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PSYCHOPHARMACOLOGY OF ALCOHOL

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INTRODUCTION

Significant strides have been taken in the last few years in this interdisciplinary field that combines biological, behavioral, and biochemical approaches to the study of the potent psychopharmacological actions of alcohol. The principal reasons for this are twofold. First, the experimental investigation of alcohol's effect on the central nervous system and the disease process produced by the drug have newly achieved a measure of scientific respectability. No longer is the sight of a rat, hamster, or pig drinking an alcoholic beverage in a laboratory setting greeted by a singular scowl or unrestrained amusement. Second, although the etiology of alcoholism may stem partially from deeply rooted psychological or sociocultural problems, the pathological manifestations of drinking all have a biological basis; these include the permanency of one's addictive liability and the well-known inherent predisposition toward alcohol imbibition. As a result, the difficult question pertaining to alcohol's multiplicity of effects is now being examined by investigators from different disciplines joining together. Today, an enzymologist may be as fascinated by the alcohol-drinking pattern of an animal as by the catabolism of the compound; and a behaviorist can be concerned as much with the question of drug receptor interactions as with the characteristics of a withdrawal symptom seen in an alcohol-dependent animal.

A number of monographs, monumental reviews (1, 2), and collections of papers based on conferences or symposia have given coverage to a large part of the wealth of information on the psychopharmacology of alcohol. These treatises are devoted to issues such as the action of alcohol on the central nervous system (CNS) (3–7), the factors that alter the self-administration of alcohol by an animal (8–12), the biochemical and metabolic aspects of the fluid (13–18) and the more general problem of drugs that affect alcohol consumption, intoxication and withdrawal (19–21).

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This review focuses on the factors of pharmacological significance that influence an animal's pattern of alcohol drinking in an experimental situation. Coverage is also given to the effect of alcohol itself, acting as a CNS drug, upon certain processes that are mediated by cells in the brain.

SUBSTANCES AFFECTING ALCOHOL PREFERENCE

The ingestion of alcohol by an experimental animal has been variously termed *self-selection, self-administration, autoselection* or defined in terms of the preference-aversion (acceptance-rejection) characteristics related to this fluid. The paradigm used in the laboratory typically involves the simultaneous presentation of a solution of ethyl alcohol together with water, and in some cases, a third fluid which serves as an alternative choice (21). Undoubtedly, some of the discrepancies and controversy concerning disparate research findings can be traced to the specific self-selection procedure adopted by a given investigator. Curiously, the fundamental pharmacological precept underlying a dose-response analysis is all too frequently ignored in this field (21). In many experiments, a single concentration of alcohol is used[1] as the test solution rather than multiple concentrations which are ordinarily presented in increasing strength over days, as a choice against water (22, 23). Within the past few years, however, the precept has been recognized, and it is encouraging to note that many scientists now are using a technique in which a variety of concentrations of alcohol are offered over 7–12 days. In this way, a preference-aversion curve or an acceptance-rejection pattern of alcohol drinking can be ascertained. By offering solutions of alcohol of varying strength, the danger of extrapolation from a single solution or dose of the fluid is supervened with respect to alcohol's multifaceted pharmacological properties and its taste, smell, and caloric value.

Alcohol and Aldehyde Dehydrogenase

The act of drinking, intoxication, tolerance, and physical dependence upon alcohol are all due to unknown mechanisms in the central nervous system. Although metabolized chiefly in the liver by alcohol dehydrogenase (ADH) to yield acetaldehyde (24), the role played by this metabolite in the brain and the enzyme required for its own degradation, aldehyde dehydrogenase (AldDH), is still unclear (25). Interest-

[1]To illustrate, here are three typical laboratory situations and concomitant findings. First, rats *A* and *B* are offered 10% alcohol simultaneously with water. *A* drinks 2.0 g/kg of alcohol over 24 hr while *B* drinks nil. Second, if the test solution presented is lowered on the next day to 7%, rat *A* still consumes 2.0 g/kg but its counterpart in the neighboring cage, *B*, now ingests 4.0 g/kg of alcohol. Third, on the next day, if *A* and *B* are offered 13% alcohol, both reject the fluid and drink only water. Thus, depending solely upon which single concentration of alcohol is arbitrarily selected by the experimenter as the test fluid, four distinct deductions could be incorrectly drawn, by logic, about the volitional intake of the two animals: 1. *A* is a greater drinker of alcohol than *B*; 2. *B* is a greater drinker of alcohol than *A*; 3. *A* and *B* are both alcohol drinkers; and 4. *A* and *B* are not alcohol drinkers.

ingly, the rat of an alcohol-preferring strain exhibits a lower level of acetaldehyde, as alcohol is oxidized, than an animal of an alcohol-rejecting strain (26). Moreover, the isozyme pattern of liver AldDH is distinguishable in the rat that has a high or low preference for alcohol (27). Further, liver ADH activity is surprisingly lower in the alcohol-preferring rat when compared to the animal that rejects the fluid (28). In spite of the observation that alcohol acts as a direct inducer of the metabolism of such drugs as phenobarbital (29), the forced intake of alcohol may not necessarily cause a significant increase in the activity of AldDH in liver cytosol; this would indicate that a preference for alcohol exhibited by an animal is not related directly to the inducibility of this enzyme or to its level in vivo (30). Nevertheless, studies continue today on the role of acetaldehyde in alcohol dependence (31), as well as on the action of drugs that specifically inhibit ADH or AldDH activity, and which relate to the process of alcohol self-selection.

