Influence of the endogenous opioid system on high alcohol consumption and genetic predisposition to alcoholism

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There is increasing evidence supporting a link between the endogenous opioid system and excessive alcohol consumption. Acute or light alcohol consumption stimulates the release of opioid peptides in brain regions that are associated with reward and reinforcement and that mediate, at least in part, the reinforcing effects of ethanol. However, chronic heavy alcohol consumption induces a central opioid deficiency, which may be perceived as opioid withdrawal and may promote alcohol consumption through the mechanisms of negative reinforcement. The role of genetic factors in alcohol dependency is well recognized, and there is evidence that the activity of the endogenous opioid system under basal conditions and in response to ethanol may play a role in determining an individual's predisposition to alcoholism. The effectiveness of opioid receptor antagonists in decreasing alcohol consumption in people with an alcohol dependency and in animal models lends further support to the view that the opioid system may regulate, either directly or through interactions with other neurotransmitters, alcohol consumption. A better understanding of the complex interactions between ethanol, the endogenous opioids and other neurotransmitter systems will help to delineate the neurochemical mechanisms leading to alcoholism and may lead to the development of novel treatments.

Des données probantes de plus en plus nombreuses appuient l'existence d'un lien entre le système opioïde endogène et la surconsommation d'alcool. La consommation aiguë ou légère d'alcool stimule la libération, dans des régions du cerveau qui sont associées à la récompense et au renforcement, de peptides opioïdes qui déclenchent, du moins en partie, les effets de renforcement de l'éthanol. Une consommation importante et chronique d'alcool provoque toutefois une déficience centrale des opioïdes qui peut être perçue comme un sevrage des opioïdes et peut favoriser la consommation d'alcool par les mécanismes du renforcement négatif. Le rôle des facteurs génétiques dans la dépendance de l'alcool est bien connu et des données probantes indiquent que l'activité du système opioïde endogène dans des conditions de base et en réaction à la présence d'éthanol peut jouer un rôle dans la détermination de la prédisposition d'une personne à l'alcoolisme. L'effica-

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cité des antagonistes des récepteurs des opioïdes dans la réduction de la consommation d'alcool chez les personnes qui ont une dépendance à l'égard de l'alcool et chez des modèles animaux appuie encore davantage l'opinion selon laquelle le système opioïde peut régulariser la consommation d'alcool, directement ou par interaction avec d'autres neurotransmetteurs. Une meilleure compréhension des interactions complexes entre l'éthanol, les opioïdes endogènes et d'autres systèmes neurotransmetteurs aidera à définir les mécanismes neurochimiques à l'origine de l'alcoolisme et pourrait déboucher sur la mise au point de traitements nouveaux.

Introduction

Alcoholism is a major public health problem that not only causes enormous damage to health and quality of life, but also undermines the well being of family and society. In an attempt to deal with alcohol-related problems at the beginning of the 20th century, the focus was on the prohibition of alcohol use, and for a time in the United States, there were sanctions against the sale and use of alcohol. More recently, however, the focus has been placed on better understanding the medical and psychosocial problems associated with excessive alcohol consumption, as well as the neurochemical substrates mediating alcohol reinforcement.[1] Studies on the genetic epidemiology of alcoholism, such as twin, family and adoption studies, clearly demonstrate that genetic factors play an important role in the development of alcoholism.[2] These findings are further supported by the development of inbred[3–6] and outbred[7–13] lines and strains of animals with high or low preferences for ethanol solutions. These animals are used to study the biochemical basis of alcoholism.

Among the neurotransmitter systems proposed to be important in controlling alcohol-seeking behaviour is the endogenous opioid system.[14–31] It has been proposed that alcohol may stimulate the release of certain opioid peptides, which in turn, could interact with the centres of the brain associated with reward and positive reinforcement and lead to further alcohol consumption.[32–36] It has been suggested that increased activity of brain enkephalin or β-endorphin opioid peptide systems, either under basal conditions or in response to ethanol exposure, may be important for initiating and maintaining high alcohol consumption.[37–41] Likewise, increased density of δ or μ (or both) opioid receptors in brain regions known to mediate the positive reinforcing effects of drugs of abuse may also be important in initiating and maintaining high alcohol consumption.[42–47] Conversely, increased dynorphin activity or increased κ binding site density may inhibit high ethanol consumption.[14,36]

In this review, we present the experimental evidence that suggests the endogenous opioid system plays a role in controlling alcohol consumption, examine the opioid system's possible contribution to the genetic predisposition to alcohol dependency and summarize the effectiveness of pharmacotherapy based on opioid antagonists.

Endogenous opioid system

The endogenous opioid system is involved in 3 major functions: modulation of the response to painful stimuli and stressors; reward and reinforcement; and homeostatic adaptive functions, such as regulating body temperature and food and water intake.[48] The 3 distinct families of endogenous opioid peptides are defined by their precursor molecules.[49]

- Pro-opiomelanocortin (POMC) gives rise to β-endorphin, which is synthesized in the brain in the arcuate nucleus and a small group of neurons in the nucleus tractus solitarii.[50,51] β-Endorphin neurons of the arcuate nucleus project to various brain regions including the ventral tegmental area (VTA), nucleus accumbens, septum, amygdala, hippocampus, frontal cortex and periaqueductal gray.[49]
- Proenkephalin gives rise to 4 methionine (met)-enkephalin molecules and 1 of each met-enkephalin-Arg^6-Phe^7, met-enkephalin-Arg^6-Gly^7-Leu^8 and leucine (leu)-enkephalin.[52]
- Prodynorphin gives rise to dynorphins, α-neoendorphins and leu-enkephalin.[53] Neurons synthesizing enkephalins and dynorphins are widely distributed throughout the brain.[49]

At least 3 major classes of opioid receptors — μ, δ and κ — have been identified and characterized. The opioid peptides present different affinities for each of the opioid receptors. β-endorphin binds with about equal affinity to μ and δ opioid receptors, met- and leu-enkephalins bind with 10- to 25-fold greater affinity to δ than μ opioid receptors, and dynorphins bind selectively to κ opioid receptors[54] (Table 1).

