Alcohol and Opiates: A Review of Common Neurochemical and Behavioral Mechanisms

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Introduction

Among drugs of abuse, none have achieved such wide popularity as ethanol and opiate derivatives. Although these drugs are consumed by a large segment of our population, many consequences of acute and chronic intoxication with alcohol and opiates are not readily understood.

Alcohol, on one hand, is a central nervous system depressant, as are the opiates, but differs from them in that it is a nutrient whose rapid oxidation in the liver causes marked disruption of normal metabolic processes. There are differences between these two commonly abused drugs when chronically consumed: alcohol is more cytotoxic than opiates and potentially more dangerous when abruptly removed. Other differences include effects on the autonomic nervous system, electrical activity of certain pathways in the brain, and antinociceptive response (1,2).

The widespread abuse of opiates and ethanol in modern society has resulted in tremendous scientific investigation into the mechanisms of action of these two diverse classes of drugs. Although it is well known that one drug is often associated with concurrent abuse of the other (3-7), there has been little effort devoted to establishing a common underlying biochemical mechanism between the two. This is not surprising, as it is difficult to envisage the biochemical, physiological or metabolic pathways that complex phenanthrene-type alkaloids would have in common with a simple 2-carbon molecule.

In this chapter we shall attempt to evaluate the "state of the art" concerning a biochemical link between opiates and ethanol. Thus, we will deal with behavioral and neurochemical similarities and finally an evaluation of the possible role of tetrahydroisoquinoline (TIQ) alkaloids in modulating these effects.

The results that follow demonstrate the numerous attempts have been made to define the locus of the behavioral and the tolerance- and dependence-producing properties of opiates and ethanol. However, caution must be used in interpreting these results because of the complex interrelationships among various neural elements and their respective neurotransmitters. Thus,
while a particular agent is considered to affect only one system, and while biochemically that may indeed be true, the loss (or increase) of that specific system may inhibit or excite several others. Nevertheless, studies of this nature are extremely important in elucidating not only the neurochemical and behavioral mechanisms of opiates and ethanol, but also in unravelling the complex interrelationships that exist in the nervous system.

**BEHAVIORAL SIMILARITIES**

Opiate-Ethanol Interaction Studies

There is considerable evidence in the literature indicating a relationship between opiates and ethanol. There are reports of acute interactions between these substances in both humans (8) and experimental animals (9,10). Sinclair (11) has shown that morphine suppresses voluntary alcohol consumption (VAC) in hamsters and Ho et al. (12) have demonstrated that a single injection of an opiate agonist significantly suppresses AC in both mice and rats. Ross et al. (13) have reported the same effects in hamsters and have also shown that dextrophan had no significant effect on alcohol consumption indicating the necessity for an active opiate enantiomer.

In another study (14), single injections of naloxone or naltrexone produced a slight but non-significant increase in VAC in hamsters six to eight days following a single injection of 2.5 or 5 mg/kg naltrexone. It is difficult to understand the delay in the response after the injection of opiate antagonist, as the half-life of the drug is considerably shorter than six to eight days. Nonetheless, the effect is reproducible and may relate to heretofore unappreciated pharmacological aspects of the drug.

Chronic administration of morphine to adult rats for fourteen days produces an increase in VAC during morphine withdrawal (11). Similar results were obtained during withdrawal with neonatal rats treated with morphine for forty-four days. Further evidence for a relationship between ethanol and the opiates has been obtained through the use of the narcotic antagonists naltrexone and naloxone to ethanol-dependent animals. It is well recognized that both of these drugs are capable of blocking the acute effects of opiate agonist and the development of tolerance and dependence to opiates (15). The first experiments with narcotic antagonists in ethanol-dependent animals
showed that administration of naloxone to ethanol-dependent mice did not precipitate jumping behavior, as it does in opiate dependent mice (16). However, recent experiments (17) show that concurrent administration of naloxone during ethanol-vapor exposure significantly attenuates the resultant withdrawal convulsions. As well, naloxone or naltrexone at 5 mg/kg can inhibit ethanol narcosis in mice, while higher doses of the narcotic antagonists (10 mg/kg) potentiate the narcosis (18).

Additionally, Blum et al. (19) have shown that the ethanol-withdrawal syndrome in mice is significantly suppressed by a single injection of 10 mg/kg morphine at the fifth hour post-ethanol exposure. Jones and Spratto (20) have recently demonstrated that concurrent administration of ethanol can affect morphine withdrawal in rats, and Uyeno (21) has observed that withdrawal of ethanol after chronic administration increases morphine self-administration in monkeys.

CONCLUSION

While these studies indicate that there may be similarities between opiates and ethanol as far as behavioral parameters are concerned, there is no evidence that the same, or even similar, mechanisms are involved. The following sections will discuss the effects of intoxication caused by alcohol and opiates on basic neurochemical organization in the CNS and, also, the effect of prior manipulation of endogenous neurohumoral amines on the behavioral consequences of administration of these agents.

NEUROCHEMICAL SIMILARITIES

Both opiates and ethanol produce alterations in neuroamine metabolism and concentrations. These effects occur after acute administration, during chronic administration and also during the withdrawal phase.

Norepinephrine (NE)
Morphine has been shown to decrease (22,23), increase (24), or have no effect (25) on NE concentrations. Similar results have been reported for ethanol, that is, decreases (26), increases (27), or no effect (28). The conflicting results obtained concerning NE concentrations may reflect differences in the sensitivity of the techniques employed, the timing of NE measurement, the doses or the species and thus prevent any definite conclusions regarding similarities between opiates and ethanol after acute administration.

Although the effect of an acute dose of ethanol on NE is uncertain, there is general agreement that during chronic administration ethanol induces an increase in NE turnover (29-32) and concentration (32). This same effect is also evident in chronically morphinized rats (24,33,34), although no effect on NE was observed in morphinized dogs (35).

