2.0	0.9	0.45	0.43
Octopamine	0.4	0.07–0.15	0.35	0.25	0.24	0.19
Noradrenaline	0.1–1	0.19–0.50	0.08	0.08	0.08	0.09

take processes. Thus any comparison of the results of a simulation study with those obtained experimentally cannot be expected to give quantitatively good agreement at the same concentration of applied amines.

With these reservations in mind, the patterns of metabolite formation given by the simulation studies are compared in Table 2 with those obtained by direct observation. It is not possible to predict the total concentration of a given amine in the brain from the observed metabolite pattern because of the storage of amines in forms that are not accessible to monoamine oxidase and the possible existence of permeability barriers. The generally good agreement between the variation of the patterns of amine metabolites with amine structure and concentration (see below) with that expected might, however, suggest that any permeability barriers between the enzymes involved are not kinetically significant.

Increase in the concentration of an amine results in an increase in the proportion of the alcoholic metabolite formed as the aldehyde dehydrogenase approaches saturation. Such behaviour is in accord with that previously reported for the simulated metabolism of tyramine (Tipton & Turner, 1974). This behaviour provides an explanation of the change in metabolite ratios observed by Sandler & Youdim (1968) after administration of the drug reserpine. The increased production of the alcoholic metabolites caused by ethanol consumption has been attributed to an effect of its metabolite acetaldehyde (Lahti & Majchrowicz, 1969; Turner & Tipton, 1972*a*; Duncan & Sourkes, 1974; Tipton & Turner, 1974). Simulation of the effects of acetaldehyde acting as a competing substrate for aldehyde dehydrogenase without affecting the activities of the other enzymes in the system (Figs. 6 and 7) indicates that increasing the concentration of acetaldehyde will indeed cause increases in the excretion of alcoholic metabolites that are similar to those observed by direct measurements in a number of species (see e.g. Feldstein, 1971).

The pathway considered here does represent a simplification of the system that might be expected to occur in the intact brain. In some circumstances the pathway *in vivo* might be presented with more than one type of amine at the same time and under such conditions the amines and their product aldehydes would compete with each other for the enzymes involved. In addition the system considered here does not involve the activities of catechol *O*-methyltransferase and the NAD^+-dependent alcohol dehydrogenases that are present in brain. Of the amines considered in this study only noradrenaline and dopamine would be expected to function as substrates for catechol *O*-methyltransferase. Unfortunately there are no data available on the kinetic parameters of the pig brain aldehyde-metabolizing enzymes for 3-methoxy-4-hydroxyphenylglycolaldehyde or on the kinetic properties of pig brain catechol *O*-methyltransferase and thus it was not possible to consider the function of this enzyme in the metabolism of the catecholamines. The reasons why the NAD^+-dependent alcohol dehydrogenases may be considered to play an insignificant role in the metabolism of the biogenic amines have been previously discussed, as have the problems of the possible localization of the amine-metabolizing enzymes in discrete brain areas or cell types (Tipton & Turner, 1974).

The pig brain amine-metabolizing system has been shown to contain only a single type of monoamine oxidase (Tipton & Spires, 1968) although it has been reported that a number of other tissues contain multiple forms of this enzyme [see e.g. Squires (1972) and Youdim (1972) for reviews]. There is evidence that in rat liver and human brain these multiple forms may be due to the binding of lipid material to a single enzyme species (Houslay & Tipton, 1973*a*; Tipton *et al.*, 1973) causing alterations in the substrate specificities, inhibitor sensitivities and electrophoretic mobilities of the enzyme. It is possible that the existence of the enzyme in differing lipid environments within a tissue may result in enzyme species with differing properties *in vivo* [see Houslay & Tipton (1973*a*) for discussion]. Any analysis of such a system must, however, await a fuller understanding of the properties of such monoamine oxidase species.

The results in this paper indicate that it may be indeed possible to understand the behaviour of this metabolic system in terms of the kinetic properties of the individual enzymes involved. Such an approach may be of use in the evaluation of the importance of drugs on this system. It is of particular note that the effects of the drugs reserpine, disulfiram and ethanol all entail an elevation of the steady-state concentrations of the 'biogenic aldehydes'. Similar effects will be caused by drugs, such as barbiturates and chlorpromazine (Erwin *et al.*, 1971; Turner & Tipton, 1972*b*), that inhibit aldehyde reductase activity and these will be particularly marked when β-hydroxylated amines are involved. Such effects may result in increased metabolism of the 'biogenic aldehydes' by normally minor pathways such as condensation with amines to form tetrahydroisoquinoline alkaloids (Sandler *et al.*, 1973; Turner *et al.*, 1974; Davis *et al.*, 1974). There is evidence that the 'biogenic aldehydes' themselves may act as neuromediators being particularly important in the regulation of sleep (Jouvet, 1969; Sabelli *et al.*, 1969) and body temperature (Barofsky & Feldstein, 1970). The use of a simulation approach may allow the effects of drugs on the aldehyde concentration to be evaluated and hence may lead to a fuller understanding of the diverse effects of drugs that affect the metabolism of biogenic amines.

Catecholamines have been shown to be intimately involved in affective disorders [see e.g. Bourdillon &

Ridges (1970) for review] and it is hoped that this simulation may be of use in evaluating the metabolic changes that are seen in such conditions. For example, the increased excretion of tryptamine noted in schizophrenics (see e.g. Himwich, 1970) could be due to a direct inhibition of monoamine oxidase or a greatly increased availability of this amine. These simulation studies indicate, however, that an alternative explanation would be provided by a lowered activity of aldehyde dehydrogenase resulting in an elevation of aldehyde concentrations which would decrease the monoamine oxidase activity by product inhibition.

