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BIOGENIC AMINE-ALDEHYDE CONDENSATION PRODUCTS: TETRAHYDROISOQUINOLINES AND TRYPTOLINES (β-CARBOLINES)

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INTRODUCTION

Tetrahydroisoquinolines (TIQs) are condensation products between catecholamines and aldehydes, and tryptolines (β-carbolines) are products of the reaction between indoleamines and aldehydes. In this review we confine ourselves primarily to those compounds that conceivably could be produced in mammals. Other compounds are discussed only when they help provide a better understanding of the formation or actions of these compounds. In a review such as this, with space restrictions, we make no pretense at an encyclopedic coverage of the subject. Undoubtedly some papers will not be mentioned, but the aim is to put the field in perspective in the first extensive review of this subject in the *Annual Reviews.* The major focus of interest in these compounds recently has been in the area of alcohol actions. However, they may be important in a number of other areas as well, such as *l*-dopa therapy for parkinsonism (1, 2) and in phenylketonuria (3). A number of reviews have appeared recently which contain diverse points of view (4–7).

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FORMATION

Initial work on TIQ compounds arose because of their widespread presence in plants (8). The first synthesis of tetrahydropapaveroline (THP) by Pyman (9) was by reduction and demethylation of papaverine and is still the preferred synthetic route. Later researchers (10, 11) reported that catecholamines condensed with aldehydes to form TIQ alkaloids by the Pictet-Spengler condensation. These early researchers demonstrated that dopamine (DA) and its N-methyl congener, epinine, would condense with aldehydes under physiological conditions to form the corresponding TIQ alkaloids. In plants, reaction of the ketoacid with the amine and subsequent decarboxylation is found (12). In 1964, Holtz (13) et al demonstrated the formation of THP following incubation of dopamine with monoamine oxidase. Since then, many investigators have reported the nonenzymatic formation of TIQ alkaloids by condensation of catecholamines, under conditions of physiologic pH and temperature conditions, with various aldehydes, including formaldehyde (14), acetaldehyde (16), 3,4-dihydroxyphenylacetaldehyde (17), and pyridoxal phosphate (18).

The second order rate constant for the formation of salsolinol is 0.38 liters/mole sec at pH 7.4 and 37°C (19). Other possible routes to the same end product would be condensation of *l*-dopa with acetaldehyde (0.16 liters/mole sec) followed by decarboxylation. In either case the product will be racemic. Formaldehyde reacts much faster than acetaldehyde (5.3 liters/mole sec) to produce TIQ. In an in vitro system, Weiner (20) is able to find significant amounts of dihydroxyphenylacetaldehyde and dopamine after incubation of dopamine within liver slices. While THP is also found, it indicates that the reaction to form THP from dopamine and its aldehyde is slower than production of the aldehyde in this system.

Epinephrine (E) and norepinephrine (NE) will also condense with aldehydes to form 1,2,3,4-tetrahydroisoquinoline alkaloids. These alkaloids form readily when 5 to 10 mM of catecholamine is mixed under physiological conditions with 2 M concentrations of acetaldehyde or formaldehyde (15). At pH 6, the condensation reaction was complete within 1 to 2 min, whereas the reaction with acetaldehyde required 40 to 50 min. These investigators reported that the yield of the 1-methyl-4,6,7-trihydroxy-TIQ from norepinephrine was 70–80% and the yield of 1,2-dimethyl-4,6,7-trihydroxy-TIQ from epinephrine was 50% when reacted with acetaldehyde (see Figure 1).

While these in vitro studies on the formation of TIQ compounds are extremely useful, the concentrations of aldehydes in vivo are much lower than those used in most of these studies. Concentrations of biogenic amines are very high in synaptic vesicles, but not elsewhere in the body. Also for

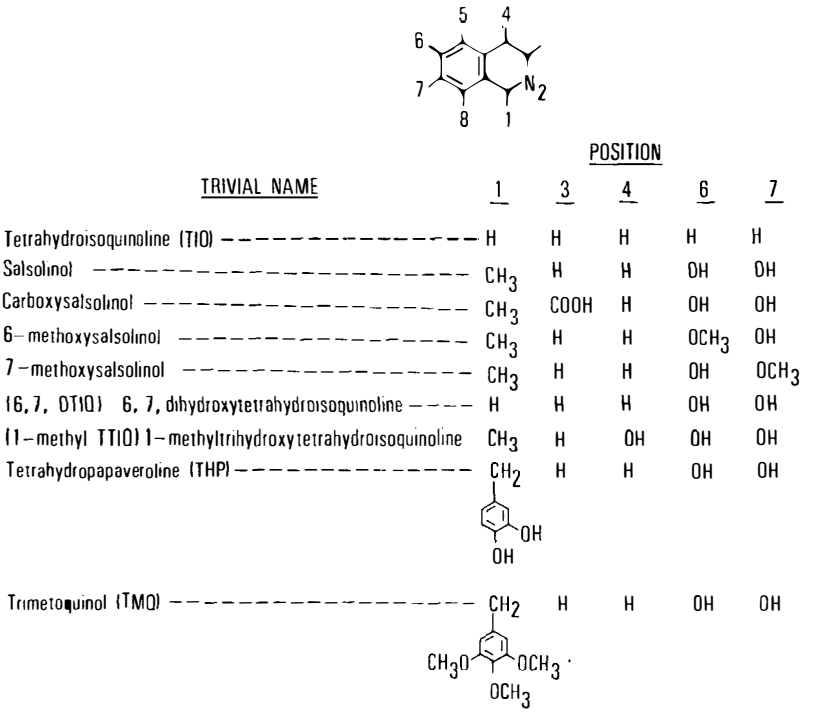

Figure 1 Structures of some common tetrahydroisoquinolines.

these reasons, second-order rate constants in vivo for reactions between amines and aldehydes are somewhat more useful than pseudo first-order rate constants where the aldehyde concentrations are unreasonably high.

