IMPLICATIONS OF ENDOGENOUS OPIOIDS AND DOPAMINE IN ALCOHOLISM: HUMAN AND BASIC SCIENCE STUDIES

CHRISTINA GIANOULAKIS*

Departments of Psychiatry and Physiology, McGill University, and the Douglas Hospital Research Centre, Verdun, Quebec, Canada

(Received 31 August 1995)

Abstract — We investigated the endogenous opioid system and its role in mediating the reinforcing effects of ethanol that lead to high ethanol consumption as a biochemical marker of an individual's vulnerability to excessive ethanol consumption. We performed studies using human subjects with [high risk (HR)] and without [low risk (LR)] a family history of alcoholism to supplement our studies with experimental animals bred selectively for high- or low-ethanol consumption. HR subjects had lower basal plasma β-endorphin levels as compared with LR subjects, but they had a more pronounced release of β-endorphin after exposure to ethanol. Findings from animal studies indicated that ethanol-preferring (C57BL/6) mice (analogous to the HR human subjects) had higher levels of hypothalamic β-endorphin activity than did ethanol-avoiding (DBA/2) mice (analogous to the LR human subjects) under basal conditions. However, the C57BL/6 mice had a more pronounced release of hypothalamic β-endorphin than did DBA/2 mice after exposure to ethanol. Thus, although hypothalamic β-endorphin system activity in human and animal models of alcoholism differs under basal conditions, there is enhanced hypothalamic β-endorphin system activity after exposure to ethanol in both models. We have also performed studies comparing the density and distribution of opioid receptors in brains of ethanol-preferring animals, such as C57BL/6 mice and ALKO-alcohol (AA) rats, and ethanol-avoiding animals, such as DBA/2 mice and ALKO-non-alcohol (ANA) rats. Interestingly, it was observed that in distinct brain regions known to be important for mediating the process of reinforcement, the C57BL/6 mice had a higher density of delta-opioid receptors than the DBA/2 mice, while the AA rats had a higher density of mu-opioid receptors than the ANA rats. Thus, in the ethanol-preferring animals, the increased release of β-endorphin following exposure to ethanol was associated with a higher density of delta- or mu-opioid receptors in brain regions important for reinforcement, such as the nucleus accumbens and the ventral tegmental area, and may interact with the dopaminergic system and promote ethanol's reinforcing properties, leading to excessive drinking and alcoholism.

INTRODUCTION

Alcoholism is a metabolic disease presenting the clinical features of craving, loss of control, tolerance, and physical dependence. Findings from both epidemiological (Cloninger et al., 1985; Goldman and Linnoila, 1986) and animal (Eriksen and Rusi, 1978; Keane and Leonard, 1989) studies have indicated that genetic factors may play an important role in determining an individual's vulnerability to excessive ethanol consumption. In addition, alcoholism is not characterized by single gene or single allele inheritance. Rather, multiple genes and environmental factors interact to increase or decrease an individual's vulnerability to becoming an alcoholic. A major objective of current research is to determine and characterize behavioural, physiological and biochemical factors closely associated with the incidence of alcoholism that could help to predict an individual's vulnerability to excessive ethanol consumption. The endogenous opioid system and its role in mediating the reinforcing effects of ethanol that lead to high consumption is one biochemical marker under investigation.

The endogenous opioid system consists of opioid peptides and opioid receptors. Three distinct families of opioid peptides have been characterized: the endorphins, enkephalins, and dynorphins. They are derived from three distinct genes that give rise to three distinct high-molecular-weight precursor proteins: proopiomel-
anocortin gives rise to endorphins, proenkephalin gives rise to enkephalins, and prodynorphin gives rise to dynorphins (Hughes et al., 1975; Bradbury et al., 1976; Goldstein et al., 1979; Khachaturian et al., 1985).