During withdrawal from chronically administered opiates, NE levels have been reported to decrease in dogs and rabbits (23,33,35), while there is no apparent change in the NE levels in rats subjected to either abrupt or precipitated (nalorphine) withdrawal (33,36). Withdrawal from ethanol generally produces an increase in NE turnover in rats (32) and mice (37). In rats, the increase in NE turnover is maintained even when withdrawal signs are no longer evident (32).

Dopamine (DPA)

There is considerably less information concerning the effects of opiates and ethanol on dopamine (DPA) concentration and metabolism than that pertaining to NE.

Nonetheless, acute injections of 20 mg/kg morphine to mice has been shown to decrease DPA levels (22) and this depletion is blocked by naloxone. However, another report (38) indicates that 40 mg/kg morphine had no effect on DPA levels in mice. Similar results, that is decreases (39) or no change (30) in DPA levels have been reported following acute ethanol administration.

Chronic administration of morphine increases DPA turnover in rats (25) and chronic ethanol produces increases (30), decreases (33,35), or no effect (40) on DPA turnover, whereas central DPA concentrations after chronic administration of ethanol are reported to be unaffected (30,40). While withdrawal of opiates from dependent rats (33,41) and dogs (35) produces decreases in DPA concentrations little information on the effect of ethanol withdrawal on DPA concentration is presently available from animal studies. However, Gitlow et al. (42) reported
elevated excretions of the DPA catabolites homovanillic acid (TVA) and 3-methoxy-tyramine (3-MT) in human subjects withdrawing from ethanol. These results suggest that ethanol modifies the metabolism of DPA under these experimental conditions.

5-hydroxytryptamine (5-HT)

Acute administration of opiates increases (43), decreases (44) or have no effect (45) on 5-HT concentrations. Similar results have been reported after acute ethanol injections (26,44,46). Chronic morphinization has no effect (47) on 5-HT concentrations and chronic ethanol administration has not been found to affect 5-HT levels (48). The results obtained during withdrawal from opiates or ethanol are similarly contradictory with increases (37), decreases (37,49), and no effect on 5-HT concentrations (23,44,49,50).

Gamma-Aminobutyric Acid (GABA)

Attempts have been made to correlate the actions of morphine with alterations of content and/or metabolism on yaminobutyric acid (GABA), a putative inhibitory neurotransmitter in the central nervous system. Ho et al. (51) demonstrated that administration of GABA enhances the development of morphine tolerance and dependence in mice and Yoneda et al. (52) found that GABA may be involved in morphine analgesia, although single injections of morphine do not affect brain GABA content in rodents (52,53). However, based on the work of Yoneda et al. (52), functional alterations of the GABA system in the CNS may also be an important factor for the occurrence of both acute and chronic actions of morphine.

GABA and ethanol possess anticonvulsant properties (54) and thus a number of investigators have attempted to establish a relationship between these two compounds (55).

Ethanol, unlike morphine, was reported to increase GABA levels in rat brain in vivo (56). Ethanol-induced elevation of brain GABA, was also found by other investigators in rats (57) and cats (58); but some investigators found no change or a decrease (59,60). The apparently conflicting results were not reconciled on the basis of strain differences (61), inadequate nutrition (62), subcellular distribution, (63) or mode of administration.
It is possible that GABA may play a role in both acute and chronic effects of ethanol, as postulated for morphine, but any definitive conclusions on common mechanisms with regard to this is premature.

**Acetylcholine (ACH)**

Administration of morphine causes an increase in ACH concentrations in rodents (64,65,66). It has also been shown to increase the amount of "bound" ACH while decreasing the amount of "free" ACH (67). Similar increases in ACH levels of rat brain have been reported with acute injections of both ethanol and acetaldehyde (66,69) and acetaldehyde (70) in frog brain.

Chronic administration of ethanol for twenty-two weeks decreased rat brain concentrations of ACH (71) and Ho (72) found a reduced amount of brain ACH in rats made dependent following a two month forced feeding regiment. However, a five week course of ethanol to guinea-pigs did not affect ACH levels (73).

**Adenosine 3'5'-Monophosphate (cyclic AMP)**

Contradictory findings concerning the effects of acute administration of both opiates and ethanol on brain cyclic AMP levels have been reported. Acute injections of opiates and ethanol have been found to increase (74,75,76), decrease (75, 76) or produce no change (77,78,79). However, chronic intoxication with ethanol has been found to affect the cyclic AMP system in the brain. Israel et al. (80) reported that administration of ethanol in a liquid diet for two weeks increased adenylate cyclase activity in mouse brain cerebral cortex. Similarly, increases in basal cerebral adenylate cyclase activity was obtained with chronic administration of morphine (81).

During ethanol-induced withdrawal French and Palmer (82) reported that the cyclic AMP system is affected by ethanol withdrawal. These authors incubated brain slices with NE and
found that formation of labelled cAMP from prelabelled ATP was higher in cortical slices of rats withdrawn from an ethanol-containing diet than in slices from control animals. Similarly, Mehita and Johnson (83) reported an elevation of brain cAMP during naloxone precipitated withdrawal in morphine dependent rats.

These results suggest that the sensitivity of adenylate cyclase, and thus formation of cAMP, may play an important role in dependence on, and withdrawal from ethanol and opiates.

**CONCLUSION**

It is apparent from the results reported in the preceding sections that there is little agreement concerning the effect that ethanol or opiate intoxication and withdrawal can produce on neurochemical mechanisms.

The conflicting results obtained are most likely related to a combination of factors, in the experimental protocols, including different routes of administration, different monoamine measuring techniques and/or the timing of the measurements, or the difference in the utilized doses to produce the desired effect (acute intoxication or dependence). While this list is by no means exclusive, it does point out several reasons why there is no general agreement concerning the neurochemical alterations elicited by either ethanol or opiates.