Butyraldoxine, a strong inhibitor of AldDH in vivo, produces a marked and protracted decline in the preference for 12% alcohol in C57BL mice, a strain exhibiting a natural preference for alcohol (32). Certain organic nitrates also cause a sharp reduction in the activity of liver ADH and AldDH (33). For instance, compounds such as ethyleneglycol dinitrate, glycerol trinitrate or propyleneglycol dinitrate diminish the selection of a 10% alcohol solution in the ALKO strain of rat which is termed *alcohol-addicted* (34). Pyrazole, a well-known potent inhibitor of liver ADH, evokes a similar sort of decline in the selection of a weak 4% solution of alcohol in the Sprague-Dawley rat (35), a nonpreferring animal; 3-methylpyrazole which does not inhibit liver AldDH causes only a minor transitory effect on alcohol drinking when administered systemically. In a study related to this issue, Geller & Messiha (36) report that 2-aminoethylisothiouronium bromide, which lowers the level of NAD in the liver, attenuates the self-selection of a 6% solution of alcohol in the presence of water. Since NAD is a required cofactor for both ADH and AldDH enzymes (37), this alteration in the rat's drinking pattern could again be due to the incapacity of the animal to metabolize alcohol.

With respect to the differentiation of the two enzymes in brain tissue, it is of interest that the forced drinking of 15% alcohol for two weeks significantly elevates the content of ADH in the brain without affecting AldDH levels within this organ (38). Raskin (38) suggests that the acquisition of tolerance follows a similar time course to a biochemical adaptation of the brain to ADH. However, Eriksson et al (39) have concluded that a strong relationship does not exist between the quantity of acetaldehyde in the brain of an animal and acute intoxication following a systemic injection of alcohol. Thus, additional research into this question is required, particularly in view of the observation that the level of acetaldehyde in the blood, after being raised by p,p'-DDT given systemically to the rat, does not seem to induce any notable shift in its voluntary consumption of alcohol (40).

Nutritional, Dietary, and Other Peripheral Factors

Alcohol selection in the experimental animal can be altered as a result of its nutritional status (41, 42). Similarly, the condition of the endocrine system, including

that of the thyroid and reproductive organs, is instrumental in the modification of the self-selection of alcohol as witnessed by the effect of drugs that interfere with normal plasma titres of a given hormone (43–45). Some recent experimental emphasis has been devoted to the composition of the diet itself as well as to the profile of amino acids both in the periphery and in the CNS.

When a rat is simultaneously offered the choice of 10% alcohol and water, and is subsequently fed an imbalanced diet of 5% protein, 80% carbohydrate, and 15% fat, the voluntary selection of alcohol declines significantly (46). The animal fed this high carbohydrate, low protein diet also exhibits a marked decrease in the rate of alcohol elimination and a concomitantly increased accumulation of blood acetaldehyde when challenged with a test dose of alcohol. In addition, plasma-free tryptophan and total tryptophan is significantly lower in these diet-restricted rats.

Corresponding to this result, Sprince et al (47) have found that an increase in the amino acid content of the rat's diet enhances its selection of a 15% solution of alcohol. When excess tryptophan is included in the food of an animal of the Charles River strain, its intake of an alcohol solution is not only increased by as much as twofold, but the preference shift persists for a month (47). That the tryptophan enhancement of alcohol drinking is contingent upon the amount of the amino acid added to the diet has been documented (48); however, the magnitude of alcohol consumption depends entirely upon the strain of rat tested. On the one hand, a rat of the Royal Victoria strain shows the same augmented drinking (48) as an animal of the Charles River strain (47); conversely, a Sprague-Dawley animal does not respond to excess tryptophan in terms of alcohol selection. This finding suggests that a basic genetic difference exists in the pathway underlying the metabolism of essential amino acids which in this case, may be a principal determinant of the acceptance or rejection of alcohol. Of course, an alcohol-related reduction in plasma tryptophan would presumably bring about a change in the level of 5-HT in the brain, but not alter the level of the other amines (49).

A potentially powerful diagnostic tool for alcoholism, which is based on a blood amino acid profile has been announced. Shaw et al (50) indicate that the ratio of α-amino-n-butyric acid to leucine is elevated not only in the plasma of the well-nourished or undernourished alcoholic, but also in the blood of the baboon that is forced to consume alcohol. Since this amino acid ratio correlates positively with the degree of alcoholism, as determined clinically, the ratio value could become an objective, empirical marker for the detection and quantitative assessment of the disease and its progression. In this connection, the brain-plasma ratio of α-aminoisobutyric acid declines in the mouse on acute treatment with alcohol, but is not changed following chronic ingestion for four months (51).