METHODS OF ANALYSIS

Tetrahydroisoquinolines

Techniques for separation, detection, and quantitation of TIQ compounds are vital for any study of the function of these substances. A wide variety of techniques have been used. Thin layer chromatography (TLC) after solvent extraction has been used to separate (^{14}C) DA from (^{14}DA) metabolites and (^{14}C) THP. Detection was accomplished with iodine spray and radioautography (21). No significant amount of THP could be detected in tissues or blood from guinea pigs given (^{14}C) DA. Early work by Greenberg & Cohen (22) and Cohen (23) used TLC to demonstrate the presence of TIQs derived from NE and E from adrenal glands perfused with 23 μM acetaldehyde.

In their original studies on THP and its metabolites, Davis and her colleagues used ion exchange column chromatography for separation of labeled material (14). Walsh et al (24) and Yamanaka et al (25) demonstrated that THP was formed when DA was incubated with rat brain stem or liver homogenates in vitro and that its formation was dependent upon the concentration of dopamine added to the homogenates and upon the amount of NAD available for further oxidation of 3,4-dihydroxyphenylacetaldehyde. Other workers have employed a combination paper chromatography and paper electrophoresis to separate NE, DA, their aldehyde, alcohol, and acid metabolites as well as salsolinol and THP. Detection was accomplished by spraying with Folin's reagent (26).

A new radioenzymatic assay for salsolinol (27) involves separation of salsolinol by TLC and then reaction with (^{14}C) S-adenosylmethionine (SAM) and catechol-O-methyl transferase (COMT).

More recently the problem has shifted to one of detection of the unlabeled compounds in tissues from control and ethanol-treated animals. This is a much more difficult task and several methods have been employed. High performance liquid chromatography (HPLC) with either ultraviolet (UV) (28) or electrochemical detection (19, 29, 30) has proved to be very useful. The UV detection method is essential if no phenolic groups are present, but the electrochemical detection method offers high sensitivity (detection in the pg range) and some selectivity by adjustment of the current supplied to the carbon electrode.

Gas chromatography separation (GC) with detection by electron capture (EC) (31) or mass spectrometry (MS) (32) are sensitive techniques but do require derivatization of the compounds and entail some loss of sample. Recovery of standard (^{14}C)-labeled amines added to brain is of the order of 40–80% (31). By administering pyrogallol to inhibit O-methylation and aldehyde dehydrogenase, followed by ethanol, Collins & Bigdeli (33) were able to find 17 ng of salsolinol per gram of midbrain, caudate, and brain stem. Additional administration of pargyline, a monoamine oxidase and aldehyde dehydrogenase inhibitor, raised the amount found to 118 ng/g tissue. O'Neill & Rahwan (34), on the other hand, failed to find salsolinol in whole brain of mice treated with ethanol alone. Their limit of detection was 8 ng/g brain. Turner et al (35) reported the in vivo formation of THP in brain after treatment of rats with *l*-dopa and a dopa decarboxylase inhibitor, or with *l*-dopa, the decarboxylase inhibitor and ethanol but not when the animals were given ethanol alone (10% w/v in drinking water). Their limit of detection was 2 ng/g brain. They utilized gas chromatographic-mass spectrophotometric techniques and obtained the complete mass spectrum of THP and its trifluoro-acetylated derivatives. Similar techniques have been utilized by Sandler et al (36) to demonstrate the presence of

salsolinol and THP in the urine of parkinsonian patients receiving both *l*-dopa therapy and alcohol.

The use of GC/MS techniques has the advantage of high sensitivity in the selective ion monitoring mode and of product identification in other modes. Ideally, standards are the deuterium-labeled compounds themselves which allow for correction for recovery with each sample. Cashaw and Davis and her co-workers are active in this area (32, 37). Durden et al (38) have suggested that the 1-dimethylaminonapthalene-5-sulfonyl (dansyl) derivatives might be useful. The minimum detection level is 20 pg of free base with this technique.

As pointed out by Cashaw et al (32, 37) and other workers (35), the failure to detect THP in brain may be a result of its rapid conversion to further products such as tetrahydroprotoberberines, aporphines, and their O-methylated derivatives. Recently it has been shown that tetrahydropapaveroline can be converted metabolically to three major tetrahydroberberine alkaloids identified by gas chromatography, radio assay, and mass spectral analysis (39). The major products were 2,3,10,11-tetrahydroxyberberine, 2,3,9,10-tetrahydroxyberberine and a 2- or 3-monomethylated derivative of tetrahydroxyberberine. The 2,3,10,11-tetrahydroxyisomer was the main tetrahydroprotoberberine metabolite found, both in vivo and in vitro. Davis and co-workers (39) have identified tetrahydroberberine alkaloids as urinary excretion products in rats after administration of THP and in parkinsonian patients receiving *l*-dopa therapy. These experiments indicate that the metabolic pathways are present in mammalian tissues not only for the formation of tetrahydroisoquinoline alkaloids, but also for the formation of more complex alkaloid systems.

More recently Collins (40) has found both salsolinol and O-methylsalsolinol in greater quantities in the urine of alcoholics immediately after admission for detoxification than in nonalcoholic controls. The alcoholics had a mean of 111 μg/24 hr of O-methylsalsolinol and 29 μg/24 hr of salsolinol in the alcoholics and the controls 21 μg/24 hr of O-methylsalsolinol and 1.1 μg/24 hr of salsolinol in controls.

Cohen's group (41) have presented evidence recently for the formation of 6 and 7 O-methylsalsolinol, and Hamilton et al (42) reports finding O-methylsalsolinol in the brain of alcohol treated rats. All of these studies are important since the O-methylated dopamine is unlikely to condense with acetaldehyde at any appreciable rate during the workup necessary to analyze the various samples. Its presence indicates that salsolinol was formed and subsequently O-methylated (43). The physiological activity of O-methylated TIQs has largely been ignored but in view of the rapid formation of such metabolites inclusion in future studies would seem warranted.