Interactions of endorphins and enkephalins with μ

and δ opioid receptors increase dopamine (DA) release in the nucleus accumbens and may initiate processes associated with reward and reinforcement,[55] whereas dynorphins binding to κ opioid receptors, which has been shown to produce aversive states and decrease DA release, may prevent reinforcement.[55]

Brain reward system

The anatomical pathway of the brain reward system consists of a midbrain–forebrain–extrapyramidal circuit centred on the nucleus accumbens. The main regions associated with the reward system are the VTA, the nucleus accumbens, the septal area, the amygdala, the hypothalamus, the hippocampus and the frontal cortex.[55–57] Significant experimental evidence suggests that the reinforcing effects of many drugs of abuse, including ethanol, are mediated by the mesolimbic DA pathway,[55–57] consisting mainly by the A_{10} group of DA neurons. The A_{10} cell bodies in the VTA project to nuclei of the forebrain, mainly the nucleus accumbens, caudate, olfactory tubercles, frontal cortex, amygdala and septum.

Systemic administration of many drugs of abuse increases DA release in the nucleus accumbens.[55–57] Although evidence suggests that DA release is sufficient to produce reward, it may not be "required"; nondopaminergic mechanisms may be also involved.[55–57] Interestingly, data indicate that the acquisition of alcohol drinking behaviour may be dependent on the activation of mesolimbic DA neurons, but the maintenance of the behaviour does not require the functional integrity of mesolimbic DA neurons.[57–59] Therefore, different neuronal mechanisms may mediate the acquisition and the maintenance of alcohol drinking behaviour.[57–60] Furthermore, ethanol-induced activation of DA neurons may be mediated by the endogenous opioid system at the level of VTA and nucleus accumbens,[57,61,62] thus supporting a role of the endogenous opioid system in controlling alcohol consumption (Fig. 1).

To better understand how the endogenous opioids may influence alcohol consumption, it is helpful to review the effects ethanol has on the various opioid peptides and receptors.

Table 1: High-molecular-weight precursor molecules, major opioid peptides and relative affinity for opioid receptors

High-molecular-weight precursor	Major opioid peptides	Relative affinities for opioid receptors
Proopiomelanocortin	β-Endorphin 1–31	μ = δ
	β-Endorphin 1–27	μ = δ
Proenkephalin	Met-enkephalin	δ >> μ
	Leu-enkephalin	δ >> μ
Prodynorphin	Dynorphin 1–8	κ
	Dynorphin 1–17	κ
	Leu-enkephalin	δ >> μ

Ethanol and β-endorphin

Evidence suggests that ethanol alters the activity of the

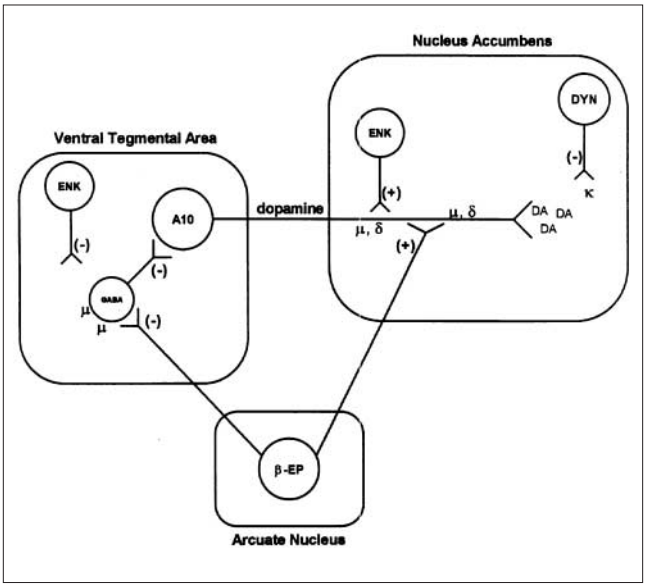

Fig. 1: Diagramatic representation of the possible interactions between the endogenous opioid system and the brain nuclei responsible for mediating the positive reinforcing effects of ethanol. A_{10} dopaminergic (DA) neurons, whose cell bodies are located in the ventral tegmental area (VTA) and whose axonal terminals are in the nucleus accumbens, are under tonic GABAergic inhibition. This inhibition may be removed when μ opioid receptors (located in the cell body of the GABA interneuron) are stimulated either by β-endorphin (originating in the arcuate nucleus and projecting to the VTA) or by enkephalins. In addition, DA release may be increased by stimulation of δ or μ opioid receptors in the nucleus accumbens. Ethanol stimulates β-endorphin or enkephalin release, and this may lead to increased DA release in the nucleus accumbens. In contrast, stimulation of κ opioid receptors in the nucleus accumbens by dynorphin peptides decreases DA release and may produce aversive states. GABA, γ-aminobutyric acid; β-EP, β-endorphin, ENK, enkephalin; DYN, dynorphin; (–) indicates inhibition; (+) indicates stimulation. Reproduced from Jamensky and Gianoulakis,[36] with permission of the publisher.

endogenous opioid peptides in the brain and pituitary, and these alterations may modulate, at least in part, many of the behavioural and neuroendocrine effects of ethanol, including that of reinforcement. Although all 3 opioid peptide systems have been implicated in this process, most investigations to date have focused on the effects of ethanol on β-endorphins in the brain and pituitary.