A glandular factor in the brain, involved in diurnal cyclicity, is also implicated in the mechanism underlying a rat's drinking of alcohol which occurs principally during the hours of darkness (52, 53). The systemic administration of melatonin, the principal secretory hormone of the pineal gland, can cause the rat to increase its intake of 4% alcohol (54). If the pineal gland is surgically removed in the congenitally blind rat, which drinks a considerable amount of 5% alcohol, the onset

of an enhanced preference for alcohol is delayed (55). In a species with a manifestly high preference for alcohol, the Syrian hamster, pinealectomy lowers its preference for 5% alcohol. Similarly, pinealectomy, which results in a reduced melatonin content, exerts the same effect in the rat kept in the dark (56, 57). A report by Burke & Kramer contradicting the involvement of melatonin is based upon their observation that the removal of the pineal gland has no influence on the rat's natural preference for alcohol; however, a subcutaneous injection of melatonin given repeatedly over 7 weeks did augment the intake of alcohol when the fluid was offered to the rat in a 4% concentration (58). Although methodological differences (see Footnote 1) and other factors (59) could contribute to this unusual discrepancy, the possible role of the pineal hormone in alcohol selection has yet to be elucidated.

BIOGENIC AMINES IN THE CENTRAL NERVOUS SYSTEM

Ever since it was reported in 1968 that a compound that lowers the content of serotonin (5-HT) in the brain, *p*-chlorophenylalanine (pCPA), influences an animal's preference for alcohol (60), a number of investigators have sought to determine the relationship between monoamines in the brain and the behavior of alcohol drinking. Many of these studies have been evaluated and reviewed recently (18, 61, 62). As would be expected, when administered to the rat or mouse, alcohol does cause a wide variety of changes in the content, metabolism, and turnover of 5-HT in the brain (63–66) and in 5-HIAA transport (67). Although the reduction of 5-HT levels in the brain does not affect the withdrawal from alcohol (68, 69) the blockade of 5-HT receptors enhances withdrawal-related convulsions (70). When dependence on alcohol is artificially induced, the content of monoamines rises in the brain (71), whereas their metabolites are affected differentially (72).

Serotonergic Mechanisms

A brief overview of many of the results obtained when an animal is offered a choice of alcohol and water indicates that pCPA, administered to seven different strains of laboratory rat in doses of 75 to 316 mg per kg, produces an aversion to alcohol under nearly every experimental condition (*a*) while the drug is administered intragastrically or intraperitoneally throughout an actual preference test, (*b*) following the discontinuation of pCPA administration, or (*c*) under both of these experimental conditions (73–78). In relation to the human situation is the observation that a baboon which has learned to prefer and drink large quantitites of a 30% solution of alcohol in fruit juice reduces its intake significantly following the systemic treatment with pCPA in a dose of 40 mg/kg twice a day (79). Other compounds that also reduce cerebral and peripheral 5-HT content possess the same sort of action in diminishing alcohol drinking (80–82). An exception to the ameliorative effect of pCPA on alcohol selection is reported for the rat given eight concentrations of alcohol from 3 to 25%, as well as in the mouse given a single test solution of 10% alcohol (83, 84). The precise reason for the discrepancy is not readily apparent.

The possibility that pCPA elicits learned aversion to alcohol through a conditioning of the noxious aftereffects associated with the drinking of the fluid has received support in several experiments (85–87), but not in others (76, 77, 88, 89). Nevertheless, since pCPA readily causes a conditioned aversion to another fluid such as saccharin, it is not unreasonable to deduce that a part of pCPA's pharmacological action on alcohol preference is due to an aversive conditioning to the drug itself (86).

If a drug given systematically exerts its action primarily through a peripheral mechanism, the reactivity of the CNS to the drug may well be overridden. For this reason, the way that pCPA acts has recently been questioned (18). Jofre de Breyer (90) reports that the principal effect of pCPA is on the liver and perhaps on other peripheral organs, because pCPA causes a systemic buildup of acetaldehyde when alcohol is present in the circulation. As a result, an animal of necessity would refrain from consuming alcohol in order to prevent the toxic side effects of accumulating acetaldehyde. Accordingly, pCPA most likely causes three temporally related responses that alter the alcohol selection of an animal: (*a*) a rebound increase in the synaptic activity of 5-HT; (*b*) a short-term accumulation of trace amounts of acetaldehyde if alcohol is consumed; and (*c*) a learned aversion that may or may not be related to the first two changes (18).

To overcome some of the interpretive difficulties often inherent in results obtained when the systemic route of drug administration is employed, several investigators have used substances which, when injected directly into the cerebral ventricle, lesion 5-HT pathways. Initially, Ho and his co-workers infused 5,6-dihydroxytryptamine (5,6-DHT) intracisternally in the Sprague-Dawley rat offered a single solution of alcohol and water. This 5-HT neurotoxin significantly enhances the intake of alcohol for several days but does not alter the preference-aversion characteristics for a quinine solution (91). In the same strain of rat, the acute injection of 5,6-DHT into the lateral cerebral ventricle equally elevates the rats' preference for alcohol solutions ranging in concentration from 3–30% and offered over a 12-day test period (92). In addition, a somewhat more selective 5-HT lesioning agent, 5,7-dihydroxytryptamine (5,7-DHT), also augments alcohol drinking under the same test conditions. However, these effects of cerebral serotonin depletion are genetically dependent and determined entirely by the strain of animal tested with rats of the Wistar strain being unaffected (93).

