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TBHQ
Ethanol
Addiction

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COMMENTARY

ALKALOID PRODUCTS IN THE METABOLISM OF ALCOHOL AND BIOGENIC AMINES

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Tetrahydroisoquinoline (TIQ) alkaloids comprise a large group of naturally occurring (plant kingdom) as well as synthetic compounds, many of which exhibit pharmacologic actions on nerves and smooth muscles. Recently, two hypotheses attempted to relate the potential biosynthesis of TIQ alkaloids from catecholamines in mammalian tissues to some of the actions of alcoholic beverages and the sequelae of alcohol intoxication. Both hypotheses invoked the ethanol metabolite, acetaldehyde, as a critical intermediate. Acetaldehyde is generated mainly in the liver where a small portion escapes metabolism and passes into the blood stream. As a result, all tissues of the body are perfused with acetaldehyde.

TIQ alkaloids

Simple TIQ alkaloids. One hypothesis [1–3] proposed that acetaldehyde condensed directly with endogenous catecholamines in tissues to form substituted 6,7-dihydroxy-TIQs (Fig. 1). The similarity in structure between the TIQs and the catecholamines opened the possibility that TIQs would interact with mechanisms that normally regulate the physiologic properties of catecholamines. For example, TIQs might be sequestered within adrenergic nerve terminals and subsequently leaked or discharged into adrenergic receptor areas, there to function as activators (agonists) or inhibitors (antagonists) of catecholamine receptors. Or, TIQs might bind competitively to enzyme systems that synthesize or limit the actions of catecholamines. The physiologic end result was envisaged as an unusual alteration in function within the affected adrenergic system. In this way, TIQ alkaloids in adrenergic systems might contribute to the development of dependence upon alcohol and or to the general pharmacologic effects of ethanol ingestion.

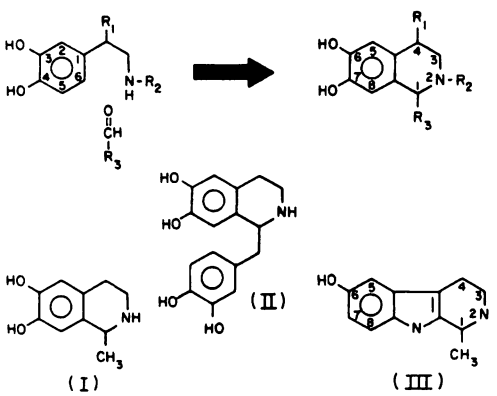

Fig. 1. Top panel: the Pictet–Spengler condensation of catecholamines with aldehydes to form substituted 1,2,3,4-tetrahydroisoquinolines (TIQs). Bottom panel: (I) salsolinol, the condensation product of dopamine with acetaldehyde; (II) tetrahydropapaveroline, the condensation product of dopamine with 3,4-dihydroxyphenylacetaldehyde; and (III) 1-methyl-6-hydroxy-1,2,3,4-tetrahydro-β-carboline, the condensation product of serotonin with acetaldehyde.

The experimental basis for the hypothesis was the demonstration that TIQs were formed within the catecholamine-rich cells of the adrenal medulla during perfusion of cow adrenal glands with solutions of acetaldehyde [1, 2]. Synthesis of TIQs was observed with a concentration of acetaldehyde as low as 1 μg ml (2×10^{-5} M), a level reported in the blood stream of persons ingesting alcoholic beverages [4].

Complex TIQs and "morphine-like" alkaloids. Another hypothesis [5, 6] proposed the biosynthesis of a special TIQ, not formed directly from acetaldehyde. Since acetaldehyde can competitively inhibit the aromatic aldehyde dehydrogenase, it was suggested that the aldehyde product of dopamine (DA), produced in brain by monoamine oxidase, would be diverted from further oxidation to an acid. This aldehyde (namely, 3,4-dihydroxyphenylacetaldehyde) can condense with DA to form the TIQ derivative tetrahydropapaveroline (THP, see Fig. 1). Davis and Walsh, the proponents of this hypothesis, were interested in the possibility that THP, formed in mammalian cells, would be transformed to complex multiring structured alkaloids, termed "morphine-like" alkaloids. The basis for this supposition was the observation that THP served as an intermediate in the synthesis of morphine in the opium poppy. The biochemical basis for physical dependence on alcohol was envisaged as formation of THP, which might have an addictive liability of its own, and which would be further transformed to addictive alkaloids of the morphine type. The molecular mechanisms for addiction to ethanol were not further specified, except for the presumption that they would be similar to morphine.