Highly sensitive and specific assays are needed to detect the amounts of the TIQ compounds and their metabolites that are pharmacologically active in the brain, as discussed in later sections.

β-Carbolines

In addition to formation of the TIQ alkaloids, the condensations of indoleamines with carbonyl compounds, i.e. aldehydes, have been shown to form tetrahydro-β-carboline alkaloids. The formation of β-carbolines in animals has a relatively long history beginning with the demonstration by McIssac et al (44) that administration of ethanol, serotonin, and a monoamine oxidase inhibitor (MAOI) to rats resulted in the excretion of the β-carboline,6-hydroxyl-1-methyltryptoline. The development of methods for detection of these compounds follows much the same pattern as for the TIQs. In early work, the methods were based on the use of labeled precursors and separation of metabolites by thin layer chromatography. The lack of rigorous product identification plagued some of this work and probably resulted in misidentification of some indoleamine compound as *N*-or O-methylated derivatives rather than as condensation products. Miller et al (45) demonstrated that incubation of *N*-methylserotonin with erythrocyte hemolyzate and (^{14}C) *S*-adenosylmethionine led to a condensation product of (^{14}C) formaldehyde and *N*-methylserotonin. Many papers appeared nearly simultaneously, all of which led to the conclusion that 5-methyltetrahydrofolic acid (5-MTHF) could also serve as a donor of formaldehyde. Hsu & Mandell (46) demonstrated the conversion of tryptamine to 1,2,3,4-tetrahydro-β-carboline in the presence of 5-methyltetrahydrofolic acid. Again TLC was used for separation, and mass spectrometry was employed for identification. Simultaneously, Wouters-Leysen & Laduron (47) demonstrated that (^{14}C) 5-methyltetrahydrofolic acid gave rise to (^{14}C) formaldehyde, and Wyatt et al (48) showed that an enzyme from human brain could give rise to a β-carboline in the presence of tryptamine and 5-methyltetrahydrofolic acid. Meller et al (49) found similar results with catecholamines and Mandel et al (50) with tryptamines. Barchas et al (51) and Rommelspacher et al (52) demonstrated that the condensation of tetrahydro-β-carboline takes place readily if serotonin is incubated with 5-methyltetrahydrofolic acid. The reaction required the cytosolic fraction from rat brain as an enzymatic source. Tetrahydro-β-carbolines were formed when tryptamine or serotonin was incubated with 5-methyltetrahydrofolic acid in the presence of an enzymatic source from rat or chick tissues or human platelets. Further, these investigators showed that formaldehyde generated by the 5-methyltetrahydrofolate in the tissue extracts was essential for completing the condensation with serotonin to form tetrahydro-β-carboline. The enzyme responsible for release of formaldehyde from 5-methyltetrahydrofolate was identified as N^5,N^{10}-methylenetetrahydrofolate reductase (53).

More recently a novel technique for demonstration of amine-aldehyde condensation products in brain has been developed. This is the technique of ultraviolet laser fluorimetry. β-carbolines emit a bright yellow-green fluorescence at 445, 470, and 520 nm when irradiated in situ at 325 nm with a He-Cd laser. Treatment of rats with acetaldehyde 100 mg/kg i.p. increased the fluorescence in the arcuate nucelus by 40%. Extraction of pooled arcuate nuclei and subsequent TLC allowed the authors to identify tentatively the responsible compounds as 6-methoxy-1,2,3,4-tetrahydro-β-carboline and 1-methyl-β-carboline (54).

Honecker & Rommelspacher (55) have developed an assay for β-carboline which involved acetylation with (^{14}C) acetic anhydride and separation by TLC. They found substantial amounts present in untreated rat brain (47 ng/gm). Bidder et al (56) have developed a method based on solvent extraction and silicic gel column chromatography and TLC to separate β-carbolines from tissue. Identification is by GC/MS without derivatization, and quantification is accomplished by fluorimetry. The sensitivity of the fluorescent assay is such that about 10 ng of most of the compounds can be detected.

ENZYME INTERACTIONS

Interest in the biochemical actions of the tetrahydroisoquinolines was evident in 1969 when studies of Hattori et al (57) demonstrated that 1-trimethoxybenzyl and 1-dimethoxybenzyl-6,7-dihydroxytetrahydroisoquinoline were inhibitors of rat liver mitochondrial monoamine oxidase. These investigators also showed that the two compounds were inhibitors of catechol-O-methyl transferase (COMT) activity from rat liver. However, the mechanism of inhibition was not investigated. Rubenstein & Collins (58) reported that, like norepinephrine, 4,6,7-trihydroxytetrahydroisoquinoline derivatives were O-methylated by (COMT) isolated from brain and liver homogenates. The O-methylation of the TIQs was sensitive to inhibition by pyrogallol, a known inhibitor of COMT. Similarly, Collins et al (59) indicated that the primary metabolic route of metabolism for the TIQ alkaloids is by O-methylation of one or more of the hydroxyl groups catalyzed by COMT. The Michaelis constants (K_m) determined for salsolinol were 290 μM compared to that of 230 and 660 μM for dopamine and norepinephrine, respectively. The K_m value for THP was considerably lower at 30 μM. Both salsolinol and THP were competitive inhibitors of dopamine O-methylation in vitro with K_i values of 130 and 20 μM, respectively.