Opposite to these findings is the report that an intraventricular injection of 5,6-DHT given similarly has no effect on alcohol intake even though the reduction in 5-HT content in the brain was approximately 30% (78). Moreover, a lesion to midbrain raphe nuclei, which reduces the forebrain content of 5-HT by as much as 69%, also does not alter the intake of a single 10% alcohol solution by the same strain (94). In this experiment, the test animal was a highly outbred rat of the ALKO strain selected especially for its elevated intake of 10% alcohol. Thus, a genetic difference could account for this apparent disparity.

In contrast to the effect of lowering the level of 5-HT in the brain, an artificial elevation of the indoleamine in this structure generally causes a different effect on alcohol selection. When the metabolic precursor of 5-HT, 5-hydroxytryptophan

(5-HTP), is injected intraperitoneally, alcohol drinking is significantly reduced either during the administration of 5-HTP or for several months thereafter (74, 76, 95). In direct agreement with the notion that the precursor could be acting centrally, it is also clear that the infusion of either 5-HTP or 5-HT directly into the cerebral ventricle of the rat reduces alcohol consumption substantially while water intake is unchanged (76, 96).

In assessing the overall role of cerebral 5-HT in alcohol drinking, the predominant effect of tryptophan and pCPA could be on peripheral systems with their central action being only secondary or nonexistent (18). This interpretation would coincide with the idea that excessive metabolism, synthesis, or presynaptic release of 5-HT within the brain would have the net effect of attenuating alcohol imbibition. On the other hand, a synaptic insufficiency of available 5-HT, at least in some structures of the CNS, would have the opposite action and induce the consumption of abnormal volumes of alcohol (18). Unfortunately, this viewpoint cannot be adopted without being tempered by considerations of both the species and strain of animal used, upon which the idea has evolved and is now based. Even so, some sort of defect in 5-HT metabolism, or activity at the nerve ending, could be related to one of the causal factors in the disease of alcoholism.

Indeed, the present evidence, albeit scant, is somewhat promising. For example, Ahtee & Eriksson find a higher content of 5-HT and 5-HIAA in the brain of an alcohol preferring rat than in that of a nonpreferring animal. What is more, prolonged exposure to alcohol exacerbates this difference (97). A similar relationship may also exist for the mouse (98), but in one genetic study, even this has not held (99). Morphologically, the greatest elevations in 5-HT activity occur in the hypothalamus, thalamus, and midbrain of the alcohol drinking rat (100). Hence, this indoleamine or one of its metabolites (see below) may play an active part in the development of aberrant alcohol drinking and its associated pathology.

Catecholaminergic Mechanisms

A large literature surrounds the effect of alcohol on the metabolic activity and other properties of catecholamine-containing regions of the brain (101–104). For example, the acute treatment with alcohol or its chronic ingestion can cause a substantial change in the turnover of norepinephrine or dopamine in the brain (105–108). It is also known that the locomotor excitation caused by alcohol (109) can be modified by substances that affect the level of central catecholamines (110, 111). Further, dopamine and norepinephrine have been implicated in the symptoms of dependence and withdrawal following alcohol administration (112–122). When an animal is treated with alcohol, both the in vitro release of ^{3}H-NE from synaptosomal particles (123) and the regional activity of dopaminergic neurons, particularly in the rat's neostriatum (124), are differentially affected.

Attempts to lower the concentration of cerebral catecholamines pharmacologically have been made by several investigators, who determined how such a change would affect the natural selection of alcohol in the mouse or rat. In 1968, it was

shown that α-methyl-*p*-tyrosine (aMpT), given orally during a preference test, exerts a short-lived action on alcohol selection (60). Even though the tyrosine hydroxylase inhibitor reduces cerebral catecholamine levels considerably, the alcohol drinking of the rat, offered a wide range of concentrations, declines only transiently.

A more direct approach is the lesioning of the catecholaminergic pathways in the brain by an intraventricular infusion of 6-hydroxydopamine (6-OHDA). Following an acute injection in the rat of the Sprague-Dawley strain, the catecholaminergic neurotoxin considerably lowers the preference and total intake of alcohol solutions presented in a wide range of concentrations (92). Again however, this action of 6-OHDA is strain dependent. Although rats of the Long-Evans strain exhibit this diminished preference for alcohol, animals of the Holtzman and Wistar strains show no effect of 6-OHDA (93).

If 6-OHDA is microinjected directly into the dorsal noradrenergic bundle so as to deplete forebrain norepinephrine, the self-selection of a 10% alcohol solution of ALKO "alcohol addicted" rats is enhanced identically with that of the Sprague-Dawley animal (94). Moreover, the high absolute intake of alcohol, as well as the preference, persists for up to 3 to 6 weeks following the 6-OHDA microinjection. This finding gives rise to the suggestion that a part of the postulated noradrenergic or dopaminergic reward mechanism may be impaired in such a way that compensatory drinking of alcohol ensues (125).