In the short term, in vivo ethanol administration increases the release of β-endorphin by the pituitary gland, the hypothalamus and other distinct regions of the brain.[41,63,64] The increased release by the pituitary is mediated by the ethanol-induced increase of hypothalamic corticotropin releasing hormone (CRH) and parallels the activation of the hypothalamic–pituitary–adrenal axis, as indicated by the changes in plasma levels of adrenocorticotropic hormone (ACTH) and glucocorticoids. The ethanol-induced increase of hypothalamic CRH mediates, at least in part, the enhanced release of β-endorphin, not only by the pituitary, but also by the hypothalamus (Fig. 2).

In vitro exposure of tissue of the pituitary gland or the hypothalamus to ethanol stimulates the release of β-endorphin in a dose-dependent manner;[40,65–67] low concentrations of ethanol induce a more pronounced increase in β-endorphin release than high concentrations, leading to an inverse U-shaped dose–response curve[40,66,68] (see Fig. 3). Furthermore, time-course studies indicate that this enhanced release is not maintained under prolonged exposure of the tissue to the same concentration of alcohol.[65,67] Indeed, ethanol induces a fast transient increase of β-endorphin release lasting about 15–20 min, and this is followed by a return to basal levels by both the pituitary and the hypothalamus.[65,67] It is noteworthy that in vivo studies also indicate a nonsustained ethanol-stimulated release of pituitary β-endorphin (Guillaume and Gianoulakis, McGill University, unpublished data, 1997).

Results of studies investigating the effects of long-term alcohol administration on pituitary and hypothalamic β-endorphin have been inconsistent. Some studies report that long-term alcohol administration leads to a significant increase in POMC mRNA, as well as in the biosynthesis of POMC and its post-translational processing to β-endorphin by the pituitary.[69,70] Others report a reduction in the biosynthesis and release of POMC-derived peptides;[71,72] another study reported an initial increase of POMC mRNA and a gradual return to control or even below-control levels, suggesting the development of ethanol tolerance by POMC-producing cells of the anterior pituitary.[73]

The effects of long-term alcohol administration on hypothalamic β-endorphin are also inconsistent, with some studies reporting enhanced activity,[74–76] some no change[77] and others decreased activity.[78] The inconsistencies are likely due to the length and method of

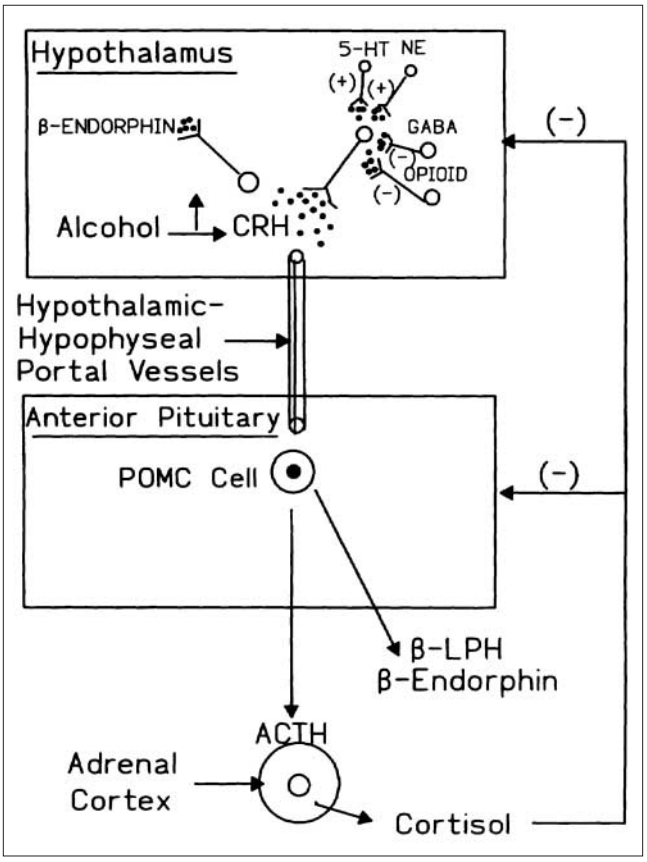

Fig. 2: Major neuroendocrine components of the hypothalamic–pituitary–adrenal axis. Hypothalamic neurons synthesize and release corticotropin releasing hormone (CRH), which is transported to the anterior pituitary via the hypothalamic-hypophyseal portal vessels, interacts with pro-opiomelanocortin (POMC) producing cells and stimulates the synthesis and release adrenalcorticotropin (ACTH), β-lipotropin (β-LPH) and β-endorphin. CRH also interacts with hypothalamic endorphinergic neurons and stimulates the release of β-endorphin in the brain. ACTH stimulates cells of the adrenal cortex to increase the synthesis and release of cortisol, and this increase in plasma cortisol inhibits the release of CRH and ACTH via a negative-feedback mechanism. The release of CRH is also inhibited by opioidergic and GABAergic neurons and stimulated by serotonergic (5-HT) and noradrenergic (NE) neurons. Ethanol stimulates the release of CRH, and this leads to increased release of β-endorphin, both by the pituitary and the hypothalamus.

ethanol administration (i.e., drinking, liquid diet, vapor inhalation), as well as to the quantity of ethanol consumed and species and strain differences. The conflicting results may also be associated with differences in the development of tolerance. The development of tolerance to specific effects of ethanol, such as the hypothermic effect, or the development of physical dependence was investigated by some,[70,74,78] but most studies[69,71–73,75–77] did not report tolerance-related effects.