The lack of agreement in this area with either of these substances above, obviously precludes a definite conclusion concerning similarities, or differences, in the neurochemical alterations induced by acute or chronic treatment.

**EFFECT OF MONOAMINE ALTERATION**

Further evidence for a common mechanism of action has been obtained through pharmacological manipulation of central monoaminergic function. Considerable research has implicated changes in brain biogenic amines, induced by opiates and ethanol administration, as
mediating at least some of the effects of acute or chronic drug intoxication. Although the exact mechanism and direction of changes in biogenic amines induced by ethanol and opiates remains controversial, that changes occur is generally accepted. This has prompted several investigators to examine the effects of biogenic amines on behavioral changes induced by these two drugs. Here we review the results of investigations of neurochemical alterations on opiate and ethanol-induced tolerance, dependence and withdrawal and attempt to point out possible common mechanisms.

Dependence and Tolerance

Effect of Protein Synthesis Inhibitors

The possibility that either opiates or ethanol induced tolerance, or physical dependence, or both, may result from modification of a macromolecule in the brain has been considered by several laboratories. Cochin (84) reported that inhibitors of protein synthesis blocked the development of tolerance to morphine. Loh and associates (85) found that the development of physical dependence on and tolerance to morphine can be inhibited in the mouse by the concomitant administration of cycloheximide. These investigators also found that cycloheximide, while inhibiting development of tolerance did not alter analgesic response to morphine (85).

Similar findings concerning the effects of protein synthesis inhibition on tolerance and physical dependence induced by administration of ethanol have been reported. LeBlanc and associates (86) found that cycloheximide inhibited behavioral adaptation (tolerance) to ethanol and the development of physical dependence to ethanol in mice can be markedly reduced by the concomitant administration of large doses of cycloheximide (87).

These results suggest that de novo protein synthesis is involved in the development of tolerance and physical dependence to both opiates and ethanol. It does not mean, however, that the same macromolecule is involved in both cases, and it is also possible that the effects observed with cycloheximide are not due to inhibition of protein synthesis at all, but rather to some other "side-effect" of the drug.
Effect of Neurotransmitter Alterations

Various pharmacologic agents have been utilized to affect, as selectively as possible, the synthesis, storage, release or degradation of NE, DPA, 5-HT, GABA, ACH and cAMP during administration of opiates and ethanol. The consequences of such modification of amine activity on the tolerant-dependent and withdrawal states will be reported in the following sections.

Catecholamines (CA’s)

Based on numerous investigations, it appears that catecholamines participate in the acute pharmacologic effects of morphine (88) and in signs and symptoms observed during withdrawal (89). Martin and Eades (90), Way et al. (91) and Blasig et al. (92) have suggested that CA’s are not primarily involved with either tolerance or physical dependence development, but that NE may be related to morphine antinociception. Experiments with mice rendered tolerant-dependent by morphine pellet implantation showed that 6-OHDA induced decreases in brain NE and DPA concentrations does not effect the development of either tolerance or dependence, but the 6-OHDA pretreatment was accompanied by a decrease in analgesic response to morphine (i.e. an increase in the morphine (AD50). This was apparent to the same degree in both the non-tolerant animal and the tolerant animal as well. Blasig et al. (92) found that when CA’s were kept low throughout the morphine exposure and also at the time of withdrawal, the intensity of withdrawal, as measured by jumping and wet dog shakes, was not significantly affected. At the same time though, there was a great increase in the frequency of another withdrawal sign, writhing.

Other experiments suggest that the non-involvement of catecholaminergic systems in morphine tolerance and dependence is not so clear cut. Administration of the ß-adrenergic receptor blocking drug, dichloroisoproterenol, significantly attenuated the development of tolerance and physical dependence in mice (88). Furthermore, Huidobro et al. (93) found that concurrent administration of Dopa to morphine treated rodents attenuated the intensity of the resultant abstinence syndrome precipitated by injection of naloxone.

Experiments dealing with the role of CA’s on ethanol induced tolerance and dependence reveal that ß-adrenergic function may play an important role in the development of the tolerant-dependent state. It has been reported that agents that reduce (functionally or through depletion) catecholamine activity throughout ethanol exposure produce an exacerbation of withdrawal (94,95). Agents studied included a-methyl-ptyrosine (AMPT), phenoxybenzamine (POB), and 6-OHDA and the findings suggest that dependence is antagonized by central
catecholaminergic mechanisms, and that interference with these mechanisms, through reduction of receptor-mediated antagonism produces a greater degree of dependence and thus higher withdrawal scores. Ritzmann and Tabakoff (96) obtained evidence which indicates that an intimate relationship exists between the noradrenergic system and the development of tolerance to ethanol after chronic treatment. These authors found that control animals consuming an ethanol-containing diet became quite tolerant to the effects of ethanol, while the animals treated with 6-OHDA prior to chronic ethanol administration did not develop any tolerance to the temperature lowering or hypnotic effects of ethanol. In these experiments, no difference in withdrawal symptomatology was evident between the 6-OHDA-treated animals and the control physically dependent animals indicating that 6-OHDA did not affect the development of physical dependence.

Similar to morphine, results from our laboratory (95) indicate inhibition of physical dependence development to ethanol with (d,1)-propranolol, a B-adrenergic blocker. There are at least two possible mechanisms to consider: i) a chronic blockade of 0-receptors which reduces the development of dependence to ethanol, or ii) the membrane stabilizing effects of (d)-propranolol (97) which protects central neurons from the disruptive membrane effects of ethanol.