Although THP is not recognized as a product of DA metabolism in mammalian tissues under basal conditions, earlier work by Holtz *et al.* [7] had shown that THP was formed when liver mitochondria were incubated with DA. The experimental support for the Davis and Walsh hypothesis was based on similar studies with homogenates of rat brainstem [5, 6]. In this system, when [^{14}C]DA was added, 47 per cent

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of the deaminated product appeared as [^{14}C]THP. When acetaldehyde was added in concentrations of 0·5, 1·0 and 2·0 mM, the amount of [^{14}C]THP rose in increments to 58, 64 and 65 per cent respectively. During these experiments, not only THP was formed but, additionally, the acetaldehyde condensed directly with [^{14}C]DA to yield the simple TIQ, [^{14}C]salsolinol (Fig. 1). Consideration was given to the possibility that salsolinol might also play a role in mediating some of the actions of ethanol [8].

In more recent work, Davis *et al.* [9] have reported that [^{14}C]norepinephrine ([^{14}C]NE) added to rat brainstem homogenates was transformed to a substance possessing the physical properties of an hydroxylated form of THP. Product formation was enhanced by the addition of barbiturates. Additionally, the metabolism of injected [^{14}C]THP was studied in rats, and 2·5 per cent was excreted as a group of complex protoberberine alkaloids [10].

Portions of the morphine-alkaloid hypothesis have been criticized [11–13] and Davis and Walsh [14, 15] have responded. One technical point that requires clarification is that while acetaldehyde is invoked as an inhibitor of the oxidation of aromatic aldehydes, similar inhibition is obtained with antabuse (disulfiram), a drug frequently used in the treatment of alcoholism. It would seem that antabuse by itself (no alcohol) should promote formation of THP in brain.

Although the remainder of this commentary will not deal further with the hypothesis concerning "morphine-like" alkaloids and alcoholism, experiments with THP are included in some of the discussion about the properties of TIQs.

Synthesis and biosynthesis of TIQ alkaloids

Organic chemists have utilized the condensation reaction of aldehydes with phenylethylamines (Pictet–Spengler condensation) under conditions of strong acidity and high temperature to synthesize a variety of simple and complex TIQs [16]. As early as 1934, it was shown that two catecholamines, DA and epinine, condensed spontaneously with acetaldehyde at neutral pH and ambient temperature [17] and this route was proposed as a biosynthetic pathway in plants. The hydroxyl group in the 3-position (Fig. 1), but not a methoxyl group, activates the benzene ring and facilitates spontaneous ring closure of the intermediate Schiff's base at neutral pH [18].

The Pictet–Spengler condensation reactions of epinephrine (E), NE, DA and L-dopa with aldehydes, such as formaldehyde, acetaldehyde and pyridoxal phosphate, have been studied in aqueous neutral solution [2, 3, 17, 20] and in the presence of tissue homogenates [6, 8]. Inadvertent synthesis of the TIQ condensation product of dopa and acetaldehyde was reported in samples of stored [^{3}H]dopa [21]; apparently, acetaldehyde was generated from the ethanol preservative during radio-decay of the [^{3}H]dopa. TIQs are also recognized intermediates in the formaldehyde condensation method for visualizing DA, NE or E under the fluorescence microscope [22].

Condensation products are formed in adrenal chromaffin cells during perfusion of cow adrenal glands with acetaldehyde [2, 23–25]. Total conversion of endogenous E and NE to the corresponding TIQs *has* been observed after perfusion of glands with 1 mg formaldehyde/ml [3]. In perfusion studies with [^{14}C]acetaldehyde, over 95 per cent of the ^{14}C within the adrenal chromaffin granules was in the form of [^{14}C]TIQs [24].

Formation *in vivo* of small quantities of TIQs has been reported. Evidence for the formation of formaldehyde-derived TIQs in the adrenal glands of rats during methanol intoxication was obtained with fluorescence and ^{14}C-tracer methods [26, 27]. Collins and Bigdeli [28] used a gas chromatographic method to demonstrate the formation of salsolinol in the brains of rats treated with ethanol combined with other drugs. Sandler *et al.* [29] used a gas chromatograph mass spectrometer combination to observe the presence of salsolinol and THP in the urine of Parkinson patients in treatment with L-dopa, who drank a test dose of ethanol; levels of salsolinol before ethanol intoxication, as originally reported, were subsequently found to be due mainly to trace aldehyde contamination of the solvents used for extraction (M. Sandler and M. Lengyel, personal communication).

Transmitter-like properties of TIQs

Uptake. TIQ condensation products of DA or NE with formaldehyde or acetaldehyde are taken up into rat brain synaptosomes [30] and into sympathetic nerve endings in the heart, iris, pineal and salivary glands [31–33]. Uptake is blocked by traditional agents such as desmethylimipramine and cocaine [31, 32]. Additionally, TIQs inhibit uptake of catecholamines into rat brain synaptosomes and tissue slices [30, 34–36]; the inhibition by salsolinol is of the competitive type [35]. Therefore, the uptake systems for TIQs appear to be similar to those for the catecholamines. TIQs are also weak inhibitors of the uptake of serotonin into brain slices [34, 37].