Like the opioid peptides, opioid receptors belong to three major classes: the mu, delta, and kappa receptors (Unterwald and Zukin, 1990). Pharmacological, anatomical and physiological studies have indicated that each of the endogenous opioid peptides may interact with the various opioid receptor types (Charness, 1989). Thus, enkephalins bind to both mu- and delta-opioid receptors, although their affinity for the delta-opioid receptors is 10–25 times higher than their affinity for the mu-opioid receptors (Akil et al., 1988; Charness, 1989). β-Endorphin binds to both mu- and delta-opioid receptors with about equal affinity, whereas dynorphins bind preferentially to kappa-opioid receptors (Charness, 1989).

Endorphins, as well as enkephalins and dynorphins, have been shown to be involved in a number of physiological processes, including analgesia, reward and reinforcement (Olson et al., 1990). Since ethanol does not have specific receptors in the brain, its rewarding and reinforcing properties may be mediated through its effects on various neurotransmitter and/or neuropeptide systems, which may include the endogenous opioid system (Gianoulakis and de Waele, 1994). The similarity of certain neuropharmacological responses to ethanol and opiates supports this hypothesis (Kalant, 1977). Furthermore, studies have shown that administration of the non-specific opioid antagonists naloxone and naltrexone reduced voluntary ethanol intake in a number of experimental paradigms (Altshuler et al., 1980; Kiianmaa et al., 1983). Administration of the specific delta-receptor antagonist ICI-174864 had a similar effect (Froehlich et al., 1991). Naltrexone treatment was also found to decrease ethanol consumption in alcohol-dependent humans (Volpicelli et al., 1992; O’Malley et al., 1992). Administration of low doses of mu-opioid agonists to rats, either peripherally (Reid and Hunter, 1984) or centrally (Linseman, 1989), increased their ethanol consumption.

In addition to the behavioural and physiological data indicating an interaction between ethanol and the endogenous opioid system, there are biochemical data supporting such an interaction. First, ethanol may interact with the endogenous opioid system at the level of the endogenous opioid peptides by altering their rate of synthesis, release, or processing. Second, ethanol may interact with opioid receptors by altering their affinity for the opioid peptides or their density in distinct regions of the brain. A number of studies have indicated that acute ethanol administration increases the in vivo and in vitro release of β-endorphin from both the hypothalamus and the pituitary gland (Keith et al., 1986; Gianoulakis and Barcomb, 1987; Gianoulakis et al., 1989; Gianoulakis, 1990; de Waele et al., 1992). Long-term ethanol administration has also been shown to alter the activity of the brain and pituitary β-endorphin system. However, significant inconsistencies in results from these studies have been reported between and even within laboratories. These inconsistencies may be caused by the various methods of ethanol administration, the various doses used, and/or the duration of ethanol exposure (Dave et al., 1986; Seizinger et al., 1984a, b; Wand, 1990; Wand and Levine, 1991; Angelogianni and Gianoulakis, 1993).

Several researchers have performed studies to investigate the effect of ethanol on opioid receptors. The results from these studies indicate that the effect depends on the experimental conditions and the animal species and strain used, the specific brain region investigated, the mode of ethanol administration, and the duration of ethanol exposure (Hiller et al., 1981; Gianoulakis, 1983; Levine et al., 1983; Tabakoff and Hoffman, 1983; Charness, 1989).

Since ethanol has been shown to stimulate the activity of the brain and pituitary β-endorphin system, it is reasonable to propose that humans and animals with a genetic predisposition to excessive ethanol consumption have inherited an enhanced sensitivity of the endogenous β-endorphin system [and/or other component(s) of the endogenous opioid system] to ethanol. It is this ethanol-induced, enhanced activity of the endogenous opioid system that may initiate and maintain excessive ethanol consumption by mediating the reinforcing effects of ethanol. We have performed a number of studies using human subjects with and without a family history of alcoholism to supplement our studies with experimental animals bred selectively for their high- or low-ethanol consumption.
HUMAN STUDIES