The demonstration that propranolol prevents the cerebral cortical cAMP response to NE in vitro (82) suggests that hyperactivity induced by ethanol withdrawal may be mediated through B-adrenergic pathways (82). If the supersensitivity to NE observed in the studies by French and co-workers (82,98) reflect an increase in the 0-receptors located on the post-synaptic membrane, this may provide an explanation for the beneficial effects observed with propranolol in our studies and during the abstinence phase of chronic alcoholics (99, 100). However, these findings are not in agreement with the observation by Goldstein (116) that propranolol administered to mice undergoing abstinence from ethanol, produced a slight exacerbation of withdrawal convolution scores. Nevertheless, which of these mechanisms is operant remains speculative, but we feel the second alternative represents a distinct possibility and warrants further investigation.

In addition, similar to the findings of Huidobro et al. (93), daily administration of large doses of L-dopa (620 mg/kg) during ethanol vapor exposure to mice significantly attenuated ethanol induced dependence suggesting possible involvement of DPA (101). Thus, it is of interest that Iwamoto et al. (102) reported that the stereotyped jumping which occurs in morphine-dependent mice or rats after abrupt or naloxone-precipitated withdrawal may depend upon a sudden elevation of brain DPA levels. When naloxone was given to mice and rats rendered dependent on morphine by pellet implantation, brain levels of DPA, but not those of NE or 5-HT, increased 20% to 40% above control levels within five minutes, a time that corresponds to the peak in precipitated stereotyped jumping. Catecholamine synthesis inhibition with AMPT partially blocked the increase in DPA after naloxone and increased the amount of naloxone required to
induce jumping. Furthermore, elevation of ACH by cholinesterase inhibition with physostigmine blocked the sudden rise of DPA levels as well as the jumping response. This suggests that cholinergic-dopaminergic pathways may mediate the jumping response of naloxone-precipitated withdrawal.

**Serotonin (5-HT).**
The exact role of 5-HT in the morphine tolerant-dependent state is still controversial despite a large amount of interest and work in this area. Juidobro et al. (93) have found that administration of 5-HT during the development of morphine dependence had no significant effect on subsequent naloxone-precipitated withdrawal. However, in the same study, administration of the 5-HT precursor tryptophan during dependence development reduced the severity of the resultant abstinence syndrome. In contrast, to these studies, Ho et al. (103) have reported that morphine pellet implanted mice show a higher degree of tolerance and physical dependence with concomitant tryptophan administration.

Pretreatment with para-chlorophenylalanine, a relatively specific and long-lasting inhibitor of 5-HT biosynthesis, demonstrated both reduced tolerance and physical dependence to morphine in mice and rats. Similar results (104) have been reported using intracerebrally administered 5,6-dihydroxytryptamine, a substance reported to selectively destroy tryptaminergic nerve endings (105).

In mice rendered dependent on ethanol by inhalation of ethanol vapor, concomitant treatment with pCPA had no significant effect. As well, there are no consistent and reproducible effects of administration of 5-HT (intracerebral), 5-hydroxytryptophan (i.p.) (99) or methysergide (i.p.) (106) during the induction of ethanol dependence. However, Collier et al. (107), monitoring a different withdrawal sign (head twitches), found that both pCPA and parachloroamphetamine reduced the degree of ethanol dependence.

The conflicting results obtained with 5-HT, its precursors or inhibitors on either the opiate or ethanol induced tolerant-dependent state preclude a definite role for 5-HT as yet, in these two syndromes.

**Acetylcholine (Ach).**
Inhibition of cholinesterase (e.g. with physostigmine) was found to decrease the morphine ED50
for analgesia in mice (108). However, this effect was evident to the same degree in both morphine tolerant and non-tolerant animals. Additionally, cholinesterase inhibition did not significantly modify either the development of tolerance or physical dependence to morphine (108). These results suggest that Ach does not play a primary role in the tolerance or dependence to opiates. It is possible, though, that Ach may modulate morphine antinociception, perhaps through an Ach-NElinked pathway.

A review of the literature reveals little or no available data concerning the effect of modification of central Ach levels on ethanol-induced tolerance or dependence.

**γ-Aminobutyric Acid (GABA).**

There is increasing evidence that GABA acts as an inhibitory neurotransmitter in the CNS (109). This substance was found to antagonize morphine antinociception acutely in the mouse, but with repeated administration it also accelerated the development of both morphine tolerance and physical dependence (88). Amino-oxyacetic acid, which inhibits the transamination of GABA, (i.e. degradation to glutamine) (52) had similar effects. Bicucalline, a GABA receptor blocker, inhibited both the development of tolerance and dependence to morphine (88,109).

There are few reports of the effects of GABAminergic pathways on the acute neuropharmacological actions of ethanol (110). It is known that a GABA metabolite, γ-hydroxybutyric acid, potentiates ethanol induced sleep and produces sleep in its own right (55), but, in contrast to morphine, little or no information exists with regard to the role of GABA in the development of tolerance and dependence to ethanol. Thus, any conclusions with respect to GABA-mediated common mechanisms between ethanol and morphine would be premature.

**Cyclic AMP (cAMP).**

Because of the well-documented (111) relationship between cAMP and virtually all the putative neurotransmitters, the effect of this agent on the development of tolerance and physical dependence to opiates or ethanol presents some difficulties. However, there have been some reports of the effect of functional increases in cAMP on morphine tolerance and dependence.
Intercerebroventricular administration of cAMP antagonized
the analgesic effect of morphine (i.e. increased morphine AD50) (112); similar results are obtained with dibutyrl cAMP and theophylline (113). Chronic treatment of morphine pellet implanted mice with cAMP for three days doubled the morphine AD50 when compared to placebo implanted mice (114). The suggestion that cAMP increases the degree of tolerance of these animals to morphine is demonstrated by the fact that pretreatment with 10 mg/kg i.v. cAMP before morphine pellet implantation significantly increased morphine AD50 compared to non-pretreated animals (114).