In relation to the proposed involvement of the catecholamines in alcohol drinking, drugs have been examined that inhibit the in vivo activity of dopamine-β-hydroxylase (DBH), the enzyme that converts dopamine to norepinephrine. In one series of studies, Amit and his colleagues demonstrated convincingly that the inhibition of DBH by compounds such as disulfiram or FLA-63 sharply suppresses the ingestion of alcohol offered to Wistar rats in the 6 to 30% range of concentrations (126, 127). In a parallel study Amit et al have further documented a concomitant reduction in morphine self-selection after FLA-63 administration (128), which, in itself, implies a fascinating relationship between the mechanisms underlying the self-administration of these two addictive compounds.

Of special promise is a clinical study done by Ewing and his co-workers who find that plasma DBH activity in the human does correlate with the mood state during alcohol drinking (129). Volunteer subjects with high plasma levels of DBH drink more alcohol, manifest a higher level of blood alcohol, feel better, are less drunk, and are not as sick following a drinking bout (129). Therefore, the intrinsic ratio between dopamine and norepinephrine in the neurons within the limbic forebrain pathways, may be just as important to the etiology of alcohol selection, and its consequent effects, as the synthesis, release or turnover of the two catecholamines (130). In both the rat and human, propranolol, which antagonizes β-adrenergic receptors, significantly enhances the pharmacological effects of alcohol (131, 132); however, because of the extremely intricate nature of the dose-response relationship, some caution should be exercised in respect to a simple interpretation of an adrenergic mechanism that mediates the intoxicating effect of alcohol (132).

DRUGS AND ALCOHOL DRINKING

A general theory of addiction proposed by Nichols (133) implies that a common biological mechanism engenders the susceptibility to an opiate alkaloid and alcohol. Along with a presumed genetic proneness, a modicum of evidence for such a commonality in the CNS is just now beginning to accumulate (134). For instance, Ross and co-workers have shown that both morphine and alcohol administered systemically to the rat lower the in vivo level of calcium in different regions of the brain (135). The effect on the cation is antagonized by the stereospecific narcotic antagonist, naloxone (135). Even though the clinical symptoms of alcohol and morphine usage are not necessarily identical with respect to the nature of withdrawal, cross-dependence, or tolerance, it is well-known that the patient addicted to a narcotic may have had a history of alcohol drinking to abuse or may substitute alcohol for a preferred opiate when the latter is not available.

A Link Between Morphine and Alcohol?

Experimentally, Sinclair et al have demonstrated that morphine, if given in a 60 mg/kg dose to a rat that drinks alcohol, markedly suppresses the animal's intake of a 10% solution of the fluid (136). This ameliorative effect of morphine is manifest whether the animal is given free access to alcohol for one day or one month (137). Furthermore, in the hamster that consistently prefers a 10% alcohol solution over water, the administration of morphine reduces the intake of alcohol to near zero volumes, whereas levorphanol, the analgesically active isomer, reduces alcohol consumption but only by about one half (138). A single dose of either compound exerts this effect for about one day. Of significance to the mechanism of action is the finding that a similar treatment with naltrexone, the long-acting narcotic antagonist which is thought to bind to the opiate receptors stereochemically, has the opposite effect on the drinking hamster and increases its voluntary alcohol consumption (138).

When morphine is injected acutely in the alcohol-preferring C57BL mouse, a similar sort of suppression of preference for the fluid occurs (139). In addition, morphine-treated rats undergoing withdrawal and given the free choice between a sucrose solution and one mixed with alcohol exhibit an intense preference for the latter solution at least in the 5 to 11% range of concentrations (139). Given acutely, a single injection of methadone, levorphanol, or L-α-acetylmethadol produces a similar sort of suppression of voluntary alcohol intake (139). During the forced drinking of alcohol following pretreatment with morphine, the rat shows abstinence signs that are far more severe than without morphine; this suggests that a narcotic exacerbates the degree of physical dependence on alcohol (139).

In spite of the striking experimental relationship between these two classes of compound, Gelfand & Amit (140) report that a rat that prefers and drinks a saccharine-adulterated solution of morphine is not affected by an intraperitoneal injection of 4 ml/kg of 20% alcohol in terms of lessening the intake of morphine. However, as pointed out by these authors, the length of exposure to morphine, the extent of physical dependence, or other factors could account for this result. With

respect to a generalization to other addictive compounds, Rondeau et al (141) find that the alcohol intake of a rat offered a 3 or 7% solution every third day is affected by the subcutaneous injection of phenobarbital. Although alcohol consumption can increase on the day of the barbiturate injection, the main response is a decline in the ingestion of the fluid on subsequent days. Whether the barbiturate possesses a specificity to opiate or other receptors in the brain, or induces a conditioned aversion to alcohol, are questions for further research.

Lithium and Other Compounds

Clinical therapeutics has been a major determinant of the direction in which laboratory research with animals has moved. The alcoholic patient undergoing lithium therapy shows a considerably reduced readmission rate for treatment of the drinking problem and a concomitantly lower incidence of disabling drinking episodes (142). In addition, if the chronic alcoholic patient is experiencing mild withdrawal, the oral administration of lithium every 8 hr helps to ameliorate the subjective symptoms of discomfort and may even serve to normalize the performance of the individual on a motor tracking task (143).