Subject selection

High-risk (HR) and low-risk (LR) subjects were selected by experienced personnel of the Alcohol Research Program at Douglas Hospital Research Center, Verdun, Quebec, Canada. Histories were taken from as many family members as possible, and family pedigrees were constructed. For family members who were available for interview, the diagnosis of alcoholism was based on the Michigan Alcoholism Screening Test (MAST) (Selzer, 1971) and the Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition (DSM-III-R) (Spitzer et al., 1987). For family members who were unavailable for an interview (i.e. family members who were dead, living outside Montreal, or were unwilling to participate in the study), Family History—Research Diagnostic Criteria were used. The Family History—Research Diagnostic Criteria were developed to establish a consistent set of criteria for diagnosing psychiatric illnesses in index subjects when it is not possible to examine the relatives of these subjects directly. These criteria are very similar to those of the Research Diagnostic Criteria, which are used when subjects are directly examined (Endicott et al., 1975).

Families who had a minimum of a two-generation history of alcoholism (father and paternal grandfather with alcoholism) were considered to have a strong positive history. Sons and daughters in these selected families who were not alcoholics themselves but were assumed to have a high familial risk for the future development of alcoholism, made up the HR group. LR subjects were recruited from families with a strong negative history for alcoholism (absence of alcoholism) by using the same criteria applied to HR families. Sons and daughters of these families were assumed to have a low familial risk for the future development of alcoholism.

Since it has been shown that genetic vulnerability to alcoholism is equally transmitted to daughters from their fathers or mothers (Kendler et al., 1994), both daughters and sons of alcohol-dependent parents could have inherited the vulnerability to alcoholism and could be included in the HR group. All HR and LR subjects participating in the study were between 20 and 30 years of age. Subjects were screened for alcohol consumption by using the MAST (Selzer, 1971) and a drinking behaviour scale (Cahalan and Cisin, 1968). In addition, all individuals underwent a complete medical examination.

Exclusion criteria included heavy drinking; long-term use of a prescribed medication for a major psychiatric disorder; history of alcoholism; presence of liver, brain, or kidney disorders; diabetes or other chronic disease; and use of other drugs and heavy cigarette smoking (more than 10 cigarettes per day). Subjects with antisocial personality disorder were included in the study. The project was designed to include a sample size of 24 HR and 24 LR subjects in each group (12 men and 12 women) matched for sex, age, drinking behaviour and cigarette smoking. However, one man and two women in the HR group and one man in the LR group dropped out of the study. Their matched pairs were also withdrawn from the study. Thus, 20 HR (10 men and 10 women) and 20 LR (10 men and 10 women) subjects completed the study.

The investigations were approved by the Douglas Hospital Human Research Committee and were conducted in accordance with the guidelines proposed in the Declaration of Helsinki (World Medical Assembly, 1976). Informed consent was obtained from all of the subjects, and they could withdraw from the study at any time.

The following brief summaries of the experimental design and results are based on data by Gianoulakis et al. (1996).

Experimental design

In this double-blind study, matched pairs of subjects participated in four testing sessions, receiving 0.0 (placebo), 0.25, 0.50 or 0.75 g of ethanol per kg body weight. The minimum interval between sessions was 5 days. All subjects were required to abstain from ethanol for 48 h before testing. Female subjects had to be at the follicular stage of the reproductive cycle. On the day of testing, the subjects arrived at the research unit at 0800; a catheter was placed in an arm vein, after which subjects were allowed to rest. At 0830, the subjects were given a light breakfast that consisted of two slices of toast (without butter or jam), to avoid the feeling of nausea experienced when subjects receive ethanol on an empty stomach. Nausea could act as a stressor and could increase the plasma content of $\beta$-endorphin, thus
making it difficult to distinguish between the effects of stress and the specific effects of ethanol on hormone levels. Subjects were allowed to drink water with their breakfast but not coffee or tea, and they were not allowed to smoke for the duration of the experiment. At 0900, a blood sample was drawn, after which each subject was given either a placebo drink or one of the drinks containing ethanol, and asked to consume the beverage within 5 min. The placebo drink consisted of one part of degassed tonic water mixed with two parts of unsweetened orange juice. The lip of the glass was dipped in ethanol to provide the taste and smell of ethanol. To prepare the ethanol-containing drinks, one part of 95% ethanol was mixed with two parts of unsweetened orange juice. Additional blood samples were obtained at 15, 45, 120 and 180 min after a drink was consumed to estimate the blood ethanol content and plasma β-endorphin levels.