As well, pretreatment with cAMP two hours before morphine pellet implantation increased the degree of dependence developed in these animals as evidenced by a decrease in the amount of naloxone required to precipitate withdrawal, and a two to three-fold increase in weight loss on withdrawal (114). This same study demonstrated that concomitant administration of cycloheximide antagonized the effect of cAMP (114). However, in this experiment cycloheximide by itself did not produce any significant effect on the development of dependence, in contrast to earlier reports (85), making these results somewhat difficult to interpret.

There are few similar reports in the literature concerning the effects of cAMP on the development of tolerance and dependence to ethanol. In a preliminary experiment, theophylline administered to mice each day during exposure to ethanol vapor did not have any significant effect on the development of dependence (115).

**Withdrawal**

The purpose of this section is to relate the results of experiments which provide insight into the underlying neurochemical mechanisms of the abstinence syndrome following chronic ingestion or administration of ethanol and opiates.

A search of the literature reveals that a greater number of papers deal with the effect of drugs which modify withdrawal states induced by ethanol rather than opiates (88,136). Therefore, withdrawal from ethanol and its modification will constitute the major portion of this section; but drug-induced changes in opiate withdrawal will be considered where data is available.
Effect of Neurotransmitters

Various neuropharmacological tools have been employed to effectively alter the central level and activity of biogenic amines. It is our purpose in this chapter to delineate what effect(s) modifying biogenic amines have on the abstinence syndrome obtained from abrupt removal of ethanol or opiates. The biogenic amines considered will be CA’s (NE and DPA), 5-HT, ACH, GABA and cAMP.

CA’s (NE and DPA).
Goldstein (116) found that several drugs that interfere with CA’s facilitated ethanol-induced withdrawal seizures. Blockade of CA receptors at the 5th hour after termination of ethanol exposure, with phentolamine (a-blocker) or propranolol (S-blocker) produce a transient increase in withdrawal severity (116). Mice treated with AMPT, again at the 5th hour post-ethanol, demonstrated a slight exacerbation of withdrawal convulsions. Reserpine was most dramatic in its ability to increase seizure scores; however, this effect of reserpine is complicated by the finding that normal mice treated with single injections of reserpine showed the same characteristic convulsions on handling as mice undergoing alcohol withdrawal reactions (117). Collier et al. (107) have reported the effects of drugs affecting CA mechanisms on head twitches in mice induced by withdrawal of ethanol.

In these studies, both DPA and NE inhibited ethanol withdrawal head twitching, as did L-dopa. Other drugs that had sympathomimetic activity such as apomorphine (DPA-agonist) and amphetamine (CA releaser) also lessened withdrawal head twitching, whereas AMPT, which inhibits endogenous biosynthesis of DPA and NE (107), increased it.

Other studies (95,120) have extended these findings through the use of various CA agonists and receptor blockers. Although for the most part these studies agree with both Goldstein (117) and Collier et al. (107) there are differences.

Results from our experiments reveal that intracerebral injections of NE, and Clonidine, a central a-receptor activator (118,119), during ethanol withdrawal exacerbates the ethanol...
induced withdrawal convulsions (95). In contrast, a similar injection of DPA produced a very marked inhibition (i.e. amelioration) of the withdrawal reaction (120).

Based on these findings, it appears that activation of central a-receptors (noradrenergic) exacerbates ethanol-induced withdrawal convulsions, while central stimulation of DPA receptors ameliorates withdrawal. The suggestion that DPA ameliorates withdrawal is supported by the demonstration that haloperidol, a central DPA-receptor blocker (121) exacerbates ethanol-induced withdrawal convulsions (122,123). Exacerbation of withdrawal by NE is consistent with the hypothesis of French and Palmer (82), who suggest that withdrawal from ethanol is mediated, to a large extent, through supersensitive central NE receptors.

In light of these findings it appears that ethanol withdrawal-severity is directly related to NE and inversely to dopamine release. That is, NE exacerbates withdrawal while dopamine ameliorates it. Withdrawal reflects the release of NE, the severity being determined by amount released, and/or the state of the NE-receptors (i.e. supersensitive). This hypothesis further suggests, however, that dopamine, or dopamine agonist, may be useful in reducing the severity of ethanol withdrawal.

These results reported for ethanol seem to be compatible with the assumption that long lasting depletion of brain CA's is compensated for by induction of neuronal supersensitivity for NE and DPA. The recent finding by Engel and Lilgequist (124) that long-term ethanol treatment resulted in an enhanced sensitivity of DPA receptors in the nucleus accumbens supports this hypothesis.

Blasig et al. (92) similarly proposed that neuronal supersensitivity for CA's is an important factor in considering the mechanisms involved in expression of morphine abstinence. Evidence for this hypothesis is based on the work of Way (91), Maruyama and Takemori (125) and Herz et al. (126). In the work by Maruyama and Takemori (129) the authors conclude that "the full expression of abstinence syndrome in morphine-dependent mice appears to require the integrity of the central stores of NE and DPA, especially the latter amine". In contrast, Herz et al. provide evidence which supports the notion, that noradrenergic mechanisms are involved in the expression of withdrawal, while the role of DA is not clear. The authors conclude that contradictory results concerning the role of biogenic amines in morphine abstinence may be due to the type of symptom studied. They suggest that brain CA protection against excessive abstinence signs (127) should be restricted to convulsive activity rather than predicting a generalized effect.
5-HT

Goldstein (116) reported that drugs aimed at serotonin had no effect on the withdrawal reaction induced by ethanol. Mice treated with PCPA to block 5-HT synthesis or with tryptophan to increase brain levels of 5-HT showed the same withdrawal scores as controls.