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References

Barofsky, I. & Feldstein, A. (1970) *Experientia* **26**, 990–991
Bourdillon, R. E. & Ridges, A. P. (1970) in *Biochemistry, Schizophrenias and Affective Illnesses* (Himwich, H. E., ed.), pp. 123–147, Williams and Wilkins Co., Baltimore
Breese, G. R., Chase, T. N. & Kopin, I. J. (1969*a*) *Biochem. Pharmacol.* **18**, 863–869
Breese, G. R., Chase, T. N. & Kopin, I. J. (1969*b*) *J. Pharmacol. Exp. Ther.* **165**, 9–13
Chase, T. N., Breese, G. R., Gordon, E. K. & Kopin, I. J. (1971) *J. Neurochem.* **18**, 135–140
Davis, V. E., Cashaw, J. L., McLaughlin, B. R. & Hamlin, T. A. (1974) *Biochem. Pharmacol.* **23**, 1877–1889
Deitrich, R. A. & Erwin, V. G. (1971) *Mol. Pharmacol.* **7**, 301–307
Duncan, R. J. S. & Sourkes, T. L. (1974) *J. Neurochem.* **22**, 663–669
Duncan, R. J. S. & Tipton, K. F. (1971) *Eur. J. Biochem.* **22**, 538–543
Eccleston, D., Moir, A. T. B., Reading, H. W. & Ritchie, I. M. (1966) *Brit. J. Pharmacol. Chemother.* **28**, 367–377
Eccleston, D., Reading, H. W. & Ritchie, I. M. (1969) *J. Neurochem.* **16**, 274–276
Erwin, V. G., Tabakoff, B. & Bronaugh, R. L. (1971) *Mol. Pharmacol.* **7**, 169–176
Feldstein, A. (1971) in *The Biochemistry of Alcoholism* (Kissin, B. & Begleiter, H., eds.), vol. 1, pp. 127–159, Plenum Press, New York
Feldstein, A. & Williamson, O. (1968) *Brit. J. Pharmacol. Chemother.* **34**, 38–42
Himwich, H. E. (ed.) (1970) in *Biochemistry, Schizophrenias and Affective Illnesses*, pp. 79–122, Williams and Wilkins Co., Baltimore
Houslay, M. D. & Tipton, K. F. (1973*a*) *Biochem. J.* **135**, 173–186
Houslay, M. D. & Tipton, K. F. (1973*b*) *Biochem. J.* **135**, 735–750
Illingworth, J. A. (1972*a*) *Biochem. J.* **130**, 45P
Illingworth, J. A. (1972*b*) *FEBS Symp.* **25**, 345–359
Iversen, L. L. (1967) *The Uptake and Storage of Noradrenaline in Sympathetic Nerves*, pp. 176–181, Cambridge University Press, Cambridge
Jonason, J. & Rutledge, C. O. (1968) *Acta Physiol. Scand.* **73**, 411–417
Jouvet, M. (1969) *Science* **163**, 32–41
Kellogg, C., Vernadakis, A. & Rutledge, C. O. (1971) *J. Neurochem.* **18**, 1931–1938
Lahti, R. A. & Majchrowicz, E. (1969) *Biochem. Pharmacol.* **18**, 535–538
Maas, J. W. & Landis, D. H. (1968) *J. Pharmacol. Exp. Ther.* **163**, 147–162
Ridge, J. W. (1963) *Biochem. J.* **88**, 95–100
Rutledge, C. O. & Jonason, J. (1967) *J. Pharmacol. Exp. Ther.* **157**, 493–502
Sabelli, H. G., Giardina, W. J., Alivisatos, S. G. A., Seth, P. K. & Ungar, F. (1969) *Nature (London)* **223**, 73–74
Sandler, M. & Youdim, M. B. H. (1968) *Nature (London)* **217**, 771–772
Sandler, M., Bonham-Carter, S., Hunter, K. R. & Stern, G. M. (1973) *Nature (London)* **241**, 439–442
Smith, A. A. & Wortis, S. B. (1960) *Biochem. Pharmacol.* **3**, 333–334
Squires, R. F. (1972) *Advan. Biochem. Psychopharmacol.* **5**, 355–370
Tabakoff, B., Anderson, R. & Alivisatos, S. G. A. (1973) *Mol. Pharmacol.* **9**, 428–437
Tacker, M., Creaven, P. J. & McIsaac, W. M. (1970) *Biochem. Pharmacol.* **19**, 604–607
Taylor, K. M. & Laverty, R. (1969) *J. Neurochem.* **16**, 1367–1376
Tipton, K. F. (1968) *Eur. J. Biochem.* **5**, 316–320
Tipton, K. F. (1972) *Advan. Biochem. Psychopharmacol.* **5**, 11–24
Tipton, K. F. (1973) *Brit. Med. Bull.* **29**, 116–119
Tipton, K. F. & Spires, I. P. C. (1968) *Biochem. Pharmacol.* **17**, 2137–2141
Tipton, K. F. & Turner, A. J. (1974) *Biochem. Pharmacol.* **23**, 1906–1910
Tipton, K. F., Houslay, M. D. & Garrett, N. J. (1973) *Nature (London)* **246**, 213–214
Turner, A. J. & Tipton, K. F. (1972*a*) *Eur. J. Biochem.* **30**, 361–368
Turner, A. J. & Tipton, K. F. (1972*b*) *Biochem. J.* **130**, 765–772
Turner, A. J., Baker, K. M., Algeri, S. & Frigerio, A. (1974) in *Mass Spectrometry in Biochemistry & Medicine* (Frigerio, A. & Costagnoli, N., eds.), Raven Press, New York, in the press
Youdim, M. B. H. (1972) *Advan. Biochem. Psychopharmacol.* **5**, 67–77