Storage. TIQs formed in the adrenal gland during perfusion with acetaldehyde are stored in chromaffin granules [24, 38]. Electron microscopy has shown that 6,7-dihydroxy-TIQ is stored in the catecholamine-binding vesicles of the iris and pineal gland [33]. Fluorescence microscopic evidence indicates that the latter TIQ is taken up into vesicles, even in reserpinized animals [32]. 4,6,7-Trihydroxy-TIQ (NE condensed with formaldehyde), on the other hand, does not enter reserpinized vesicles [32].

Release of catecholamines. The addition of TIQs to rat brain synaptosomes or tissue slices labeled with [^{3}H]catecholamine results in efflux of the [^{3}H]catecholamine [30, 35, 39]. This is probably due to the displacement of catecholamines from storage sites. The releasing action of 6,7-dihydroxy-TIQ on [^{3}H]DA in rat brain slices can be distinguished from a stronger inhibitory action on the uptake and accumulation of [^{3}H]DA [39]. Release of [^{3}H]NE from sympathetic nerve terminals of the heart *in vitro* by several TIQs administered subcutaneously has been described.* There is evidence that direct injection of 6,7-dihydroxy-TIQ into the lateral ventricles of the brain results in the release of catecholamines from central nerve terminals. [40].

Release of TIQs. TIQs formed *in situ* in the adrenal medulla during perfusion of adrenal glands with ace-

* E. E. Smissman, J. R. Reid, D. A. Walsh and R. T. Borchardt, manuscript in preparation.

taldehyde are released along with catecholamines during stimulation of the glands with agents such as acetylcholine or carbamylcholine [23, 25]. The release process for TIQs is Ca^{2+} dependent and is probably identical to that for the catecholamines (viz. exocytosis). In the absence of Ca^{2+}, the efflux of catecholamines during perfusion with acetaldehyde becomes dissociated from the efflux of TIQs, which are retained within the gland [25]. Depletion of 6,7-dihydroxy-TIQ from sympathetic nerve terminals of the iris during electrical stimulation of the sympathetic trunk (i.e. the preganglionic fiber) has been observed by fluorescence microscopy [32]. In addition to release by stimulation, there is a propensity for TIQs to "leak" from the unstimulated adrenal and from decentralized sympathetic nerves [23, 32].

Receptor responses. During electrically stimulated (preganglionic stimulation of the superior cervical ganglion) release of 6,7-dihydroxy-TIQ from sympathetic nerve terminals of the eye in NE-depleted rats, the following changes indicated activation of alpha adrenergic receptors: retraction of the upper eyelid, protrusion of the eyeball and dilation of the pupil [32]. Such responses are typical for the stimulated release of the natural transmitter (NE) in normal rats. Therefore, 6,7-dihydroxy-TIQ appears to exhibit agonist actions in this system. However, 6,7-dihydroxy-TIQ was relatively ineffective in altering blood pressure or heart rate in rats [41]. Some central and peripheral actions of a series of hydroxylated and *O*-methylated TIQs have been described by Hjort *et al.* [42, 43]. Incubation of the isolated vas deferens with 6×10^{-5} M concentrations of 6,7-dihydroxy-TIQ or S(−)-salsolinol results in modifications in the end organ response to stimulation of the sympathetic trunk; both the "twitch" (rapid contraction and relaxation) and the second phase (sustained contraction) were altered [44].

Miller *et al.* [45] have studied the activation of adenyl cyclase in the striatum by 6,7-dihydroxy-TIQ; in their system, salsolinol appeared inactive. Sheppard and Burghardt [46] reported blockade of striatal adenyl cyclase by the R(+)- and S(−)-stereoisomers of salsolinol and THP. There is extensive literature on beta-agonist action by THP and other 1-benzyl-substituted TIQs on, for example, the guinea pig trachea [47] and rat adipose tissue [48]. The S(−) conformation appears to be favored in these systems [36, 47–49]. Injection of 6,7-dihydroxy-TIQ or salsolinol into the brain evokes changes in body temperature [40, 50], which may be due largely to release of endogenous catecholamines [40].

Other properties of TIQs

Metabolism of TIQs. *O*-methylation of TIQs by catechol-*O*-methyl-transferase has been studied in tissue homogenates and with purified enzyme preparations [51–54.*]. *O*-methylation of both DA-derived TIQs [52–54.*] and NE-derived TIQs [51] was reported. Creveling *et al.* [52] reported that both the 6- and 7-positions of two DA-derived TIQs were methylated. Salsolinol and THP were competitive inhibitors of the *O*-methylation of DA [53]. There is no evidence that TIQs are metabolized by monoamine oxidase.