Thus, experimental data clearly indicates that short-term ethanol exposure stimulates the release of brain β-endorphin, which may interact with specific μ and δ opioid receptors in regions of the brain that mediate, at least in part, many of the neurobehavioural effects of ethanol. However, because the release of β-endorphin is not sustained under prolonged ethanol exposure, enhanced β-endorphin activity may not be involved in maintaining the alcohol-drinking behaviour. On the contrary, the decrease in β-endorphin activity after prolonged exposure to ethanol may promote and maintain alcohol consumption through the mechanisms of negative rather than positive reinforcement. Indeed, after long-term exposure, many neuronal systems undergo adaptive changes to overcome the effects of alcohol and maintain their functional activity at about normal levels. Thus, when alcohol is no longer present, abnormalities in distinct neuronal systems may cause discomfort or pain and may increase craving and motivation to consume ethanol. This motivation to avoid discomfort is known as negative reinforcement. Decreased β-endorphin release after prolonged alcohol exposure may therefore lead to an increase in consumption through negative reinforcement.

Ethanol and the enkephalins and dynorphins

Although there are significantly less data on interactions of ethanol with the enkephalin and dynorphin opioid peptides, there is some evidence to indicate that both systems are influenced by alcohol; however, the effects seem to be tissue and species, strain or line specific.

Short-term ethanol administration has been reported to increase met-enkephalin levels in the striatum and hypothalamus[77] of rats, whereas long-term administration decreased met-enkephalin levels in many, but not all, brain regions assayed.[74,77] Other studies report no significant changes in met-enkephalin levels in the striatum and hypothalamus of the rat after short-term ethanol administration.[79] Ethanol intake was found to increase proenkephalin mRNA in the nucleus accumbens,[80] and prolonged administration increased met-enkephalin-Arg^6-Phe^7 in the same region; these effects were not ob-

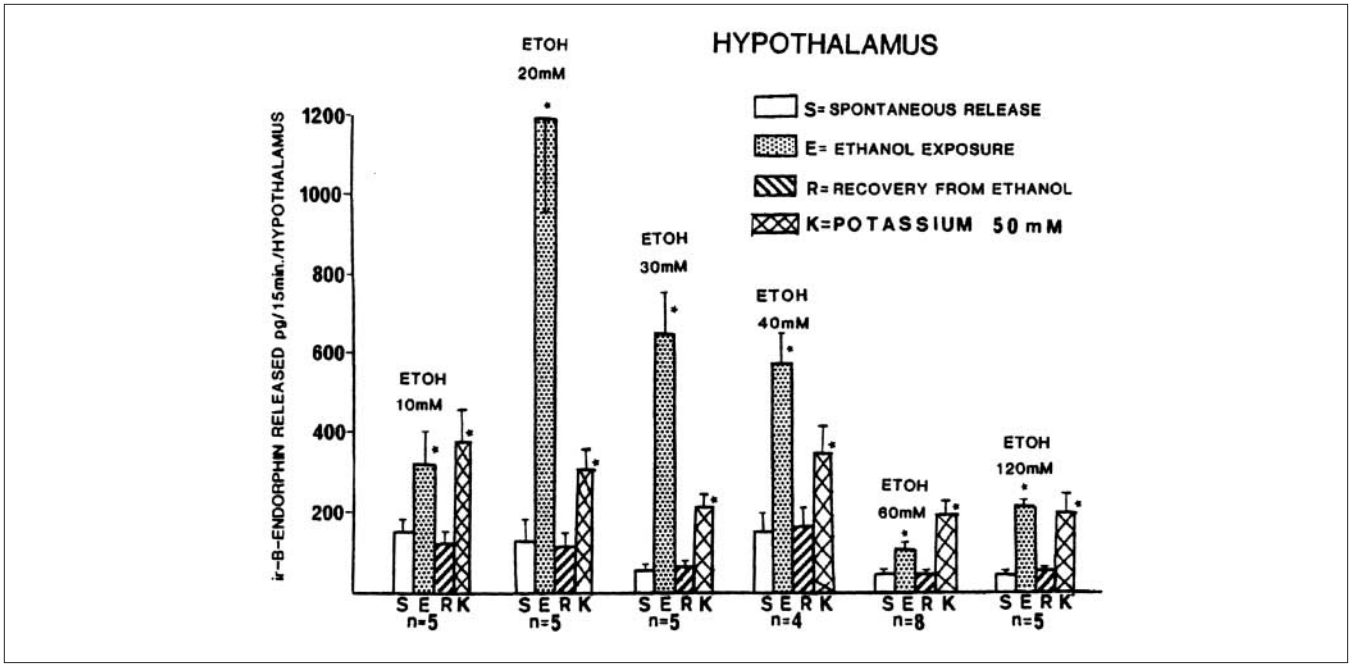

Fig. 3: The effect of various concentrations of ethanol (ETOH) and potassium (K) on the release of immunoreactive β-endorphin by the hypothalamus. Bars represent means and standard errors. *n* = number of distinct experiments. *Significantly different from spontaneous release ($p < 0.05$). Reproduced from Gianoulakis,[66] with permission of the publisher.