Results

Results indicated that the LR subjects had higher basal plasma β-endorphin levels at 0900, compared with the levels in the HR subjects. A time-dependent decrease was seen in the plasma β-endorphin levels of LR but not HR subjects after consumption of the placebo drink. A dose- and time-dependent increase was found in the plasma β-endorphin levels of HR but not LR subjects after consumption of the ethanol drink. Furthermore, although LR subjects did not demonstrate a significant increase in plasma β-endorphin levels after consumption of the ethanol drink, the time-dependent decrease in plasma β-endorphin content usually observed after consumption of the placebo drink was abolished. This finding indicates that ethanol enhanced the release of pituitary β-endorphin in the LR subjects to a significantly lower degree than it did in the HR subjects.

Since there was no significant difference between the HR and LR subjects in the blood ethanol content at the various times after ethanol intake, the difference in the response of the pituitary β-endorphin system to ethanol between the HR and LR subjects was not due to different concentrations of ethanol in the blood. Linear regression analysis indicated that the changes in plasma β-endorphin content were positively correlated with the changes in blood ethanol content in HR, but not in LR subjects. Thus, it appears that the pituitary β-endorphin system of HR subjects is more sensitive to ethanol than that of LR subjects.

It is generally accepted that, due to the blood–brain barrier, β-endorphin peptides from the peripheral circulation cannot reach and interact with the reward centres of the brain. Therefore, the significance of this ethanol-induced increase in the release of pituitary β-endorphin is not clear. However, a number of peptides and protein hormones, among them β-endorphin, have been shown to cross the blood–brain barrier in quantities that, although small, are sufficient to induce effects such as analgesia, electroencephalographic activity and alterations in learning ability (Banks and Kastin, 1987, 1990).

It is believed that (a) plasma β-endorphin may interact with regions of the brain outside the blood–brain barrier; (b) pituitary β-endorphin may reach the level of the median eminence and hypothalamus via the retrograde transport mechanism (Bergland and Page, 1979); and (c) ethanol may alter the blood–brain barrier in such a way that small peptides, such as β-endorphin, can enter the brain more efficiently and interact with various regions of the brain to mediate the reinforcing effects of ethanol (Banks and Kastin, 1993). Thus, this increased sensitivity of the pituitary β-endorphin system to ethanol may be important in mediating the reinforcing effects of ethanol and maintaining high ethanol consumption. Furthermore, since ethanol is a very non-specific drug without specific receptors to interact with, it is possible that the ethanol-induced changes in the pituitary β-endorphin release reflect similar changes in the brain β-endorphin release.

ANIMAL STUDIES

For ethical reasons, limitations must be placed on studies using healthy human volunteers to investigate the effects of ethanol on the various neurotransmitter and neuropeptide systems that may mediate the reinforcing effects of ethanol. These limitations determine the type of experimental manipulation as well as the types of samples that may be taken from subjects. Numerous studies have been performed by using...
experimental animals in an effort to understand better the effect of ethanol on various functions of the brain. Through selective breeding, a number of animal lines and strains have been developed (mainly rodent) that show either preference for, or aversion to, ethanol solutions (Eriksson, 1968; Lumeng et al., 1986). Studies have been performed by us and by others to identify the presence of genetically determined differences in the activity of the various components of the endogenous opioid system among these selectively bred strains under basal conditions, and following ethanol administration (Crabbe et al., 1983; Gianoulakis and Gupta, 1986; Froehlich, 1993; Gianoulakis and de Waele, 1994).