Inhibition of monoamine oxidase. Salsolinol and THP [53, 55] competitively inhibit the deamination of serotonin in rat brain and liver homogenates; K_i values in the range of 0·14 to 0·35 mM were reported. 6,7-Dihydroxy-TIQ, taken up into nerves of the reserpinized rat, markedly improved the accumulation of [^{3}H]NE and diminished the levels of ^{3}H-deaminated metabolites in the sympathetic nerve plexus of the heart *in vivo* [56]; such results are typical for intraneuronal inhibition of monoamine oxidase.

Stereoisomers. Substitution in the 1-position of the TIQ ring provides a center of asymmetry. Thus, two stereoisomeric forms are possible on condensation of catecholamines with acetaldehyde. Teitel and Brossi [57] have discussed the potential importance of the absolute configuration in the 1-position. If the condensation reactions in tissues were to be catalyzed by enzymes, preferential formation of one of the stereoisomers would not be unexpected. Recent studies have demonstrated differential pharmacologic properties for the R- and S-stereoisomers of several TIQs, including salsolinol and THP [36, 46, 48, 49]. When a center of asymmetry pre-exists in the parent catecholamine (e.g. L-norepinephrine or L-dopa), *cis*-or *trans*-isomers can be formed preferentially, even in non-enzymatic reactions [57, 58]. For example, acetaldehyde condenses with L-dopa to form the *cis*-product preferentially under acidic conditions, but the yield of *trans*-product can be increased from 5 to 25 per cent by carrying out the cyclization reaction in phosphate buffer at pH 7·0 [57].

Critical areas for further work

Measurement of biosynthesized TIQ alkaloids in tissues. It has been difficult to document the levels of TIQ alkaloids formed in the brains of experimental animals during exposure to alcohol. The amounts present are relatively small and there are difficulties related to the separation of TIQs from catecholamines. The single success to date has been the experiments of Collins and Bigdeli [28]; these investigators showed that TIQ levels in brain were in the range of 1 per cent of the endogenous catecholamines in animals receiving ethanol along with pargyline (a monoamine oxidase inhibitor) and pyrogallol (a catechol-*O*-methyltransferase inhibitor). The observed TIQ levels were close to the lower limit of detectability with the available methodology (a gas chromatographic–electron capture method). The importance of the work lay in its demonstration that TIQs were, in fact, formed at the proposed sites *in vivo*. What is needed now is further development of methods capable of routinely measuring TIQs in tissues, particularly when metabolic inhibitors are not used. This would provide the means to evaluate the relationships between quantities of TIQs in local brain areas and behavioral events (e.g. drinking behavior, withdrawal signs) or pharmacodynamic events (e.g. catecholamine turnover, receptor sensitivity).

A relatively simple radioenzymatic method would be a most welcome development; the method must be capable of distinguishing the TIQs from endogenous catecholamines and their metabolites. An immunologic radioassay could provide the required sensitivity and specificity. Gas chromatography mass spectrometry represents a potentially valuable, but expensive approach. There has been limited success with

a qualitative method based on the conversion of non-fluorescent TIQs to fluorescent dihydroisoquinolines (by heat in the absence of formaldehyde) for direct microscopic examination of the adrenal medulla [26]; but the method could not be applied in the study of peripheral adrenergic nerves (unpublished observation).

TIQ metabolites. In a study with [^{3}H]6,7-dihydroxy-TIQ, the *O*-methylated form(s) appeared to be retained in sympathetically innervated tissues, such as the heart and salivary glands, in amounts greater than or equal to the unmetabolized TIQ [31]. With the exception of the early studies of Hjort *et al.* [42, 43] little or no work has been directed toward the pharmacologic properties of *O*-methylated TIQs, now recognized as metabolites. It is not known whether or not *O*-methylated forms can exert neurotransmitter or other actions in adrenergic systems.

Because there is an inherent difficulty in evaluating the significance of unmetabolized TIQs excreted in the urine, metabolite studies would be most important in investigations concerned with human subjects. Do TIQ products found in urine arise from the condensation of excreted aldehyde and excreted catecholamines during storage in the bladder? Since 3-*O*-methylated catecholamines appear not to undergo spontaneous ring-closure reactions with aldehydes, the presence of the corresponding 6-*O*-methylated TIQs in urine could mean that such TIQ metabolites were not formed in the bladder. Are excreted TIQs formed in liver (a trivial site) or at adrenergic loci? This question will be more difficult to answer. Nonetheless, metabolite studies may represent the best approach for human studies.