Giovine et al (60) confirmed the previous findings that THP and salsolinol inhibited rat brain COMT activity with K_i values of 96 and 77 μM, respectively, when dopamine was utilized as a substrate. When admin-

istered intraperitoneally in doses of 60 mg/kg, THP or salsolinol had an observed effect on COMT activity within 2 hr but not at longer periods after treatment, indicating a short half-life of these alkaloids. After intraventricular injections, Melchior et al (110) found a $T_{1/2}$ for THP to be 17 min and that for salsolinol to be 12 min. Both half-lives were markedly prolonged by pretreatment with pyrogallol. Smissman et al (62) reported that various 2- and 4-substituted 6,7-dihydroxytetrahydroisoquinolines were substrates and substrate-competitive inhibitors of COMT. Methyl substituents in the 2- and/or 4- positions of 6,7-dihydroxytetrahydroisoquinoline had little effect on the interaction with COMT. In general, the substrate kinetic (K_m and V_m) and inhibitory kinetic (K_i) properties toward COMT were similar for each of these compounds. The COMT inhibitory potencies of the compounds with methyl substituents at the 2- or 4-positions did not correlate with norepinephrine-depleting activity. The norepinephrine-depleting activity showed more strict structural requirements than did inhibition of COMT.

The TIQs have been shown to inhibit MAO activity from a variety of tissues (57, 63). The relative potency of salsolinol as an inhibitor of MAO is similar with either brain stem homogenates or liver homogenates with 50% inhibition of MAO activity by approximately 2 mM salsolinol. Yamanaka et al (63) demonstrated that inhibition of brain stem homogenate MAO activity by salsolinol was competitive with serotonin. These findings were essentially replicated in the studies of Collins et al (59). Various hydroxylated and O-methylated tetrahydroberberines, as well as THP and salsolinol, were shown to inhibit both A and B forms of MAO in rat brain homogenates (64). Utilizing serotonin as a specific substrate for type A MAO 50% inhibition was achieved by 1, 0.25, 0.24, and 0.04 mM concentrations of THP, salsolinol, 2,3,9,10-tetrahydroxyberberine, and 2,3,10,11-tetrahydroxyberberine, respectively. When benzylamine was used as a preferred substrate for the type B MAO, 50% inhibition was achieved by these alkaloids in concentrations of 4.4, 50, 5.6, and 13 mM, respectively. These data would suggest that the type A MAO from rat brain homogenates is most sensitive to inhibition by these alkaloids. Inhibition was competitive with serotonin as a substrate, while inhibition by THP and salsolinol was not competitive with benzylamine as a substrate. These investigators showed that O-methylation of the 2,3,9,10- or 11-hydroxyl groups significantly decreased the potency and the selectivity of MAO inhibition.

Evidence has been presented (65) demonstrating that TIQ alkaloids inhibit MAO activity in intact neurons. For example, THP and 6,7-dihydroxytetrahydroisoquinolines were shown to inhibit MAO activity within the adrenergic nerve plexus of isolated mouse atrium and within the peripheral adrenergic neurons. THP appeared to be taken up into the nerve plexus relatively poorly, and studies by Cohen (66) demonstrated that 6,7-dihy-

droxy TIQ and salsolinol *raised* norepinephrine levels and simultaneously depressed levels of metabolites in the intact peripheral neuron. THP was not as potent in eliciting this effect. Previously, Cohen & Katz (67) had demonstrated that in heart tissue obtained from a reserpinized rat the 6,7-dihydroxy TIQ produced a 38% increase in norepinephrine content, indicating an inhibition of MAO activity in vivo. Other studies indicate a more complex interaction of TIQs with catecholamine metabolism; Livrea (68) provided indirect evidence that these alkaloids altered catecholamine metabolism by demonstrating that 60 mg/kg THP administered acutely or chronically caused an elevation in homovanillic acid (HVA) and 5-hydroxyindole acetic acid levels in rat brains. In rats treated with *l*-dopa, THP inhibited the expected increase in HVA levels in brain. The authors concluded that the results showed that THP may displace brain monoamines in vivo, but were unable to assess whether COMT or MAO activities had been altered.

The TIQ alkaloids inhibit other enzyme systems such as sodium-potassium-ATPase and magnesium-ATPase (69) and tyrosine hydroxylase activity (70). The benzylisoquinolines, tetrahydroprotoberberines, and other possible catecholamine-aldehyde condensation products were more potent inhibitors of sodium-potassium-ATPase than of magnesium-ATPase. Of the 11 different isoquinoline alkaloids studied by Meyerson et al (69), the protoberberines were the most potent inhibitors of ATPase activity. Berberine and 1,2,10,11-tetrahydroxyaporphine were competitive inhibitors with respect to ATP, whereas other compounds such as papaveroline were noncompetitive inhibitors. Although papaverine is a potent inhibitor of cAMP phosphodiesterase, a related TIQ, trimetoquinol, is not (71).

Salsolinol was shown to decrease rat brain dopamine and heart noradrenaline levels consistent with the inhibition of tyrosine hydroxylase activity (70). These authors demonstrated that tyrosine hydroxylase from rat brain was inhibited by 72% by 0.1 mM salsolinol. Little stereo specificity was observed in that the S(–) and R(+) forms inhibited tyrosine hydroxylase activity nearly equally. THP inhibited tyrosine hydroxylase activity only 19% at 0.1 mM. Weiner & Collins (72) extended these studies and determined that K_i values for salsolinol were 14 μM and that inhibition was competitive with the pteridine co-factor. THP was relatively impotent as an inhibitor. These researchers reported that salsolinol did not inhibit dopamine decarboxylase activity in vitro and found no evidence of tyrosine hydroxylase inhibition by salsolinol in vivo.

Ho and co-workers (73–75) found a number of substituted tetrahydro-β-carbolines to be potent inhibitors of MAO in vitro. These researchers reported that methyl substitution on the position N-9, the indolic nitrogen, in most cases enhanced the in vitro MAO inhibition. The IC_{50} for inhibition of mouse brain MAO activity by tetrahydro-β-carboline was 32 μM.

PHYSIOLOGICAL EFFECTS ON PERIPHERAL ORGANS

Shortly after the initial synthesis of THP in 1909 by Pyman (9), Laidlaw obtained some of the new alkaloid and tested it in a number of physiological systems (76). In a remarkable series of studies he discovered much of what was to be rediscovered and reemphasized 50 years later. He clearly showed that THP lowered blood pressure and increased heart rate; he had indirect evidence for increased force of contraction of the heart and found that THP relaxed the uterus. The doses that he used, 3 to 8 mg to a cat, were much larger than more recent investigators have used and may have contributed to his finding of tachyphylaxis.