served in all lines of animals tested, however.[80,81]

Milton and Erickson[79] found that long-term ethanol administration decreased dynorphin and α-neoendorphin levels in the hypothalamus and hippocampus, but not in the striatum, midbrain and pituitary gland of male Sprague-Dawley rats. A reported increase in prodynorphin peptides in the nucleus accumbens after prolonged ethanol self-administration was also animal-line specific.[81]

It is evident that more studies are needed to clarify the effects of ethanol on enkephalin and dynorphin opioid peptides.

Ethanol and opioid receptors

Alcohol intake may alter, not only the activity of the endogenous opioid peptide system, but also the density or affinity of specific opioid receptors in distinct regions of the brain. Such changes would alter the interactions of the opioid receptors with their respective ligands and, as a result, would alter the functional activity of the whole system.

Opioid receptor changes may mediate some of the neurobehavioural effects of ethanol, including ethanol reinforcement. Indeed, experimental evidence indicates that both short- and long-term ethanol administration may affect opioid receptors. Again, study results are inconsistent; these inconsistencies may be due to differences in the type of opioid receptors and brain regions studied, alcohol concentration, duration and mode of alcohol administration, presence or absence of alcohol in the incubation medium during in vitro binding experiments, as well as the species, strains and lines of animals tested.

Early studies reported short-term in vitro exposure of brain membrane preparations to ethanol selectively decreased the binding to δ, but not to μ or κ opioid receptors,[82–84] whereas others reported an increased binding to μ opioid receptors.[84–87] Most early studies report that prolonged ethanol administration decreases binding to δ opioid receptors,[54,84,88,89] but data on the effect of long-term treatment on μ receptors are inconsistent (i.e., increase,[84,85] decrease[90,91] and no effect[92] on binding to μ opioid receptors). However, in many of the early studies, tissue preparations contained many receptor subtypes and the ligands were not very selective and recognized (with different affinities) more than 1 receptor subtype.[54]

In more recent studies, autoradiographic techniques have allowed the investigation of the effects of ethanol in specific brain regions, and the development of more selective ligands has allowed a better characterization of the effects of ethanol on specific opioid receptor systems. Thus, voluntary ethanol consumption for 30 days by the Sardinian alcohol-preferring rats increased binding to both μ and δ opioid receptors in the caudate putamen, but had no effect in the other regions studied.[45] However, ethanol in the drinking water of Wistar rats induced a down-regulation of the μ opioid receptors in the nucleus accumbens and striatum but had no effect on δ_1 and δ_2 opioid receptors.[93] These findings confirm earlier observations that alcohol-induced changes vary with the brain region investigated as well as the species and strain of animals used.

Despite the inconsistent reports on the effects of ethanol on opioid receptors, further evidence supporting a link between the opioids and alcohol consumption can be found in studies reporting the attenuation of ethanol self-administration after the administration of specific and nonspecific opioid receptor antagonists.[15,31,95] Such studies indicated that μ and δ opioid receptor antagonists are more effective in decreasing alcohol consumption[15,31] than κ opioid receptor antagonists.[94–98]

In addition, microinjection of an antisense oligodeoxynucleotide targetted to μ opioid receptors in the nucleus accumbens disrupted ongoing alcohol drinking by the ethanol-preferring (HEP) rats,[99] and knockout mice, either lacking β-endorphin or presenting half of the normal expression of β–endorphin, worked harder to obtain ethanol delivered either orally or intravenously.[100,101] On the other hand, C57BL/6 mice lacking the expression of the μ opioid receptor showed a decreased preference for ethanol solutions.[102]

Clinical studies have also shown that opioid receptor antagonists decrease alcohol consumption in those with an alcohol dependency.[29–31]

Genetic influence on alcohol consumption: implications of the endogenous opioid system

Epidemiological studies clearly indicate that genetic factors and family history play a significant role in determining a person's vulnerability for high alcohol consumption and alcoholism. Twin studies, adoption and cross-fostering studies, as well as detailed pedigree analyses all suggest that alcoholism "runs" in families. However, there are many genes that interact with envi-

ronmental factors in a complex manner to increase or decrease an individual's vulnerability to alcoholism.[103,104] In fact, studies indicate that sons of those with an alcohol dependency have a 4- to 9-time greater risk of becoming an alcoholic than sons of nondependent parents.[103,104]

However, not all the children inherit the genetic factors associated with increased vulnerability to high alcohol consumption. The physiologic, hormonal and psychological responses to alcohol of those with a positive or negative family history of alcoholism have been compared to determine if any biological markers might be used to identify individuals in high-risk families who have inherited the vulnerability for high alcohol consumption. These markers could be behavioural (e.g., impulsive or violent behaviour),[103] physiological (e.g., electroencephalographic [EEG] abnormalities[105] or body sway)[106] or biochemical markers (e.g., enzymes, hormones, neurotransmitters and neuromodulators).[37,38,107–112] Indeed, results from such studies indicate that a number of physiological responses, including electroencephalographic, heart rate and hormonal changes, might differ between individuals with and without a family history of alcoholism. Furthermore, sociocultural studies point to a number of environmental factors, for example culture and stress,[103,104,113] that increase or decrease the risk for alcoholism. Thus, it may be proposed that alcoholism is a multifactorial disorder, with an inherited predisposition interacting with specific environmental factors.[103,104]