In the laboratory, the results are often as remarkable. Regardless of whether lithium is added to the rat's food or injected systemically, the volume of alcohol taken by an animal of the ALKO "alcohol addicted" strain is much less not only during a 30-day course of lithium treatment but in an equivalent period thereafter (144). In the nonalcohol preferring Sprague-Dawley rat offered concentrations of 4, 5, and 11% alcohol, lithium injected intraperitoneally twice a day causes a similar sort of reduction in alcohol imbibition (145); however, drinking resumes within two days after the discontinuation of the lithium regimen. In agreement with these findings, the content of ACh in the brain is significantly lower than normal during the days of lithium treatment; this is compatible with the supposition that a central cholinergic mechanism is related to the magnitude of an animal's preference for alcohol (146).

Although the amount of alcohol ingested is also less when lithium is administered to the rat which is forced to drink the fluid, the cation seems to exacerbate the symptoms of withdrawal in the alcohol-dependent laboratory rat (147). Therefore, additional investigations to determine the relationship between lithium treatment, alcohol toxicity, and the development of tolerance or dependence on this fluid will certainly be indispensable. In fact, depending upon the dose injected, lithium may have no effect whatsoever on an animal's overall intake in grams of alcohol or on the preference for the solution (148). Because of other inconsistencies in experiments with this cation, future research on lithium should be undertaken with great care and punctilious experimental control, particularly if it is to have a bearing upon the promising clinical trials that employ lithium therapy in the treatment of alcoholism (149).

Many other drugs including the β-receptor blocker, propranolol, have been judged as beneficial in the treatment of tension and other clinical symptoms displayed by the chronic alcoholic (150). Similarly, numerous compounds alter the self-selection of alcohol in a free-choice situation. To illustrate, the treatment of the

C57BL mouse with indole-imidazoline reduces its volitional intake of 10% alcohol (151). In a squirrel monkey maintained on a psychogenic polydipsia regimen so that it consumes large quantities of 3% alcohol, chlordiazepoxide injected intramuscularly in several doses raises the intake of this alcohol solution even further (152).

Alkaline metal salts other than lithium have also been investigated. Both cesium chloride and rubidium chloride, given systemically, lower the alcohol consumption of the Sprague-Dawley rat that drinks 5% alcohol instead of water (153). Although neither compound exerts a noteworthy effect on liver ADH or AldDH, cesium is the more potent of the two monovalent cations in reducing alcohol intake (153). Even the principal pharmacological ingredient of coffee has not escaped scrutiny. In respect to its efficacy on the drinking of the rat of an alcohol preferring strain, caffeine given intraperitoneally in doses of 2 to 32 mg/kg causes a dose-dependent rejection of alcohol, regardless of the sex of the animal (154).

Thus, it appears that cations, several drugs of modest molecular weight, and other substances that affect neuronal processes in the brain all possess the capacity for modifying alcohol drinking in one direction or the other. Although certain experimental discrepancies punctuate the literature, the need to acquire more information about the interactions of a drug or other chemical with endogenous neurohumoral factors is now more apparent than ever before.

BEHAVIORAL AND PHYSIOLOGICAL CHANGES INDUCED BY ALCOHOL

Over and above its important behavioral effect on the CNS in inducing a conditioned taste aversion (155–157), alcohol has been used as a discriminative cue for the learning of an avoidance task (158). In such an experiment, a drug such as pCPA or amphetamine can interfere with a conditioned discrimination acquired under the alcohol drug state (158, 159).

For years it has been known that alcohol can impair learning and may interfere with the performance of a given task (1, 21), but only recently have quantitative determinations of such behavioral deficits been elucidated. Freund & Walker find that the learning of an avoidance response by a mouse is severely disturbed by the continued and excessive intake of alcohol (160). Correspondingly, the rat's proficient ability of timing its behavior is equally damaged by prolonged alcohol consumption (161); also, the retrograde amnesia for an avoidance response is likewise lost (162). The C57BL mouse maintained on a palatable liquid diet containing alcohol has difficulty in retaining a simple conditioned response to foot shock (163). Further, if a rat drinks a comparable diet for a long interval, a substantial decrement is evident in the animal's problem-solving ability as tested in a Hebb-Williams maze (164). Equally interesting is the fact that an early exposure of the infant rat to alcohol or the intermittent inhalation of alcohol vapor by the postweanling rat interferes with the learning of a specific task (165, 166)

The typical deficits in motor performance including incoordination following systemic doses of alcohol can be altered by drugs such as pyrazole (167). After a very low dose of alcohol is given, behavioral arousal as reflected by increased motor

activity is seen. This response is altered by antagonists of catecholaminergic receptors (168) or by GABA-like drugs administered systemically (169). That the cerebellum is the principal structure involved in the well-known symptoms of ataxia produced by alcohol seems clear. In the specially bred C3H mouse, which suffers from a morphological deficiency in cerebellar Purkinje cells, alcohol administered systemically has a much more profound effect on the locomotor incapacitation of the mouse in terms of grid walking, its grasping of a tilting edge, and positioning itself on a rotating rod (170). An important point is that the exposure of an infant rat to alcohol vapor produces a striking pathological loss in the number of Purkinje cells (171); this is indicative of the uncommon vulnerability, early in life, of the cerebellar neurons to alcohol.