Utilizing a different withdrawal sign Collier et al. (107) found that drugs that are 5-HT antagonists, namely, methysergide, methergolin and MA 1420 given one hour prior to head twitch counting in ethanol dependent mice significantly reduced the incidence of this withdrawal symptom, while administration of 5-HTP fifteen minutes prior to counting, significantly increased the incidence of this sign (107). Other reports indicate that there are inconsistent effects with intracerebral administration of 5-HT during the withdrawal phase as evidenced by increases, decreases or no effect on withdrawal scores of ethanol dependent mice (99). Only a slight increase in the withdrawal reaction was obtained with 5-HTP administration, and PCPA was without any significant effects. However, the same report (99) showing exacerbation of withdrawal convulsions rather than amelioration as reported by Collier et al. (107), of withdrawal convulsions following intracerebral injections of methysergide suggests that 5-HT may modulate ethanol-induced withdrawal. Differences between these findings and those of Collier may reflect differences in the abstinence sign measured, and the time of assessing the withdrawal sign. Griffiths et al. (37) found that administration of PCPA to mice prevents the rise in brain 5-HT concentration associated with ethanol withdrawal induced by inhalation but does not affect the increase in brain CA's which occurs at the same time. The locomotor, excitement, piloerection, tremor and handling convulsions which occur during ethanol withdrawal were not affected. These results suggest that the increase in brain 5-HT which occurs in ethanol withdrawal is a consequence of increased 5-HT synthesis and that it is probably not involved in the above behavioral changes associated with the early phase of ethanol withdrawal (up to twenty-four hours). The assessment of effects of drugs which modify 5-HT on the withdrawal reaction occurred twenty-four hours after the last dose of ethanol in Collier's laboratory compared to a much earlier assessment of between one and twenty hours in other laboratories. This may suggest that 5-HT may mediate behavioral changes of ethanol withdrawal during the latter phase and possibly CA's may mediate the early phase of withdrawal.

Investigators have made several attempts to link morphine with 5-HT during the withdrawal states (88,128). Shen et al. (50) proposed that 5-HT may be associated with morphine abstinence since PCPA and 5,6-dihydroxytryptamine inhibited wet-dog shakes following naloxone administration to tolerant-dependent morphine animals. Furthermore, Way et al. (129) and Shen et al. (50) reported that PCPA, which inhibits tryptophan-5-hydroxylase and thereby the synthesis of 5-HT, antagonized withdrawal symptomatology in mice. Although Way et al. (129) have shown that chronic administration of morphine increases the rate of brain 5-HT synthesis, no change in brain 5-HT synthesis was found in mice showing a definite withdrawal syndrome (129). Thus, it is possible that the
increase in brain 5-HT synthesis during the tolerant-dependent state is not a necessary condition for the development of withdrawal symptomatology.

**ACH.**
Evidence for a possible direct cholinergic involvement in ethanol preference has been presented by Ho and Kissin (130), but there are no reports correlating other behavioral measures with effects of ethanol on ACH release (131) and acetylcholinesterase activity (132). In addition, ethanol had little or no effect on the toxicity of the anticholinesterase agent, parathion (133).

With regard to ethanol withdrawal, Goldstein (116) found that mice treated with physostigmine, atropine or dihydro-aerythroidine (a curare-like cholinergic blocker that acts centrally) showed the same withdrawal scores as controls. In contrast, utilizing a different sign of ethanol withdrawal, Collier et al. (107) found that intracerebroventricular injection of ACH or carbachol increased the incidence of ethanol withdrawal head twitching whereas nicotine reduced it. By the intraperitoneal route, physostigmine increased head twitching, while the muscarinic blocking agent, hyoscine, lessened its incidence. Similarly, the effect of drugs that alter cholinergic function on opiate withdrawal is not conclusive. Grumbach (134) reported that atropine increased, and physostigmine decreased, abstinence sign in rats. However, Crosslands (135) found opposite effects in dependent rats, that is, atropine lessened and physostigmine worsened the withdrawal syndrome induced by naloxone.

These conflicting results concerning the role of ACH in both ethanol withdrawal and opiate withdrawal prevents any conclusion concerning the function of ACH in withdrawal states induced by removal of either of these agents.

**GABA.**
The effect of drugs that affect GABAergic pathways on ethanol withdrawal has been investigated (116). Goldstein (116,136) showed that GABA appears to counteract withdrawal hyperexcitability in ethanol-dependent mice. The convulsion scores were reduced by aminooxyacetic acid, an inhibitor of GABA transaminase that is known to increase brain levels of GABA (136,137), whereas picrotoxin, a GABA antagonist (137) produced a brief but sharp increase in the scores. Goldstein (116) points out that these results suggest that GABA is an effective endogenous anticonvulsant. The possibility that the GABA system is functionally upset
during alcohol withdrawal is supported by the finding that brain levels of GABA are lower than normal during the alcohol withdrawal reaction in mice treated with the Goldstein-Pal (138) inhalation method.

Except for the work of Ho et al. (51) showing enhancement of tolerance and physical dependence with drugs affecting GABAergic activity and bicuculline, a GABA antagonist inhibiting tolerance and physical dependence, no other research has been accomplished with respect to the interaction of GABA and the chronic effects of opiates. It appears that increases in GABA tend to enhance the development of tolerance and physical dependence whereas decreases in GABA activity reduce naloxone precipitated jumping in dependent animals exposed to opiates.

**Adenosine 3’5'-cyclic Monophosphate (CAMP)**

Several investigators have attempted to correlate acute as well as chronic actions of ethanol with levels of cAMP (74,76,79-81), but much less is known about the role of cAMP in ethanol induced withdrawal. Recently, Collier et al. (107) studied the effects of drugs affecting endogenous cyclic nucleotides on ethanol withdrawal head twitches in mice. By the intracerebroventricular route, db cyclic AMP lessened the incidence of withdrawal head twitches whereas db cyclic GMP increased the incidence. Adenosine triphosphate (ATP) and guanosine triphosphate (GTP) affected the incidence of twitches in the same direction as did the dibutyryl salts of the corresponding cyclic nucleotides. The phosphodiesterase inhibitors, theophylline and 3-isobuty1-1-methyl xanthine (IBMX), increased withdrawal head twitching, but imidazole, a phosphodiesterase stimulant, was inactive. Prostaglandins El and E2, which increase brain cAMP (139), also increased head twitching but prostaglandin F2, which has little effect on brain cAMP was inactive. Collier et al. (107) suggest that drugs which increase the level of cGMP increase head twitching and drugs which increase the level of cAMP inhibit head twitching. Hence, head twitching may arise from an increase in the ratio of cGMP:cAMP, perhaps the result of a change in the balance of neurohumoral mediators, particularly catecholamines. No similar reports have been noted for opiates.