How much TIQ is required to alter adrenergic function? There is no experimental answer to this question at the current time, mainly because methodology is not available to routinely measure TIQ levels in adrenergically innervated areas. However, some appreciation of the potential effects of TIQs present in small amounts (e.g. 1 per cent or less of the corresponding catecholamines) can be gleaned from the following theoretical consideration. It has been estimated from fluorescence microscopic studies that the absolute concentrations of catecholamines in peripheral sympathetic nerves are in the range of 6×10^{-3} M in the rat [59] and 6×10^{-2} M in the mouse [60]; Jonsson [61] estimates a concentration as high as 0·5 M within the catecholamine storage vesicles. These are not outrageous estimates, as the levels of catecholamines in the adrenal medulla, measured by standard chemical techniques, are in the range of 8×10^{-2} M [62]. Condensation of 1 per cent of endogenous catecholamine with acetaldehyde in nerve terminal areas could result in endogenous TIQ concentrations in the range of 6×10^{-5} M to 5×10^{-3} M. Expressed as μg/g of tissue, TIQs might appear to be present in "trace" amounts. But, localized in nerve terminals, these concentrations could suffice to exert pharmacologic actions. When TIQs are pharmacologically inert or when they function as weak agonists, as do many of the known "false transmitters," no change in adrenergic function would be expected when the amounts of TIQ are small relative to the endogenous catecholamines. However, when there is an unusually high affinity for a receptor or enzyme and/or when TIQs possess a property not directly competitive with the catecholamines, physiologic sequelae would be anticipated.

A provocative theoretic aspect to be considered for TIQ function is their apparent tendency to "leak" from cells [23, 32]; this phenomenon could result in a relative concentrating effect for TIQ over catecholamine in the synaptic cleft. Additionally, transient elevations of TIQs relative to catecholamines at receptor sites could result from the relatively weaker affinity of TIQs for neuronal uptake mechanisms [34] as well as their failure to be metabolized by monoamine oxidase.

Availability of TIQs. Collins and Kernozek [63] have successfully synthesized 4,6,7-trihydroxy-TIQ, the condensation product of NE with formaldehyde. However, pure samples of acetaldehyde-derived TIQ derivatives hydroxylated in the 4-position (corresponding to the β-hydroxyl group of NE and E) have never been prepared. Organic synthesis of these compounds, making them available for biologic evaluation, is urgently required. The direct condensation of NE or E with acetaldehyde in aqueous solution can provide these TIQs, but contaminated with several products of uncertain identity [2, 3]; these contaminants may represent stereoisomers [57, 58] or ring-closure to the 2-position of the catecholamine ring (ortho to the activating hydroxyl group, see Fig. 1) [16, 58, 64]. Stereoisomers of TIQs derived from DA and L-dopa have been recently synthesized [57].

Pharmacological and behavioral studies. Further work is needed to evaluate the actions of TIQs on various isolated adrenergic systems, as well as on drinking behavior and other behavioral events in intact animals. Some recent studies offer promising new leads. M. Hamilton and M. Hirst (personal communication) have observed that salsolinol antagonizes the contractions induced by serotonin in rat stomach and uterus preparations; of particular interest, antagonism of responses to the pituitary hormones, oxytocin and vasopressin, was observed in isolated tissue preparations. Blum *et al.* [65] reported that intracerebral injections of 6,7-dihydroxy-TIQ increased "withdrawal" scores (hyper-excitability on handling) in mice previously exposed to ethanol. Amit and associates have observed changes in free-choice alcohol consumption in animals receiving central infusions of TIQs (personal communication; cf. Ref. 66).

Ross *et al.* [67, 68] have provided an interesting observation that links the effects of salsolinol, ethanol and morphine on brain calcium levels. The depletion of brain calcium levels by each of these agents is antagonized by naloxone, a specific morphine antagonist. Control studies with other calcium depletors (phenobarbital, reserpine) showed unresponsiveness to naloxone; similarly, naloxone did not affect *t*-butyl alcohol or isopropanol, neither of which can be transformed *in vivo* to aldehydes (TIQ precursors). Ross suggests that alcohol (via formation of a TIQ) and morphine interact with a common pool of brain calcium and, therefore, share certain common loci of action for their effects on central neurons.