Genetic differences in the activity of the endogenous opioid system may mediate the reinforcing effects of alcohol and play a role in controlling alcohol consumption. For example, in some individuals, genetic factors may cause a more pronounced release of β-endorphin or enkephalin in the VTA and nucleus accumbens in response to alcohol. Genetic factors may also lead to higher densities of μ or δ opioid receptors, creating more opportunities for interactions between opioid peptides and their receptors. In others, as proposed by the opioid deficiency hypothesis, genetic factors may be responsible for low opioid activity under basal conditions.[114]

Ethanol, by stimulating the release of opioid peptides, increases central opioid activity and stimulates the release of DA, leading to alcohol reinforcement. Indeed, genetic differences were observed between young nonalcoholic individuals with and without a family history of alcoholism. Subjects with a family history of alcoholism presented lower concentrations of plasma β-endorphin in the early morning hours and a more pronounced increase in pituitary β-endorphin release after the ingestion of moderate doses of alcohol.[37,38] Thus, low basal morning levels of β-endorphin and an increased release of pituitary β-endorphin in response to ethanol may be a biological marker and could be used together with other markers to distinguish individuals who have inherited a vulnerability for high alcohol consumption. In fact, a recent study of identical (monozygotic) and fraternal (dizygotic) twins to determine the heritability of hormonal responses to alcohol found that the β-endorphin response to alcohol presented significant heritability.[39] Moreover, increased levels of peripheral β-endorphin during physical activity or altered states of consciousness are associated with improved mood and a general feeling of well being,[115–117] suggesting that the pronounced ethanol-induced increase of pituitary β-endorphin observed in those with a family history of alcoholism may have a functional significance.

In addition to the differences in the pituitary β-endorphin system between subjects with and without a family history of alcoholism, differences have also been reported in the activity of the hypothalamic opioid system. The endogenous opioid system exerts inhibitory control over hypothalamic CRH-producing neurons.[118] Removing this inhibition by administering opioid antagonists such as naloxone increases the release of CRH, which leads to increased release of pituitary ACTH and adrenal cortisol.[118] The stronger the opioid-related inhibitory control on CRH neurons, the higher the dose of naloxone needed for disinhibition. Wand et al[118] found that significantly lower concentrations of naloxone were needed to remove the opioid inhibitory control of the CRH neurons in nonalcoholic offspring of alcohol-dependent individuals than in offspring of nondependent parents, perhaps indicating diminished hypothalamic opioid activity.[118] This deficiency may be attributed either to decreased levels of one or more opioid peptides or to decreased density of one or more opioid receptors. Presently, it is not known which component of the hypothalamic endogenous opioid system influences the hypoactivity under basal conditions.[118] However, this low central opioid activity in individuals with a family history of alcohol dependence may increase their vulnerability to alcoholism by altering the DA release from the nucleus accumbens. For example, it may be hypothesized that under basal conditions, the

opioid-stimulated release of DA is low, reflecting the low activity of the central endogenous opioid system. Alcohol stimulates the central endogenous opioid system, either by increasing the release of opioid peptides[37–41,63–68] or by altering the binding properties of opioid receptors[82–93] or both. Opioid activity will also stimulate DA release and, thus, enhance ethanol's reinforcing effect, and this may lead to increased alcohol consumption. Future brain imaging studies may provide support for this hypothesis.

Effect of alcohol abuse on the opioid system

In contrast to the effects of ethanol challenge and light alcohol consumption, both of which stimulate the brain and pituitary activity of opioid peptides,[37–39] prolonged alcohol consumption induces a decrease in brain and pituitary β-endorphin activity, as indicated by the low plasma and CSF β-endorphin levels in alcohol-dependent individuals and experimental animals exposed to prolonged alcohol treatment.[37,119–130] Thus, it may be proposed that individuals with a long history of alcohol dependence will exhibit a central opioid deficiency, which could be associated with decreased hypothalamic and pituitary β-endorphin synthesis and release, as well as with decreased opioid receptor density in distinct brain regions. Furthermore, alcoholic offspring of alcoholic parents, who have been shown to exhibit an opioid deficiency predating heavy alcohol consumption,[118] will present a more pronounced central opioid impairment than alcoholic offspring of nonalcoholic parents. This central and peripheral opioid deficiency may be perceived by the individual as a mild opioid withdrawal and may be an additional factor promoting heavy drinking, through the mechanisms of negative reinforcement.