Investigations of the acute effect of alcohol on physiological systems are currently under way as well. For example, it has been shown that a dose of only 1.0 g/kg attenuates the frequency and amplitude of the spontaneous electrical activity as well as the evoked responses from the mesencephalic reticular formation and auditory cortex of the cat (172). Klemm and his colleagues have undertaken a number of studies in the rabbit and rat that reveal that a small population of neurons in the neocortex, cerebellum, and limbic forebrain region is exceptionally sensitive to miniscule doses of alcohol, as low as 150 mg/kg (173, 174). Supplementing the finding that EEG and multiple-unit activity exhibit specific regional differences following an alcohol challenge, Klemm et al have also revealed that the Θ rhythm in the hippocampus shifts as a function of the dose of the alcohol that is administered (175).

Deutsch & Walton (176) have devised a new method whereby the effect of alcohol is examined in a volitional situation without the animal's drinking the fluid. In their design, the rat self-intubates itself intragastrically by licking a palatable solution. After three weeks, the rat on such a regimen prefers alcohol over water in a free-choice situation, possibly to alleviate withdrawal symptoms.

Psychogenic Polydipsia

Frequently referred to as psychogenic polydipsia, the phenomenon of schedule-induced drinking, discovered by Falk in the early 1960s, is today one of the most valuable behavioral techniques for inducing physical dependence on alcohol (177). Generally, a rat or other animal is placed on a feeding schedule whereby a pellet of food is delivered only intermittently; during this period, the animal turns to the drinking spout protruding into its cage and ingests whatever fluid is present. If alcohol is available in the drinking tube, in a sufficiently palatable concentration, the fluid can take on a positively reinforcing quality (178).

Recently, the methods for utilizing schedule-induced drinking, the characteristics of the induced tolerance, animal models of dependence, and other aspects of alcohol polydipsia have been exhaustively reviewed by Falk and other authors (179–181). In these excellent treatises, the trenchant interpretations of the research findings to date are presented as well as the cautions that are necessarily required in undertaking alcohol studies employing the schedule-induced phenomenon.

Amine Metabolite Theory

Both in vivo and in vitro, acetaldehyde, the highly reactive metabolite of alcohol can condense with a catecholamine to form a compound known as a tetrahydroisoquinoline (TIQ) (182–184). Similarly, an indoleamine such as 5-HT may form a tetrahydro-β-carboline (TBC) by virtue of the same sort of condensation reaction with an aldehyde, both in vivo and in vitro (185). Since a TIQ alkaloid can be a precursor to morphine in a plant i.e. the opium poppy, an acetaldehyde derivative or its opiate by-product has been postulated to be a possible endogenously active factor in the development of alcoholism (182, 183). Because a TBC is chemically similar to a hallucinogen, a 5-HT-acetaldehyde derivative might also play a role in alcohol dependence (185). Of special theoretical significance is the finding that a TIQ can actually be formed in vivo in the laboratory animal or human after alcohol is administered (186–188). It is known that a TBC is also capable of being synthesized in the brain (189–192).

Ever since 1910, when Laidlaw demonstrated that one of the TIQs, tetrahydropapaveroline (THP), possesses a marked depressor effect on its intravenous infusion (193), several condensation products have been found to evoke a wide variety of autonomic responses both centrally and peripherally (194–196). In conjunction with the problem of alcohol, a TIQ can prolong the period of alcohol-induced sleep in mice (197, 198) or markedly intensify a convulsive episode during withdrawal in the mouse exposed to alcohol for three days (199). In a rat of the Sprague-Dawley strain offered 4 or 6% alcohol, the acute administration of one of several structurally related β-carbolines produces a precipitous fall in the intake of alcohol (200, 201). Again, if the TBC is injected intraperitoneally once a day over several days, the suppression of alcohol consumption is clear-cut (95).

In a recent series of experiments, the CNS portion of the amine-metabolite theory has been tested directly. In order to simulate the chronicity of a condensation product's presumed action within the brain during the prolonged ingestion of alcohol (202), THP has been infused around-the-clock into the cerebral ventricle of the rat. When animals of the nonalcohol drinking Sprague-Dawley strain are offered alcohol and water in a free-choice paradigm, as THP is infused every 30 min in a dose as low as 100 pg/μl, the rat's volitional intake of 3–9% alcohol suddenly rises (203). Surprisingly, when the solution of alcohol is systematically increased in strength to aversive concentrations ranging from 11–30%, the THP-infused rats drink even more alcohol—as much as 13 to 16 g/kg on a given day. Marked ataxia, an elevated blood alcohol level, and other intoxication-like symptoms characterize this unusual drinking (204). If the intracerebral applications of THP are cut back to a once per day infusion, thereby reducing drastically the total dose of the TIQ to which the brain is exposed, the rat's normal aversion to alcohol nevertheless disappears. Again, a marked preference develops for the fluid (205), with the rat voluntarily consuming up to 10 g/kg per day of alcohol in concentrations of 15 or 20%.