Related areas of interest

Beta-carbolines. The condensation reactions of tryptamines with aldehydes yields a class of 1,2,3,4-

tetrahydro-β-carbolines. This reaction is analogous to the formation of TIQs from catecholamines. The reaction *in vitro* of 5-methoxytryptamine with acetaldehyde has been studied by McIsaac [69]. Urinary excretion of tetrahydro-β-carbolines by rats receiving ethanol has been reported [69, 70]. Tetrahydro-β-carbolines are of interest because they are structurally related to the class of harmala alkaloids (e.g. harmaline) which are hallucinogenic and are strong inhibitors of monoamine oxidase. The tetrahydro-β-carboline condensation product of serotonin with acetaldehyde (Fig. 1) may play a physiologic role at serotonergic sites, similar to the one proposed for TIQs at adrenergic sites.

Endogenous alkaloids. Laduron and coworkers have pioneered the use of 5-methyltetrahydrofolate as a cofactor in the methylation of biogenic amines; these [71–72] and other investigators [73–75] found, however, that the reaction products were not the expected *N*-methylated biogenic amines. Instead, TIQs [71–73] and tetrahydro-β-carbolines [71, 74, 75] were formed. The reaction in tissue extracts is promoted by an enzyme which catalyzes the formation of a reactive 1-carbon fragment. The intermediate appears to be formaldehyde [71–73]. One reason for interest in this research area is the possible synthesis of aberrant alkaloid metabolites of serotonin or catecholamines in schizophrenia [73, 74]. However, if the reaction pathway with 5-methyltetrahydrofolate is operable in intact cells under basal conditions, synthesis of alkaloids may take place normally and these alkaloids may subserve a normal function, perhaps as neurotransmitters in, as yet unidentified neuronal tracts.

TIQs and Parkinsonism. Although the formation of TIQs such as salsolinol or THP would be considered to be an unusual cellular event, there is a special circumstance in which the mammalian system may be predisposed to their formation. In the treatment of patients with Parkinson's disease, unusually large amounts of the amino acid, L-dopa, are used; as much as 7·0 g or more are given to patients on a continuous day-to-day basis. These circumstances are favorable for the formation of TIQs via the condensation of either DA or L-dopa with endogenous aldehydes (e.g. the aldehyde evolved when monoamine oxidase acts on DA). Sourkes [76] has suggested that THP and other complex alkaloids may be responsible for some of the actions of L-dopa. A recent report [77] suggested the presence of THP in the brains of rats treated with large amounts of L-dopa. The urinary excretion of THP in Parkinson patients treated with L-dopa (in the absence of ethanol) has been described [29]. Inhibition of the DA-sensitive adenylate cyclase in the striatum of rat brain by salsolinol or THP has been reported [46]. These latter observations may indicate that THP or other TIQs formed *in vivo* can be responsible, in part, for the "on-off" effect during L-dopa therapy or for the failure of some subjects to respond favorably to L-dopa.

Concluding remarks

The supposition that TIQs would be recognized in adrenergic systems as analogues of catecholamines has to some extent been borne out. TIQs possess properties of false or surrogate transmitters in some adrenergic systems. In others, they act as inhibitors of physiologic mechanisms that regulate the actions of catecholamines. These results are supportive of the idea, but do not establish that TIQs are involved in bodily responses to alcohol.

Although present in relatively small amounts, TIQs can achieve a precision of action by their discharge from nerve terminals directly into adrenergic receptor areas. The capacity of TIQs to be taken up and stored in nerve endings and their failure to serve as substrates for monoamine oxidase provide a way to conceive how a chemical residuum of alcohol can persist into post-intoxication states.

TIQs may conceivably play a role in modulating either the pleasurable or unpleasant aspects of exposure to alcoholic beverages. The higher blood levels of acetaldehyde that occur in alcoholic subjects as compared to normal subjects [78] may act as a spur to TIQ synthesis in the alcoholic group. The variety of bodily changes seen during social drinking or on chronic exposure to alcohol range from sedation and loosening of social constraints during intoxication, to psychomotor agitation and "hangover" as immediate after-effects, to tremulousness, hallucinosis and seizure after heavy or long-term drinking. The following questions remain to be answered. Are any of these changes dependent on the presence of TIQs in adrenergic systems? Are some actions of TIQs masked during alcohol intoxication, but made more evident as the general sedative or depressant action of alcohol wears off? Can an understanding of the pharmacology of TIQs lead to an understanding of the addictive aspect of alcoholism?