The hypothalamus, septum, and nucleus accumbens (brain regions important in mediating the rewarding and positive reinforcing effects of many drugs of abuse including ethanol) (Routtenberg, 1976) are rich in endorphinergic innervation; therefore, we have performed studies investigating the activity of the \( \beta \)-endorphin system in the hypothalamus of C57BL/6 (ethanol-preferring) and DBA/2 (ethanol-avoiding) strains of mice. Findings from initial studies have demonstrated the presence of genetically determined differences between these strains of mice in the content of \( \beta \)-endorphin peptides in the pituitary gland under basal conditions, as well as in the release of \( \beta \)-endorphin peptides by the pituitary gland and hypothalamus following an intraperitoneal injection of ethanol (Crabbe et al., 1983; Gianoulakis and Gupta, 1986).

Further studies have indicated that while the total tissue content of hypothalamic \( \beta \)-endorphin peptides under basal conditions is similar in the two strains of mice, the content of hypothalamic \( \beta \)-melanocortin messenger RNA is higher in the C57BL/6 than in the DBA/2 mice. Exposure \textit{in vitro} of the hypothalamic tissue to various concentrations of ethanol revealed that (a) the \textit{in vitro} spontaneous release and ethanol-stimulated release of hypothalamic \( \beta \)-endorphin peptides was higher in the C57BL/6 mice; (b) low concentrations of ethanol (10, 20, 25 mM) induced a more pronounced increase in the release of hypothalamic \( \beta \)-endorphin than high concentrations of ethanol (30–60 mM); and (c) maximum release for both strains of mice was obtained with 20 mM ethanol (de Waele and Gianoulakis, 1992).

A study of the effects of ethanol on the release \textit{in vitro} of \( \beta \)-endorphin demonstrated that hypothalamic endorphinergic neurons from both ethanol-preferring (C57BL/6) and ethanol-avoiding (DBA/2) mice showed a fast, transient increase in \( \beta \)-endorphin release in the presence of 20 mM ethanol. These neurons became insensitive to subsequent exposure to similar or higher concentrations of ethanol for approximately 60 min. There were differences in the magnitude and duration of the ethanol-stimulated release of \( \beta \)-endorphin, which were more pronounced and longer lasting in the C57BL/6 mice. In addition, the length of time in which there was no response to a second exposure to ethanol was shorter in the C57BL/6 mice (de Waele and Gianoulakis, 1993). These genetically determined differences in the activity of the \( \beta \)-endorphin system, both in the absence and presence of ethanol, may contribute to the differences in the voluntary ethanol consumption exhibited by these strains of mice.

The results of the human studies of subjects at high and low risk for the future development of alcoholism indicated that HR subjects have a low level of \( \beta \)-endorphin activity under basal conditions, while they have a more pronounced release of \( \beta \)-endorphin after exposure to ethanol. This supports the opioid deficiency hypothesis. Results from the animal studies, on the other hand, indicated that ethanol-preferring (C57BL/6) mice (which, for this study, we are assuming are equivalent to HR human subjects) had a higher level of hypothalamic \( \beta \)-endorphin activity under basal conditions and a more pronounced release of hypothalamic \( \beta \)-endorphin after exposure to ethanol than did the ethanol-avoiding DBA/2 mice. This supports the opioid surfeit hypothesis. Thus, although the human and animal models of alcoholism differ in the activity of their \( \beta \)-endorphin systems under basal conditions, the ethanol-preferring subjects in both models (HR human individuals and ethanol-preferring C57BL/6 mice) present a more pronounced response of the \( \beta \)-endorphin system to ethanol than do the subjects who do not prefer ethanol (LR human subjects and DBA/2 mice). In both models, there is enhanced activity of the \( \beta \)-endorphin system after ethanol exposure, which may play an important role in reinforcing ethanol consumption and lead to excessive drinking and alcoholism.