In the 1960s Holtz (13, 77, 78) and Santi (79) confirmed that THP was a powerful β-agonist at doses of 3 μg/kg in cats and at higher doses in rabbits. Lipolytic activity was also demonstrated in vivo and in rat fat pads in vitro. Japanese workers then became interested in the THP and analogues as bronchodilators and found that trimetoquinol (TMQ, 3',4',5'O-methoxy, THP) was 5 to 10 times more potent as a bronchodilator than isoproterenol (80) and that the l[S(–)] isomer was responsible (81). The compound was less potent on the heart than isoproternol (82, 83), but the actions were blocked by β-blockers Sato found that the 6- and 7-methoxy derivatives of TMQ acted as β-blockers in cats in doses from 10 to 100 μg/kg. These O-methylated compounds were metabolic products of TMQ.

More recent studies of the peripheral actions of THP and salsolinol confirmed the agonist nature of THP with potencies (EC_{50} values) in the range of 0.01 to 1 μM for the S(–) isomer in bronchial or atrial muscle (84) on rat erythrocyte adenylate cyclase (85) or on lipolysis (86, 87). The R(+) isomer is much less effective. Similar results have been obtained with TMQ (71), but TMQ appears to be somewhat more potent than THP. Optical isomers are extremely useful in the study of receptor interactions, but their formation for compounds, such as many under discussion here, may be nonenzymatic, causing the products to be racemic even if they are formed in vivo.

Salsolinol, on the other hand, is relatively impotent as a β-agonist (84–86, 88) but does function as a relatively weak α-antagonist of NE on the vas deferens (89) and on the aorta (90). It does block 5-HT stimulation of the fundus and uterus and blocks the effect of oxytocin and vasopressin on the uterus (91).

The reaction product between epinephrine and acetaldehyde damages peripheral sympathetic nerves in the iris, atria, and superior cervical ganglia in adult and newborn rats (92) and causes fatty infiltration and necrosis of the liver (93). Our search of the literature has failed to find independent

reports confirming these findings, but they are obviously of considerable interest.

The protoberberines and aporphines provide THP derivatives where the ring structures are held in their spatial relationship. Sheppard et al (94) have taken advantage of this to study the structural requirements for β-receptor interaction. Surprisingly, β-agonist activity is seen with both structures with nearly the same potencies for the S(–) isomers.

Many studies using synthetic TIQs have involved searching for pharmacologically active compounds. Thus an *N*-substituted TIQ, esproquin (NC7197), was investigated as an α-blocker in animals (95, 96) and as a positive ionotropic compound in man (97). Paul (98) investigated 1-phenyl-2-phenylethyl TIQs as female antifertility agents. The book by Shamma & Moniot (8) contains information concerning a large number of TIQ derivatives from natural and synthetic sources and provides limited data on a wide variety of pharmacological actions of these compounds.

EFFECTS ON UPTAKE, STORAGE, AND RELEASE OF BIOGENIC AMINES

Cohen and co-workers (99, 100) have pursued the idea that TIQs can act as false transmitters, and most of the criteria for false transmitters have been fulfilled by one or more of these compounds. These investigators demonstrated uptake and storage of 6,7-dihydroxytetrahydroisoquinoline in peripheral sympathetic neurons in the rat iris (99, 100). Likewise, it has been shown that the TIQs are taken up by rat heart, salivary gland, iris, and adrenal of mouse (101); by capillary endothelial cells and by unidentified cells (possibly astrocytes) in the hypothalamus and hypophysis (102); and by the synaptosomal fraction of rat brain (103). In these studies uptake was reserpine independent since in a number of cases the animals were pretreated with this compound to release endogenous amines so that they would not interfere with the fluorescence of the TIQs given later. The finding that dihydroxy (DH) TIQ formed dense core vesicles and apparently utilized a reserpine-resistant mechanism (100) calls into question whether the TIQs are taken up and bound in a manner similar to the endogenous amines. However, the uptake of TIQs is blocked by cocaine and by desmethylimipramine (DMI) (99, 100, 101). The uptake into iris is also prevented by prior 6-hydroxydopamine treatment (101). Thus neuronal uptake mechanisms exist that will concentrate these compounds, but binding to granules apparently occurs by a mechanism which differs from endogenous amine binding.

Tennyson et al (104) have shown regranulation of small and large dense core vesicles by 6,7 DH TIQ in slices of pineal and iris from reserpinized

rats. Similarly, Koda et al (105) showed that slices of caudate from rat brain, when incubated with THP, accumulated small granular vesicles. This process was blocked by dopamine (5 mM in the incubation) or by substantia nigra lesions.

Another criterion for a false transmitter is that it be released upon nerve stimulation. This was shown by Mytilineou et al (100) in a classical experiment in which reserpine-treated rats received TIQs and then the superior cervical ganglion was stimulated. This caused depletion of the TIQs as measured in the iris and also resulted in contraction of the iris, retraction of the upper eyelid, and protrusion of the eyeball, all consistent with release of the TIQs from nerve terminals and stimulation of postsynaptic sympathetic receptors.

While not a requirement for a false transmitter, some of these compounds block uptake of norepinephrine and dopamine into brain slices (106) and synaptosomes (107).

In vivo experiments have also demonstrated the ability of THP to release dopamine and 5-HT from the striatum and NE from the diencephalon of rats given large doses (70–250 μg) of THP intraventricularly (108). This effect was blocked by DMI. Haloperidol partially prevented the striatal DA and NE decrease. Salsolinol, given similarly, increased striatal dopamine concentrations but lowered diencephalon concentrations of NE and 5-HT. Hannigan & Collins (109) also demonstrated that peripheral administration of carboxysalsolinol lowered 5-HT levels and 5-hydroxyindoleacetic acid (5-HIAA) levels in the hypothalamus and 5-HT levels in the striatum.