Endogenous opioids in animal models of alcoholism

The contribution of genetic factors to the predisposition to excessive alcohol consumption is supported by animal studies of inbred and outbred strains and lines of animals that differ in their preference for drinking alcohol solutions (Table 2)[3–13] and in specific responses to short- and long-term alcohol exposure (Table 3).[131–139] Such selected lines of animals can be used to test various hypotheses of the neurochemical and neurophysiological bases for ethanol-related behaviours (e.g., ethanol-induced activation, anesthesia, hypothermia) and to study the development of tolerance and the severity of withdrawal symptoms. Differences in the sensitivity of selected lines of animals to specific effects of ethanol may also underlie differences in alcohol preference. It has been proposed that the more severe the ethanol withdrawal symptoms an animal experiences, the lower its voluntary ethanol consumption.[140] For example, when withdrawal seizure prone (WSP), withdrawal seizure resistant (WSR) and nonselected control mice were withdrawn from ethanol after similar long-term ethanol exposure,[140] the WSP mice experienced 10-fold more severe ethanol withdrawal than the WSR mice, and the control mice experienced intermediate withdrawal severity.[140] When given the choice between ethanol solutions and water, the WSR mice consumed more ethanol than the WSP, and the WSC mice consumed intermediate amounts.[140] A similar relation between severity of ethanol withdrawal and amount of ethanol consumed was observed between DBA/2 and C57BL/6 inbred strains of mice. The ethanol-avoiding DBA/2 mice experienced more severe withdrawal-induced seizures than the alcohol-preferring C57BL/6 mice.[141] Thus, different sensitivities to ethanol in se-

Table 2: Animal models using animals with high and low preference for alcohol

Study reference	Species and breeding	Strain or line with preference for ethanol	Strain or line with no or low preference for ethanol
McLearn and Rodgers[3]	Mouse, inbred strains	C57BL/6	DBA/2
Eriksson[7]	Rat, outbred lines	ALKO alcohol (AA)	ALKO nonalcohol (ANA)
Lumeng et al[8]	Rat, outbred lines	Preferring (P)	Non-preferring (NP)
Lumeng et al[9]	Rat, outbred lines	High-alcohol drinking (HAD)	Low-alcohol drinking (LAD)
Fadda et al[10]	Rat, outbred lines	Sardinian preferring (sP)	Sardinian non-preferring (sNP)
Crabbe and Li[11]	Mouse, outbred lines	High-alcohol preference (HAP)	Low-alcohol preference (LAP)
Sinclair et al[12]	Rat, outbred lines	High-alcohol research Foundation (HARF)	Low-alcohol research Foundation (LARF)
Myers et al[13]	Rat, outbred lines	High-ethanol preferring (HEP)	Low-ethanol preferring (LEP)

lected lines and strains of animals may predict differences in voluntary consumption.[140,141]

Selected lines of animals have been used to investigate the biochemical basis of alcoholism at the level of the central nervous system, where the rewarding and reinforcing effects of drugs of abuse are mediated. Human and animal studies[37–40] suggest a relationship between a highly responsive endogenous opioid system to ethanol and increased vulnerability to high alcohol consumption. If we accept that the endogenous opioids can modulate alcohol consumption, then genetic differences in the activity of one or more distinct components of the endogenous opioid system, either under basal conditions or after exposure to ethanol, may be important in determining the predisposition for excessive alcohol consumption. Indeed, numerous studies have investigated differences in the activity of the endogenous opioid system between ethanol-preferring and ethanol-avoiding animals.[36,37,40,42–47] For example, using northern blot analysis and in situ hybridization, a higher content of POMC mRNA was observed in the hypothalamus of the AA (alcohol preferring) than ANA (alcohol avoiding) rats[47,122] and of the C57BL/6 than DBA/2 mice.[40,46,123] Furthermore, C57BL/6 mice presented a higher basal release and a more pronounced and longer lasting hypothalamic β-endorphin response to a single ethanol exposure.[40,67] However, the ethanol-preferring AA rats presented a lower spontaneous release of hypothalamic β-endorphin than the ANA rats, although there was no difference in the ethanol-stimulated hypothalamic β-endorphin release between the 2 lines.[124]

Daily injections of ethanol over 4 days produced a greater increase in POMC mRNA in the anterior and neurointermediate lobes of the pituitary of ethanol-preferring P rats compared with ethanol-avoiding NP rats.[125] Studies of long sleep (LS) and short sleep (SS) mice demonstrated no significant differences in the basal levels of pituitary POMC mRNA, and after 4 days of ethanol treatment, there was a significant increase in pituitary POMC mRNA of both LS and SS mice.[73] However, after 7 days of ethanol treatment, pituitary POMC mRNA remained elevated in the SS mice, but not in the LS mice which presented a 40% decrease.[73] In another study, differences in the basal levels of pituitary β-endorphin among 16 strains of mice were reported, and these differences correlated genetically with the severity of ethanol withdrawal symptoms.[142] These studies support the hypothesis that genetically dependent differences in pituitary β-endorphin function may underlie some of the differences in the severity of the ethanol withdrawal symptoms.[142]

Basal levels of met-enkephalin peptides were reported to be lower in the nucleus accumbens of the AA than ANA rats[81] and in the hypothalamus of the C57BL/6 than DBA/2 mice;[126] a higher content of proenkephalin mRNA was also observed in the prefrontal cortex of the AA than ANA rats.[47] Using northern blot analysis and sensitive radioimmunoassay, it was shown that proenkephalin mRNA and met-enkephalin peptide levels were similar in the hypothalamus, striatum, hippocampus, and medulla pons and lower in the midbrain of the C57BL/6 than in DBA/2 mice.[127] The P and NP rats presented similar levels of

Table 3: Animal models of alcohol dependency based on specific responses to alcohol