REFERENCES

1. M. A. Collins and G. Cohen. *One Hundred Fifty-sixth Am. Chem. Soc. natn. Meet.*, Div. Biol. Chem. (abstr.) 274 (1968).
2. G. Cohen and M. A. Collins. *Science, N.Y.* **167**, 1749 (1970).
3. G. Cohen. in *Advances in Mental Science III. Biological Aspects of Alcohol* (Eds. M. K. Roach, W. M. McIsaac and P. J. Creaven), pp. 267–84. University of Texas Press, Austin (1971).
4. G. Cohen. *Biochem. Pharmac.* **20**, 1757 (1971).
5. V. E. Davis and M. J. Walsh. *Science, N.Y.* **167**, 1005 (1970).
6. V. E. Davis, M. J. Walsh and Y. Yamanaka. *J. Pharmac. exp. Ther.* **174**, 401 (1970).
7. P. Holtz, K. Stock and E. Westermann. *Nature, Lond.* **203**, 656 (1964).
8. Y. Yamanaka, M. J. Walsh and V. E. Davis. *Nature, Lond.* **227**, 1143 (1970).
9. V. E. Davis, J. L. Cashaw, B. R. McLaughlin and T. A. Hamlin. *Biochem. Pharmac.* **23**, 1877 (1974).
10. V. E. Davis, J. L. Cashaw and K. D. McMurtrey, in *Advances in Experimental Biology and Medicine* (Ed. M. M. Gross). Plenum Press, in press.
11. P. V. Halushka and P. C. Hoffmann. *Science, N.Y.* **169**, 1104 (1970).
12. M. H. Seevers. *Science, N.Y.* **170**, 1113 (1970).
13. A. Goldstein and B. A. Judson. *Science, N.Y.* **172**, 290 (1971).
14. V. E. Davis and M. J. Walsh. *Science, N.Y.* **169**, 1105 (1970).
15. V. E. Davis and M. J. Walsh. *Science, N.Y.* **170**, 1114 (1970).