Utilizing push-pull cannulae, Melchior et al (61) infused several dopamine-rich sites with (^{14}C) dopamine. THP, 4,6,7 DH TIQ, and tryptoline (250 ng/min) caused enhanced release of (^{14}C) dopamine.

The tetrahydro-β-carbolines, tryptolines, inhibit the uptake of serotonin and to a lesser extent of norepinephrine into aminergic granules of various tissues. In 1973 Tuomisto (111) found that 1,2,3,4-tetrahydroharmane (tryptoline) inhibited the accumulation of histamine in rabbit blood platelets. These observations were extended by Airaksinen et al (112) in studies demonstrating that 6-methoxy and 5-methoxy tryptoline were taken up by rabbit blood platelets and that the high rate active uptake (K_m 6.6 μM) was inhibited by serotonin. Conversely, the uptake process for these tryptolines appeared to be competitive with the serotonin uptake process. Other investigators have determined the effects of various β-carbolines on serotonin uptake in granules isolated from regions of the brain. For example, Keller et al (113) determined that a number of tryptolines competitively inhibit serotonin uptake into rat forebrain homogenates: 5-Hydroxytryptoline was the most potent inhibitor with a K_i value of 0.3 μM. In subsequent studies,

Rommelspacher et al (114) demonstrated that tryptoline inhibits the high affinity uptake of serotonin in synaptosomes isolated from rat hippocampus and hypothalamus. These investigators found that the uptake mechanisms for GABA and dopamine were much less affected than for serotonin. The administration of tryptoline appears to produce a dose-dependent elevation in a level of serotonin and a corresponding decrease in 5-hydroxyindoleacetic acid concentration in rat brain (114). These studies suggest that the effects of tryptoline are short-lived but that these alkaloids can inhibit serotonin uptake in vivo.

CENTRAL EFFECTS

Since the original suggestion that the similarities of the structure of THP and morphine might provide a theoretical basis for investigation of alcohol addiction (17), much attention has been paid to the possibility that TIQ compounds might form the bridge between ethanol and opiates, in spite of the general wisdom that there is no such cross reactivity. Numerous investigators are now investigating the possibility of interactions between opiate action and that of ethanol (115–118), but the recent finding of Tampier (119) that neither THP, salsolinol, nor several tetrahydroxyberberines are potent in displacing (^{3}H) naloxone binding to synaptic plasma membranes has dampened some of the enthusiasm for this idea. However, such studies with both agonists and antagonists are important since their interactions with receptors are markedly different. For example, Weiland et al (120) found that antagonist binding to the β-adrenergic receptor is largely entropy driven whereas the binding of antagonists is accompanied by a large decrease in enthalpy.

TIQ compounds do interact with other central neuroamine receptors. THP seems to be the most potent of those tested as a dopamine cyclase inhibitor with K_i values for the S(–) isomer of 2.9 μM (121) to 10 (122) or 25 μM (85). The R(+) isomer is less potent. These values are consistent with data from binding studies (88, 121). THP as the racemic compound (88) or the S(–) isomer (121) binds to β-receptors in brain tissue with K_d values of 0.1 to 6 μM. Salsolinol is less potent as an antagonist of DA cyclase (85, 112, 121) but S(–) TMQ is reasonably potent (IC_{50} of 70 μM) (94). Likewise the protoberberines (94) have IC_{50} values in the range of 0.6 μM and the aporphines have values of about 1 μM (123). Apomorphine, an aporphine lacking the 6,7 hydroxyl groups, is a potent agonist of dopamine systems in the brain (124). TIQ itself is not very potent as a dopamine agonist when injected into the striata of guinea pigs as compared to dopamine (125).

Taken collectively, evidence from the peripheral and central nervous system indicates that the TIQs have dopamine antagonist activity, but both agonist and antagonist activity with β-adrenergic receptors.

Another interesting action of the TIQ alkaloids is that of inhibition of Ca^{2+} binding to synaptic plasma membrane by salsolinol at 10 nM (126). This is by far the most potent action reported for any TIQ alkaloid in an in vitro system.

The situation becomes ambiguous when the compounds are injected peripherially or intracerebrally. Studies of the central effects are fraught on the one hand with the uncertainty of how much enters the brain after peripherial injection and on the other of the possible brain damage upon injection intracerebrally or intraventricularly (127). Attempts to overcome these problems have been made by giving carboxysalsolinol (109) with or without a DOPA decarboxylase inhibitor (128), with the expectation that the compound will be taken across the blood brain barrier by some active transport system for amino acids.

Salsolinol decreased activity in mice bred for initial sensitivity to ethanol (LS mice) more than it did in mice bred for insensitivity to the depressant actions of ethanol (SS mice) (129). Blum (118), however, could not duplicate these studies in ICR Swiss mice. These mice convulsed and then remained immobile after a dose of 300 μg of salsolinol administered intracerebrally. Interaction with ethanol is seen in that the sleep time due to ethanol is prolonged by carboxysalsolinol (128). Salsolinol given directly into the brain in high doses causes sleep itself, and the SS mice are less sensitive to the effects of this compound than the LS mice (130).

Presumably, more direct information could be gained by application of these compounds to neurons known to contain a certain type of receptor. The dopamine receptor is a good candidate since apomorphine, a powerful dopamine agonist is an aporphine. Such studies have led to several interesting observations. Neumeyer (131) found that both apomorphine and an *N*-isopropyl analogue failed to elicit increased locomotor activity upon direct injection into the nucleus accumbens, but did block the excitation produced by dopamine. On the other hand, apomorphine, directly applied to the caudate, induces biting behavior and both apomorphine and its isopropyl analogue cause circling behavior upon peripheral administration to animals whose caudate has been obliterated on one side. These results have been used to argue for different types of dopamine receptors in different areas of the brain. THP and salsolinol applied directly to the nucleus accumbens also do not produce significant hyperactivity but the 3-methyl derivative of salsolinol did increase activity which was blocked by haloperidol (132). Thus this compound appears to behave as a DA agonist whereas

all other TIQ compounds function as antagonists, if anything, in the nucleus accumbens.