With regard to the generality of the effect of an amine metabolite on the brain, only certain TIQs exert the alcohol-inducing response (206). However, one of the

β-carbolines, noreleagnine (tryptoline) evokes intense alcohol drinking when the TBC is delivered directly into the cerebral ventricle of the rat by means of the chronic infusion procedure (206, 207).

Overall, the studies on the in vivo formation of amine condensation products, together with their profound pharmacological effect directly on cerebral tissue, provide some suggestive evidence for their role in the addictive liability to alcohol. Research is now required to determine whether picomolar quantities of the metabolites are formed or sequestered within given structures of the brain (202). The neuroanatomical identification of the structure or region within which these alkaloid conjugates act to evoke alcohol drinking is an additional puzzlement. Also, information is essential on the cellular or subcellular processes by which the amine metabolite functions, e.g. through an effect on transmitter release (202) or perhaps on an opiate receptor mechanism in the brain (208, 209).

CONCLUSION

The experimental emphasis on the relationship of alcohol to the functional activity of the monoamine-containing pathways in the CNS has been overwhelming in the past 10 years. Notwithstanding the continued need for intensive research on monoamines, the mechanisms involving the central action of dopamine, norepinephrine, 5-HT, and their metabolites may only constitute a fraction of the perplexing neurochemical activity in the brain which underlies aberrant drinking behavior. When this fluid is administered acutely or taken chronically, a myriad of changes occur in other transmitter and humoral systems in the brain. A few examples are taken from the literature to illustrate this point.

The in vivo and in vitro release of acetylcholine (ACh) from the cerebral cortex and other areas of the brain, in either the anesthetized or conscious animal, is markedly suppressed by alcohol given systemically (212–215). In the alcohol-dependent rat which is undergoing withdrawal symptoms, the levels of ACh are reduced significantly in the brain-stem, hippocampus, and caudate nucleus (216). Further, in the C57BL mouse, the specific inhibition of choline transferase by an injection of 4-(1-naphthyl-vinyl)-pyridine shifts this animal's normal preference for alcohol to water (217). In this connection, the cerebral content of acetylcholinesterase is higher in the alcohol nonpreferring DBA mouse (217). Nevertheless, drugs that modify cholinergic transmission in the CNS do not necessarily ameliorate the behavioral depression of the rat given alcohol orally (218).

In a rat treated with alcohol acutely or chronically an increase in ATPase activity is seen in brain synaptosomes (219), but at the same time, ATP and creatinine phosphate levels in the brain decline (220). In the volunteer alcoholic recruited from a detoxification program or rehabilitation ward, the level of cyclic AMP is lower in a cerebrospinal fluid sample collected after the patient ingests a dose of 3 gm/kg of grain alcohol mixed with fruit juice (221).

Amino acids are equally affected by alcohol in that the administration of the fluid inhibits the incorporation of leucine into brain proteins (222). A most striking change is seen in the sharp elevation in the level of γ-aminobutyric acid (GABA)

in the brain of the rat or mouse following acute or chronic alcohol treatment and withdrawal (223, 225, 226); a concomitant decline is seen in the enzymatic activity in the cerebellum and cerebral hemispheres of glutamic acid decarboxylase (GAD) (223).

Along with amino acids, polypeptides may also be involved in alcohol's effects. For instance, angiotensin induces alcohol drinking when injected directly into the septum pellucidum of the rat (224). If applied onto neurons in the rat's hypothalamus by iontophoresis, angiotensin can synergize with either alcohol or sodium ions to produce a dramatic effect on the nerve cell membrane (227, 228). The chronic ingestion of alcohol in the mouse or rat profoundly inhibits cerebral polypeptide synthesis as well as the production of various fragments of RNA. Alcohol also decreases the amount of incorporation of radiolabeled precursor into the RNA of free polysomes and may even interfere with the synthesis of messenger RNA (229, 230).

Finally, alcoholism is a staggering health problem, worldwide. The sociopsychological aspects of the disease continue to be extensively studied. However, the understanding of those CNS mechanisms that sustain abnormal drinking once begun, and that are permanently shifted neurochemically, is just in its infancy (210). The development of new pharmacological adjuncts to psychotherapy is contingent ultimately upon special knowledge about the metabolic features of the brain, transmitter and other cerebral systems as they are related to the actual drinking of an alcohol-containing fluid (211). With a concerted interdisciplinary exchange between psychopharmacologists, neurochemists, neuroanatomists, and other scientists, an insight into a potentially efficacious class of compounds that may reverse the addictive state will eventually evolve. Clearly as the interchange expands, much research "gold" in this difficult field will be mined at this interface.[2]

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[2]Apologies are given here to all of the researchers whose classical work has provided the historical underpinning upon which most of the current experimental papers are based. Because of space limitations, only some of the current representative papers in this field, of the more than 1000 reviewed, could be cited.

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