 Apparently, what is most important for
mediating the reinforcing effects of ethanol and maintaining a high level of alcohol consumption is the ability of ethanol to stimulate the activity of the endogenous opioid system. Thus, a third hypothesis, the 'opioid sensitivity to ethanol hypothesis', may be proposed. According to this hypothesis, it is not the basal levels of opioidergic activity that are a crucial factor for excessive ethanol consumption, but rather a significant increase in opioidergic activity shortly after initiation of ethanol drinking that may mediate the rewarding effects of ethanol, reinforce the act of drinking, and increase ethanol consumption. Therefore, individuals with a higher endogenous opioid system sensitivity to ethanol are at higher risk for excessive ethanol consumption than are individuals with a low sensitivity to ethanol, regardless of the activity of the endogenous opioid system under basal conditions.

Recently we have also performed studies that compared the distribution and density of opioid receptors in the brains of ethanol-preferring animals, such as the C57BL/6 mice and ALKO-Alcohol (AA) rats, and ethanol-avoiding animals, such as the DBA/2 mice and ALKO-non-alcohol (ANA) rats. Results indicate that mice of the C57BL/6 strain have a significantly higher density of delta-opioid receptors in distinct regions of the brain, such as the ventral tegmental area (VTA), nucleus accumbens, caudate nucleus and frontal cortex (de Waele and Gianoulakis, 1992) than do mice of the DBA/2 strain.

Lé and Chow (1992) have shown that in the C57BL/6 strain of mice, delta-opioid receptor antagonists are more effective in decreasing voluntary ethanol consumption. Their results suggest that the higher concentration of delta-opioid receptors in the regions of the limbic system of the C57BL/6 mice may be important in mediating the reinforcing effects of ethanol, thus leading to excessive ethanol consumption.

Unlike the C57BL/6 mice, the AA rats have a higher density of the mu-opioid receptors in many regions of the brain, including nuclei of the limbic system, than do the ANA rats (de Waele et al., 1995). This finding is in agreement with a published report indicating that in AA rats, mu-opioid receptor antagonists are more effective than delta-opioid receptor antagonists in decreasing ethanol consumption (Hyytiä, 1993).

INTERACTIONS OF ENDOGENOUS OPIOIDS WITH DOPAMINE TO CONTROL ETHANOL CONSUMPTION

Dopamine has been proposed as the neurotransmitter that interacts with the positive rewarding centres of the brain and induces the reinforcing effects of many drugs of abuse (Wise and Bozarth, 1987; Koob and Bloom, 1988). Interestingly, Benjamin et al. (1993) found that ethanol administration induced an increase in dopamine release at the level of the nucleus accumbens that was blocked by naltrexone, suggesting the implication of the endogenous opioid system. This ethanol-induced increase of dopamine release in the nucleus accumbens could be either the direct effect of ethanol or an effect mediated by the ethanol-induced enhancement of opioid system activity. Dopamine release at the level of the nucleus accumbens could also be altered by activation of mu-opioid receptors at the level of the VTA.

The mesolimbic dopaminergic system, with cell bodies at the VTA and nerve terminals at the nucleus accumbens, has been implicated in the mechanisms of drug reinforcement and the self-administration of many drugs of abuse (Routtenberg, 1976; Kuhar et al., 1991; Koob, 1992). The activity of the mesolimbic dopaminergic system is modulated by the endogenous opioid system. Spanagel et al. (1992) found that in vivo infusion of the mu-opioid receptor agonist [d-Ala², N-methyl-Phe⁴, Gly²-01]enkephalin (DAGO) into the VTA of Sprague–Dawley rats induced a dose-dependent increase of dopamine release into the nucleus accumbens, while infusion of D-Pen-Cys-Tyr-d-Trp-Orn-Thr-Pen-Thr-NH₂ (CTOP), a specific mu antagonist, into the VTA resulted in an inhibition of the spontaneous release of dopamine in the nucleus accumbens. Johnson and North (1992) found that electrophysiological recordings in the VTA of Sprague–Dawley rats showed the mu-receptor agonist DAGO, but not the delta-receptor agonist Tyr-d-Pen-Gly-Phe-d-Pen (DPDPE), to hyperpolarize secondary GABAergic neurons, thus removing the GABA-induced tonic inhibition on the dopaminergic neurons and increasing the release of dopamine in the nucleus accumbens.