The central effects of β-carbolines are best known in the hallucinogenic potential of the harmala alkaloids (133). The harmala alkaloids given peripherally induce a tremor (134) which is abolished by destruction of cerebellar climbing fibers (135). A great deal of work has been done with the tremorogenic effects of the harmala alkaloids (136–139). These harmala alkaloids have substitutions in the 7 position (corresponding to the 6 position of tryptamine) and as such are unlikely to arise from tryptamine in mammalian systems where the hydroxylation is in the 5 position (which will become the 6 position of the carboline). There are compounds which do arise in mammals, however (refer to the section of formation), that have significant CNS effects. Thus Rommelspacher (140) found decreased motor activity analgesia, decreased temperature, and a block of apomorphine stereotyped behavior with tryptolines. 6-Methoxy tetrahydro-β-carboline (THβC) increases 5-HT levels in rat brain after i.p. injection (141). Fang (142) found that 6-methoxy THβC stimulated prolactin release and that this action was blocked by a 5-HT antagonist. The harmala alkaloids inhibit uptake of NE into synaptic vesicles of brain (143) and adrenal medulla (144). This action may be rationalized because of the structural similarities between these compounds and reserpine. The alkaloids also inhibit the K^+ acylphosphatase reaction of $NA^+ + K^+$ ATPase but they are not very potent ($K_i = 0.9$ mM) (145) although they may be useful tools to investigate this enzyme complex.

In general it would seem that the β-carbolines could be expected to be 5-HT receptor agonists and to have reserpine-like actions in the μM range of concentrations.

Preference for Alcohol

There are an infinite number of ways that an animal's "preference" for alcohol solutions can be measured, and much of the debate in this area arises from differences in the methods used. A more fundamental question, however, is whether or not preference studies are important at all. Because animals do not usually achieve intoxicating blood levels of ethanol, they do not normally become dependent upon alcohol and do not seem to drink for the pharmacological effects of alcohol. Nevertheless, preference is an "alcohol-related" behavior and has been studied extensively.

Myers and his group (146, 147) were the first to report that intraventricularly infused TIQs and tryptoline cause rats to consume relatively large amounts of ethanol in a preference situation. Myers et al's studies remain the only ones appearing in reviewed publications. However, other groups have

reported similar (148) or conflicting results (149). Since some of the disagreements in this area are likely to revolve around techniques, a review of the differences and similarities of the techniques is given below.

Myers implanted a cannula in the lateral ventrical of 350–500 gm Sprague-Dawley rats under pentobarbital anesthesia and started the animals on chronic infusion within a day of the surgery. The rats were infused in one of three ways; once daily (5 μl on each side) for 14 days; once every 15 min for 13 sec (1 μl) for 14 days, or once every 30 min for 60 sec (4 μl) for 14 days. An automatic pump was used for around-the-clock infusions. The fluid was an artificial CSF in which the pH was lowered to 3.8 with 0.1 mg/ml of ascorbic acid and which contained various amounts of the test compounds. The animals were normally infused for two days prior to presentation of a choice between ethanol, water, or an empty bottle. The bottles were randomly rotated daily. The ethanol bottles contained increasing amounts of ethanol from 3% to 30% over a 12-day period. The data were expressed both as the ratio between fluid from the ethanol bottle divided by the amount of total fluid consumed (preference ratio) and also as the grams of ethanol per kg body wt per day. Two types of controls have been used, animals tested in the preference paradigm before implantation and infusion (146), and those tested while being infused with artificial CSF alone and then with drugs. In either case each animal served as its own control. In other experiments no prior exposure to alcohol was allowed before intraventricular infusion was begun. The animals had free access to Wayne rat chow and were on a 12:12 light : dark cycle. The techniques used by Duncan & Deitrich (148) were similar except for the use of Purina rat chow and of Long-Evans rats in addition to the Sprague-Dawley animals. Following termination of the experiment a dye was infused via the cannula to ascertain the location of the cannula tip and to verify that there was a patent pathway and that the infused material did not regurgitate up the needle track to the meninges. This is a useful technique only if carried out shortly after completion of the infusion; otherwise glial plugs will form or the cannula will become dislodged.

The procedures of Amit and his group (149) differ significantly from those of Myers. The Amit group appears to have started with the premise that TIQ compounds should *decrease* alcohol intake when given. They have used Wistar rats, 225–250 gm and have selected those animals that either drink 4–6 gm/kg ethanol per day in a preference situation or have achieved high drinking by slowly increasing concentration of the presented alcohol solution. They implanted the cannula in the lateral ventricle and waited for 5–6 days after surgery to begin testing. Then they presented ethanol on alternate days starting with 3% and increasing by 2% until the animal

stabilized at a preference ratio of 0.4 to 0.6. After 3 days of a stable base line the animals were infused for 5 to 20 days. A minimum of 9 days would elapse between cannula implantation and the start of infusion, creating serious doubt as to whether or not the infused material ever reached the ventricles because of glial plugs around the cannula. For the 20 day infusion, once daily infusions were given, while for the 5 day period, infusions were given every 30 min. Ringer's solution was used, with the pH adjusted to 3.6–4.6 with HCl, for infusions. Their animals had free access to Purina rat chow.