**IONS AND OPIATES AND ETHANOL**

The acute and chronic effects of opiates have been well documented (Chapter 15). Kakunago et al. (140) found that Ca++, but not other ions, antagonized opiate induced analgesia. Shikimi et al. (141) suggested that the analgesic action of morphine may be due to the opiates’ effect on
Ca++ flux. The same researchers (141,142) demonstrated that morphine decreased whole brain Ca++ in mice, an effect to which tolerance developed. Ross and his colleagues have extended the work of Shikimi et al. (141) by demonstrating that opiate agonist cause dose-dependent decreases of Ca++ in regional areas of the brain, and that this depletion can be inhibited by naloxone (143).

Although there are few definitive reports concerning the role of Ca++ in acute and chronic effects of ethanol, Ross et al. (143) reported that morphine and ethanol deplete Ca++ in the same regional areas of the brain. This effect is selectively antagonized by the stereospecific narcotic antagonist, naloxone. Furthermore, cross-tolerance between morphine and ethanol with reference to their ability to deplete Ca++ has been demonstrated (144). The work by Ross et al. (144) suggested that ethanol and opiates have in common at least one biochemical mechanism. In this regard, it is known that administration of Ca++ antagonizes the tolerance of development to the analgesic effect of morphine. As well, Sangri and Gershon (145) reported that Ca++ antagonized the development of dependence to opiates, while chronic administration of Ca++ during morphine exposure to mice significantly inhibited naloxone-induced jumping. As well, it has been found that calcium gluconate administered daily to mice undergoing ethanol vapor exposure significantly reduced the resultant withdrawal syndrome upon removal from the ethanol vapor chambers (146). In addition, naloxone was also found to block ethanol-induced depletion of Ca++ content in the brain of mice exposed to ethanol vapor (17).

CONCLUSION

As with the effects of administration of opiates or ethanol on endogenous neurochemical mechanisms, the effects of prior manipulation of these neurochemicals on subsequent tolerance to, dependence on, and withdrawal from these agents is similarly confusing.

It is apparent from the evidence presented that there is still considerable controversy surrounding the neurochemical effects and determinants of both opiates and ethanol. A definitive case cannot yet be made for any single biogenic amine, ion, or other endogenous substance as the initiator of dependence producing properties of either agent.

There are certain similarities between opiates and ethanol that became evident on inspection of the results presented in the previous sections and summarized in Table 1.
There are also some distinct differences that are evident in some reports. For instance, while dopamine has been reported to ameliorate ethanol-induced withdrawal (120), exacerbation of morphine withdrawal has been suggested to occur with stimulation of dopamine receptors (102). However, this exacerbation of withdrawal pertained primarily to "dominant" withdrawal signs (e.g. jumping) while "recessive" signs (e.g. diarrhea) decreased (126).

Thus, the definition of exacerbation or amelioration depends on the importance ascribed to particular withdrawal signs, and that a conclusion concerning the effects of a drug on abstinence from either opiates or ethanol rests on this definition.

TETRAHYDROISOQUINOLINES: A POSSIBLE LINK BETWEEN OPIATES AND ETHANOL

The similarities between opiates and ethanol summarized in Table 1 on behavioral parameters, alteration of endogenous neurochemical function and the effects of endogenous neurochemical function and the effects of prior modification of monoamines on dependence and withdrawal, suggest that there may exist a "link" between these two classes of addictive drugs. A possible biochemical rationale for this link was provided in 1970, when two laboratories simultaneously published articles reporting the formation of simple and complex tetrahydroisoquinolines (TIQ) alkaloids as a consequence of ethanol metabolism (147,148). As described earlier (see earlier chapters), these substances are formed by the spontaneous condensation of an aldehyde with an appropriate (3-arylalkylamine (148,149). This discovery was significant in two aspects: It was the first demonstration that mammalian tissues could "synthesize" alkaloids, and benzylisoquinoline alkaloids (e.g. tetrahydropapaveroline, THP) are requisite intermediates in the biosynthesis of morphine in the poppy plant Papaver somniferum (149,151). The recent demonstration of the endogenous formations of TIQ alkaloids during ethanol intoxication (152) and identification by Sandler and co-workers (153) of urinary excretion of two dopamine-derived TIQ's (salsolinol and tetrahydropapaveroline) in Parkinson patients receiving L-dopa and ethanol supports the hypothesis that endogenous alkaloid formation could represent important metabolic sequelae of acute and chronic ethanol intoxication. These findings formed the basis for an intriguing, though controversial hypothesis, linking the opiates to ethanol. Such a theory was proposed by Davis, and her colleagues (148) centering on the formation of tetrahydropapaveroline (THP,
norlaudnosoline), the adduct of dopamine and its aldehyde (3,4-dihydroxy-phenylacetaldehyde). The biogenesis of this alkaloid in mammalian tissues suggested that common biochemical mechanisms may exist between opiates and ethanol.