16. W. Whaley and T. R. Govindachari, *Org. React.* **6**, 151 (1951).
17. C. Schöpf and H. Bayerle, *Ann. Chem.* **513**, 190 (1934).
18. N. Zenker, *J. med. Chem.* **9**, 826 (1966).
19. H. F. Schott and W. G. Clark, *J. biol. Chem.* **196**, 449 (1952).
20. J. H. Robbins, *Clin. Res.* **16**, 350 (1968).
21. B. Waldeck, *J. Pharm. Pharmac.* **25**, 502 (1973).
22. H. Corrodi and G. Jonsson, *J. Histochem. Cytochem.* **15**, 65 (1967).
23. R. S. Greenberg and G. Cohen, *J. Pharmac. exp. Ther.* **184**, 119 (1973).
24. F. H. Schneider, *J. Pharm. Pharmac.* **26**, 325 (1974).
25. R. G. Rahwan, P. J. O'Neill and D. Miller, *Life Sci.* **14**, 1927 (1974).
26. G. Cohen and R. Barrett, *Fedn Proc.* **28**, 288 (1969).
27. M. A. Collins and G. Cohen, *Fedn Proc.* **29**, 608 (1970).
28. M. A. Collins and M. G. Bigdeli, *Life Sci.* **16**, 585 (1975).
29. M. Sandler, S. B. Carter, K. R. Hunter and G. M. Stern, *Nature, Lond.* **241**, 439 (1973).
30. R. Heikkila, G. Cohen and D. Dembiec, *J. Pharmac. exp. Ther.* **179**, 250 (1971).
31. S. Locke, G. Cohen and D. Dembiec, *J. Pharmac. exp. Ther.* **187**, 56 (1973).
32. C. Mytilineou, G. Cohen and R. Barrett, *Eur. J. Pharmac.* **25**, 390 (1974).
33. V. M. Tennyson, G. Cohen, C. Mytilineou and R. Heikkila, *Brain Res.* **51**, 161 (1973).
34. L. Tuomisto and J. Tuomisto, *Naunyn-Schmiedebergs Arch. exp. Path. Pharmak.* **279**, 371 (1973).
35. H. S. Alpers, B. R. McLaughlin, W. M. Nix and V. E. Davis, *Biochem. Pharmac.*, **24**, 1391 (1975).
36. G. Cohen, R. E. Heikkila, D. Dembiec, D. Sang, S. Teitel and A. Brossi, *Eur. J. Pharmac.* **29**, 292 (1974).
37. R. E. Heikkila and G. Cohen, *Res. Commun. chem. Path. Pharmac.* **7**, 539 (1974).
38. R. S. Greenberg and G. Cohen, *Eur. J. Pharmac.* **18**, 291 (1972).
39. R. E. Heikkila, D. Dembiec and G. Cohen, in *The Role of Acetaldehyde in the Actions of Ethanol* (Eds. O. Forsander, K. Lindros and D. Sinclair), in press.
40. H. E. Brezenoff and G. Cohen, *Neuropharmacology* **12**, 1033 (1973).
41. L. L. Simpson, *J. Pharmac. exp. Ther.* **192**, 365 (1975).
42. A. M. Hjort, E. J. deBeer and D. W. Fassett, *J. Pharmac. exp. Ther.* **62**, 165 (1938).
43. D. W. Fassett and A. M. Hjort, *J. Pharmac. exp. Ther.* **63**, 253 (1938).
44. J. Baird-Lambert and G. Cohen, *J. Pharm. Pharmac.*, in press.
45. R. Miller, A. Horn, L. Iversen and R. Pinder, *Nature, Lond.* **250**, 238 (1974).
46. H. Sheppard and C. R. Burghardt, *Res. commun. chem. Path. Pharmac.* **8**, 527 (1971).
47. Y. Iwasawa and A. Kiyomoto, *Jap. J. Pharmac.* **17**, 143 (1967).
48. R. F. Shonk, D. D. Miller and D. R. Feller, *Biochem. Pharmac.* **20**, 3403 (1971).
49. O. S. Lee, J. A. Mears, D. D. Miller and D. R. Feller, *Eur. J. Pharmac.* **28**, 225 (1974).
50. M. G. Hamilton and M. Hirst, *Pharmacologist* **16**, 279 (1974).
51. J. A. Rubinstein and M. A. Collins, *Biochem. Pharmac.* **22**, 2928 (1973).
52. C. R. Creveling, N. Morris, H. Shimizu, H. H. Ong and J. Daly, *Molec. Pharmac.* **8**, 398 (1972).
53. A. C. Collins, J. L. Cashaw and V. E. Davis, *Biochem. Pharmac.* **22**, 2337 (1973).
54. B. T. Ho, P. M. Gardner, L. F. Englert and K. E. Walker, *J. pharm. Sci.* **63**, 1261 (1974).
55. Y. Yamanaka, *Jap. J. Pharmac.* **21**, 833 (1971).
56. G. Cohen and S. Katz, *J. Neurochem.*, in press.
57. S. Teitel and A. Brossi, *Lloydia* **37**, 196 (1974).
58. J. P. Fourneau, C. Gaignault, R. Jacquier, O. Stoven and M. Davy, *Chim. Ther.* **6**, 67 (1969).
59. A. Dahlstrom, J. Haggendal and T. Hokfelt, *Acta physiol. scand.* **67**, 289 (1966).
60. G. Jonsson and C. Sachs, *Eur. J. Pharmac.* **16**, 52 (1971).
61. G. Jonsson, *Prog. Histochem. Cytochem.* **2**, 299 (1971).
62. U. S. von Euler and U. Hamberg, *Nature, Lond.* **163**, 642 (1949).
63. M. A. Collins and F. J. Kernozek, *J. heterocyclic Chem.* **9**, 1437 (1972).
64. G. S. King, B. L. Goodwin and M. Sandler, *J. Pharm. Pharmac.* **26**, 476 (1974).
65. K. Blum, J. D. Eubanks, J. F. Wallace, H. Schwertner and W. W. Morgan, *Ann. N.Y. Acad. Sci.*, in press.
66. Z. Amit and M. H. Stern, in *Biological Aspects of Alcoholism* (Eds. O. Forsander and E. K. Eriksson), pp. 225–31. Finnish Foundation for Alcohol Studies, Helsinki (1972).
67. D. H. Ross, M. A. Medina and H. L. Cardenas, *Science, N.Y.* **186**, 63 (1974).
68. D. H. Ross, *Ann. N.Y. Acad. Sci.*, in press.
69. W. M. McIsaac, *Biochim. biophys. Acta* **52**, 607 (1961).
70. S. E. Saheb and R. M. Dajani, *Comp. gen. Pharmac.* **4**, 225 (1973).
71. P. Laduron and J. Leysen, *Biochem. Pharmac.* **24**, 929 (1975).
72. J. Leysen and P. Laduron, *Fedn Eur. Biochem Soc. Lett.* **47**, 299 (1974).
73. E. Meller, H. Rosengarten, A. J. Friedhoff, R. D. Stebbins and R. Silber, *Science, N.Y.* **187**, 171 (1975).
74. R. J. Wyatt, E. Erdelyi, J. R. DoAmaral, G. R. Elliott, J. Renson and J. D. Barchas, *Science, N.Y.* **187**, 853 (1975).
75. L. R. Mandel, A. Rosegay, R. W. Walker, W. J. A. Vanden Heuvel and J. Rokach, *Science, N.Y.* **186**, 741 (1974).
76. T. L. Sourkes, *Nature, Lond.* **229**, 413 (1971).
77. A. T. Turner, K. M. Baker, S. Algeri, A. Frigerio and S. Garrattini, *Life Sci.* **14**, 224 (1974).
78. M. A. Korsten, S. Matsuzaki, L. Feinman and C. S. Lieber, *New Engl. J. Med.* **292**, 386 (1975).