Microdialysis studies in Sprague–Dawley rats have demonstrated that focal injection into the
ALCOHOL AND ENDOGENOUS OPIOIDS

Fig. 1. Schematic drawing of the possible interactions between the endogenous opioid system and the brain nuclei responsible for the mediation of the positive reinforcing effects of ethanol.

Dopaminergic neurons in the ventral tegmental area, which send axons to the nucleus accumbens, are under tonic γ-aminobutyric acid (GABA)-ergic inhibition. This inhibition may be removed by β-endorphin or enkephalin stimulation of the mu-opioid receptors. The release of β-endorphin or enkephalins is stimulated by ethanol, leading to increased dopamine release in the nucleus accumbens. Dopamine release may also be increased by stimulation of the delta-opioid receptors in the nucleus accumbens. In contrast to mu and delta receptors, stimulation of the kappa-opioid receptors at the level of nucleus accumbens by dynorphins could decrease dopamine release and produce aversive states. The arcuate nucleus contains most of the neurons synthesizing β-endorphin peptides in the brain. From the arcuate nucleus, endorphinergic neurons send fibres and innervate various regions of the brain, such as the nucleus accumbens and probably the ventral tegmental area.

Findings from studies using in vivo microdialysis have indicated that administration of β-endorphin and selective mu and delta agonists at doses that function as positive reinforcers increases dopamine release in the nucleus accumbens, while the administration of kappa agonists, which produce aversive states, decreases dopamine release in the nucleus accumbens (Di Chiara and Imperato, 1988; Spanagel et al., 1992). Thus, one may hypothesize that activation of the mu and/or delta receptors would increase dopamine release, which would initiate the processes of reinforcement and increase drinking, while activation of the kappa-opioid receptors would decrease dopamine release and decrease drinking. A hypothetical model (Fig. 1 modified from de Waele et al., 1995) of the possible interactions between the endogenous opioid system, the VTA, and the nucleus accumbens may be summarized.
as follows. The mu-opioid receptors in the VTA may interact with the endogenous opioid peptides, whose release is stimulated by ethanol, to induce a strong inhibition of the activity of the GABAergic neurons. Since GABAergic neurons exert a tonic inhibitory effect on the dopaminergic neurons in the VTA (whose axons terminate at the level of the nucleus accumbens), this decreased activity of GABAergic neurons would lead to disinhibition of the dopaminergic neurons and to an increased release of dopamine in the nucleus accumbens. Furthermore, at the level of the nucleus accumbens, β-endorphin and enkephalins may interact with the delta-opioid receptors to further potentiate dopamine release in the nucleus accumbens. On the other hand, dynorphin would interact with kappa-opioid receptors to induce a decrease in dopamine release. Thus, a high concentration of mu-opioid receptors in the VTA, and of delta-opioid receptors in the nucleus accumbens, may act as predisposing factors for a high level of ethanol consumption, while a high concentration of kappa-opioid receptors at the level of the nucleus accumbens could be partially responsible for the low level of ethanol consumption exhibited by some humans and certain experimental animals.

REFERENCES


Froehlich, J. C. (1993) Interactions between alcohol and
Eriksson, K. (1968) Genetic selection for voluntary alcohol
Froehlich, J. C, Zweifel, M., Harts, J., Lumeng, L. and
Gianoulakis, C. (1990) Characterization of the effects of
Gianoulakis, C. (1983) Long term ethanol alters the binding
Gianoulakis, C, B61iveau, D., Angelogianni, P., Meaney,
Gianoulakis, C, Krishnan, B. and Thavundayil, J. (19%)
McClearn, G. E., Deitrich, R. A. and Erwin, G. eds,
Goldstein, A., Tachibana, S., Lowney, L. I. and Hood,
Institute of Alcohol Abuse and Alcoholism Research, Washington, DC. Monograph 6.
Froehlich, J. C., Zweiel, M., Harts, J., Lumeng, L. and