Cohen and Collins (147) proposed an alternate hypothesis, suggesting that simple TIQ's could contribute to the acute and chronic effects of ethanol intoxication by interferring with adrenergic function (c.f. Chapter 8). As norepinephrine (NE) and dopamine (DPA) constitute the major catecholamines in the CNS, it is entirely possible the TIQ derivatives formed in vivo from these neuroamine following ethanol consumption, could contribute to the pharmacological effects of ethanol by interfering with catecholaminergic mechanisms in the CNS and in the periphery. These alkaloids have been shown by Cohen and his group (154-156) to have some properties in common with the catecholamines. They compete for the same uptake and storage mechanisms and possibly act as false transmitters. Under certain experimental conditions, they are NE-like in action and are secreted in a similar manner as NE (18).

Since 1970, there has been considerable effort devoted to determining the pharmacological activity of these compounds, and also proving their formation in vivo following ethanol consumption. Sandler et al. (153) and Collins and Bigdeli have identified that TIQ's are present in vivo after ethanol, but in both cases metabolic precursors (i.e. L-dopa) or other drugs were also present. In fact, there are reports that without such pretreatment, TIQ's cannot be identified from brains of ethanol-intoxicated animals (157). The inability to find TIQ's after ethanol alone may mean that current techniques are not yet sensitive enough. If this is found to be the case, then the absolute concentration of TIQ's in the CNS following ethanol will be quite small. However, if this small amount is localized in specific nerve endings, it may be sufficient to induce significant metabolic and functional changes during the course of chronic ethanol intoxication.

There has been much more success in defining the pharmacological activity of TIQ alkaloids (c.f. Chapters 8 and 10). This section will focus on the simple TIQ's derived from dopamine and L-dopa, salsolinol and 3-carboxysalsolinol, rather than the complex benzyl-TIQ's and their derivatives for the following reasons: i) the formation of the former requires the ethanol metabolite, acetaldehyde, while the latter does not, and ii) kinetically, the formation of the former two alkaloids is favored (158).

How these alkaloids might serve to link the biochemical and behavioral actions of ethanol and opiates is speculative, but enough is known of their pharmacology to suggest some possible mechanisms.
The chronic administration of ethanol and opiates produces an increase in central NE. The mechanism of this metabolic consequence is not known for either class of drug, but the formation of TIQ alkaloids may provide an explanation for the increase following ethanol. The formation of dopamine-derived TIQ's would decrease the synthesis of NE by removing the substrate for dopamine-a-hydroxylase. This decrease of NE would remove end-product inhibition and stimulate increase synthesis (turnover). Furthermore, salsolinol is known to release NE from nerve endings and inhibit its re-uptake (154-156). This would additionally decrease end-product inhibition of tyrosine hydroxylase and promote increased NE-turnover.

It is noteworthy that acute administration of salsolinol to mice undergoing withdrawal from ethanol vapor was found (depending upon the dose) to either ameliorate (low dose) or exacerbate ethanol induced withdrawal symptoms (97,101). Salsolinol as previously discussed is known to release neural stores of catecholamines (155) so the observed exacerbation could be the result of NE release and thus activation of central NE-a-receptors. Implicit in this argument is the fact that NE-a-activation supercedes DPA-a-activation because these alkaloids release both DPA and NE from neural stores (155). The biphasic action of salsolinol, although appearing at first inspection to be contradictory, may be explained by the recent observations that salsolinol can block a-receptors (159) and is an agonist at dopamine receptors (160,161). Thus, large exogenous doses of salsolinol probably exert their effect through a catecholamine release, while the smaller amount acts through direct receptor antagonism (a) and/or activation (DPA).

The finding that morphine attenuates the ethanol withdrawal syndrome (19), and that naloxone inhibits the development of dependence to ethanol (17) suggests that ethanol, or some metabolite, affects the opiate receptor. It was recently reported that salsolinol behaves as a partial opiate agonist in the guinea pig ileum (162). Additionally, salsolinol depletes legional brain Ca++, as does morphine, when administered peripherally (143). Both of the above effects of salsolinol are inhibited by naloxone (143,162), suggesting that the site of action is the opiate receptor. While these findings are highly suggestive, much more work must be accomplished before definite conclusions can be drawn.

There are further indications that salsolinol and 3-carboxysalsolinol may be important in the actions of ethanol and may interact with the opiate receptor (163,164). Salsolinol was found to stereospecifically bind to the opiate receptor in guinea pig brain with a potency of 1x10-3 that of normorphine (163). Both of these alkaloids prolong ethanol-induced narcosis (see Chapter 10) but have no effect on barbiturate induced hypnosis (165). As well, 3-carboxysalsolinol has recently been shown to produce analgesia by itself, and to potentiate morphine analgesia. Again, both of these effects...
are inhibited by naloxone (166). Intracerebral administration of salsolinol has also been found to affect morphine analgesia in mice (167). These results tend to support a partial agonist role for salsolinol with regard to opiate receptor interaction.

These speculations, while intriguing, require the demonstration that TIQ alkaloids are formed in vivo during ethanol intoxication, and that there be formation of significant amounts of these alkaloids to produce physical dependence. The term "significant" is relative in this application, because, as mentioned earlier, localized formation of these compounds in synaptic nerve endings could provide physiologically active concentrations which might be below the detectable limit for current techniques.

SUMMARY

Although a tremendous amount of scientific inquiry has been directed at defining the mechanisms responsible for the behavioral and biochemical alterations induced by ethanol and opiates, it is evident that considerable controversy exists in virtually all areas of research. There are several reasons for this, as discussed in this review, and it appears clear that these areas of controversy will not be resolved for some time. Perhaps a major cause of the differences is a lack of agreement concerning methods for induction of dependence and most important, its subsequent measurement. What constitutes a withdrawal sign, when does withdrawal begin and end, what is the relative importance of each sign, and what is the best way to objectively measure (quantify) each sign? All are areas of considerable disagreement.

Nevertheless, in our opinion, there is sufficient evidence in the literature to suggest that ethanol and opiates have biochemical and behavioral mechanisms in common, and that this hypothesis warrants further investigation.

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