To summarize the rather drastic differences in these two techniques, Myers used low preferring Sprague-Dawley rats whereas Amit used Wistar rats that either were high preferring to start, selected for high preference, or trained to drink large amounts of ethanol. Myers used ascorbate in an artificial CSF while Amit used HCl in Ringer's solution. The time course of infusions was very different, 14 days for Myers and usually 5 days for Amit. Myers started the infusion almost immediately after surgery. The protocol used by Amit required a minimum of 9 days before starting infusions, and no check of patency of the cannula was reported at the end of the experiment. Myer's data were usually given with each animal as its own control and this procedure necessitated a prior exposure of the animal to the entire range of ethanol solutions used. Amit's animals were exposed to ethanol before infusion began and were tested at different percent solutions of ethanol depending on each animal's preference. The meaningful data were presented as gm/kg/day of ethanol consumed since they were selected to have preference ratios of 0.4 to 0.6.

Myers & Melchior (146) and Melchior & Myers (150) reported on increased intake of alcohol after infusion of various TIQs. The results are significant when expressed as preference ratios or when expressed as gm/kg/day of alcohol intake. The dosages used ranged from 0.3 to 2688 μg over a 14 day period. The most potent compound was racemic THP although there was some indication that S(–) THP was more potent than the racemic mixture. They were unsuccessful in achieving increased drinking with a single 40 μg injection into the ventricle. Myers & Oblinger (147) later reported that once daily injections of 1.4–14 μg of THP daily for 14 days were also effective but 140 μg daily was not. When the compounds were given by infusion, Myers & Melchior (146, 150) found positive results with the TIQs, THP, salsolinol, carboxysalsolinol, 6-methoxy, 4,7-dihydroxy TIQ, S(–) THP, and tryptoline but not with TIQ 4,6,7-trihydroxy TIQ. THP and tryptoline caused increased drinking when given once daily. These results have not been confirmed by Amit and co-workers who found no effect of TIQ compounds on alcohol preference in rats that they used.

One possible conclusion is that TIQ or β-carboline compounds will not cause most rats to exceed their metabolic capacity for alcohol to any significant extent. Since the rats used by Amit are close to this limit already because they have been selected or trained to drink, it is impossible to push them further.

Duncan & Deitrich (148), on the other hand, have been able to replicate many but not all of the features of the Myer's data. Their animals did show increased preference for alcohol when infused with THP or salsolinol. The great majority, however, did not extend their preference to alcohol concentrations of greater than 15%. The animals did continue to prefer alcohol up to 10 months after infusion, however. Dose response curves indicated that doses above 40 nmoles/day of chronic infusion with THP over the 14 day period nearly completely stopped drinking behavior. They did not observe signs of dependence or withdrawal in the infusion paradigm.

More recently Myers & Hoch (151) attempted to localize the reactive sites in the brain by microinjection of 25 to 100 ng daily. They found increased alcohol intake most consistently when THP was placed in the hippocampus, periaqueductal gray, and the cingulate gyri. In future experiments in the area it would seem imperative to test the specificity of the preference by offering other aversive agents that have similar central nervous system effects but would not be expected to lead to the formation of TIQ compounds.

OTHER ACTIONS

The focus of the preceding sections has been on the effects of various compounds on the nervous system; however, actions on peripherial tissues are also of interest. For example, harman and norharman are carcinogenic agents (152). This opens the fields of carcinogenesis, teratogenesis, mutagenesis to investigation of these compounds. Indeed, a great deal of evidence that alcoholics have higher rates of cancer (153) makes this area of investigation attractive.

SUMMARY AND CONCLUSIONS

The suggestion made several years ago, by McIsaac (14) with the tryptamine derivatives and then more definitively by Davis & Walsh (44) and Cohen & Collins (15) for catecholamine derivatives, that alkaloids might be formed in vivo as a consequence of ingestion of alcohol raised the hopes of researchers that a handle to understanding the acute and chronic effects of alcohol had been found. Several years of careful work by a number of

laboratories pointed to several tantalizing possibilities: The compounds had some activity with a variety of neuroamine receptor systems; they affected uptake, storage, release, and metabolism of biogenic amines and thus met the criteria for false transmitters; they were found in urine of humans and other animals and in brains of rats and mice after administration of ethanol if the right conditions were met; they altered Ca^{2+} binding in the brain etc, but the tie to acute or chronic actions of alcohol was largely missing. A series of experiments by Myers and his students showed that these compounds, when placed directly into the brain in very small amounts over many days, induced drinking in previously nonpreferring animals and the effect was essentially permanent, providing at least a hint of a model for the alcoholic who dare not take that first drink after a long period of abstinence. These findings have provided a possible lead to the long-sought tie between alcohol and highly potent compounds in the brain.

There are also several properties that might be expected of a compound that would form this bridge, which have not been found. Thus the compounds should be found in the brain in response to acute or chronic exposure to ethanol. Only O-methylsalsolinol seems to fit this criterion so far and that evidence is not yet confirmed. While the β-carbolines are found in the brain and other tissues they have not been shown to increase in response to ethanol. These objections may be overcome as more sensitive and specific techniques are developed. The TIQs and β-carbolines are sufficiently potent in a number of systems to be pharmacologically active at low levels, but more potent compounds are known for almost every effect studied. None of these potent compounds, TIQs or the β-carbolines faithfully reproduce any of the effects of acute or chronic ethanol administration. One possible exception is the disputed effect of these compounds on ethanol preference, but this is demonstrated only in rats, and long-term alcohol exposure does not lead to increased alcohol intake of the magnitude or the duration found in these animals treated with TIQs. Possibly it is a combination of actions unique to these or similar compounds that may reproduce the effects seen after ethanol administration. It is also possible that these compounds form as a *result* of the actions of ethanol and have little or nothing to do with *mediating* the effects of alcohol.

The area for immediate attention would seem to be in development of sensitive and specific assays for TIQ and β-carboline compounds in the brain and in the search for new metabolites. The studies on the pharmacological actions of the TIQs and β-carbolines compounds are important in their own right, even if these compounds prove not to hold the key to alcoholism. Such studies may prove valuable far beyond the field of alcoholism.

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