Study reference	Species	Animal lines		Selection trait
McClearn and Kakihana[131]	Mouse	Long sleep (LS)	Short sleep (SS)	Anesthetic effect of alcohol as demonstrated by the duration of the righting reflex
Crabbe et al[132]	Mouse	FAST	SLOW	Alcohol-induced locomotor activity
Crabbe et al,[133] Kosobud and Crabbe,[134] Crabbe and Kosobud[135]	Mouse	Withdrawal seizure prone (WSP)	Withdrawal seizure resistant (WSR)	Severity of handling induced convulsions after chronic ethanol treatment
Wilson et al[136]	Mouse	Severe ethanol withdrawal (SEW)	Mild ethanol withdrawal (MEW)	Severity of ethanol withdrawal based on a multivariate index
Crabbe et al[137]	Mouse	Maximal ethanol-induced hypothermia (COLD)	Minimal ethanol-induced hypothermia (HOT)	Acute ethanol-induced hypothermia
Erwin and Deitrich[138]	Mouse	High acute functional tolerance (HAFT)	Low acute functional tolerance (LAFT)	Development of acute functional tolerance
Allan et al[139]	Rat	High-alcohol sensitivity (HAS)	Low-alcohol sensitivity (LAS)	Development of acute functional tolerance

preproenkephalin-derived peptides;[128] however, short-term ethanol treatment increased the preproenkephalin mRNA levels in the nucleus accumbens of the P but not of the NP line of rats. Moreover, after prolonged alcohol treatment, met-enkephalin-Arg^6-Phe^7 was higher in the nucleus accumbens of the AA than ANA rats.[81] AA rats were also found to have lower levels of prodynorphin mRNA in the mediodorsal nucleus of the thalamus[47] and lower levels of prodynorphin derived-peptides in the nucleus accumbens and VTA[81] than the ANA rats. Prodynorphin mRNA and prodynorphin-derived peptides were also significantly lower in the nucleus accumbens of the C57BL/6 than DBA/2 mice.[36]

Differences between alcohol-preferring and alcohol-avoiding animals have also been observed in the densities of μ, δ and κ opioid receptors in distinct regions of the brain known to be involved in the processes of drug reward and reinforcement.[35,36,42] AA rats were found to have higher density of μ opioid receptors in the shell region of the nucleus accumbens and prefrontal cortex but a lower density of κ opioid receptors in the ventromedial hypothalamus than ANA rats.[47] Some studies report higher density of δ opioid receptors in the nucleus accumbens of the AA rats;[35] others, using different opioid receptor ligands, report either lower density of δ opioid receptors in the AA rats[129] or no difference in δ opioid receptors density between AA and ANA rats.[130] The alcohol-preferring C57BL/6 mice were found to have a higher δ opioid receptor density and a lower κ opioid receptor density in the nucleus accumbens than DBA/2 mice,[36,42] and the alcohol-preferring P rats presented higher density of μ opioid receptors in some regions of the limbic system than the alcohol-avoiding NP rats.[143] However, no differences in μ opioid receptor mRNA were found between the HAD and LAD lines of rats.[144]

These comparative studies demonstrate that there is no single common component of the endogenous opioid system that is directly responsible for excessive alcohol consumption. Indeed, this observation is in agreement with reports demonstrating that although the μ opioid receptor antagonists are more effective in reducing alcohol consumption by the AA line of rats,[25] δ opioid receptor antagonists are more effective in decreasing alcohol consumption by C57BL/6 mice[145] as well as by the P and HAD lines of rats.[18,23,24] Furthermore, there are indications that the κ opioid receptor dynorphin peptide system also plays a role in controlling alcohol consumption.[95,146]

Considering the complexity of the endogenous opioid system and the fact that it interacts with a number of other neurotransmitter systems (e.g., GABAergic, serotonergic and DA systems), it is reasonable to conclude that the role of the opioid system in alcohol consumption is a complicated one involving different distinct components of the opioid system for different individuals and selectively bred lines of animals. However, understanding how these components, through their interactions with other neurotransmitter systems, are involved in the control of alcohol consumption may allow the development of effective treatments for alcoholism. Furthermore, future studies investigating genetically determined differences in the activity of the endogenous opioid system or in its interactions with other neurotransmitter systems should include a number of selected lines or strains of animals or a number of recombinant inbred strains. Such studies would allow us to correlate the differences in the activity of distinct components of the endogenous opioid system with differences in the sensitivity to or preferences for ethanol presented by the animals investigated.

Opioid antagonists to treat alcoholism

The administration of nonspecific opioid receptor antagonists, such as naloxone and naltrexone, as well as of μ and δ selective opioid receptor antagonists has been shown to decrease alcohol consumption in a dose-dependent manner by a number of animal species and in a number of experimental paradigms.[14–28] Furthermore, studies indicate that κ opioid receptor agonists may also attenuate alcohol consumption.[94–97] Naltrexone has been reported to be an effective treatment for individuals with alcohol dependence,[29–31] and in reducing relapse rates, as well as craving and alcohol intake, when it was combined with behavioural therapy.[31]

Currently, naltrexone (ReVia) is approved in Canada and the United States for the treatment of alcoholism. It is the first drug in 50 years to be approved in the US specifically for alcoholism. Naltrexone is, in general, well tolerated at low doses, but hepatotoxicity may occur at doses above 50 mg/day.[31,147–149] Other opioid receptor antagonists such as nalmefene have also been found to be effective in decreasing alcohol consumption in humans.[150] In addition, nalmefene is not associated with hepatotoxicity.[150]

After the initial studies on the effectiveness of naltrexone to reduce drinking in humans, a number of

studies were performed in various treatment centres and laboratories to provide a better understanding of how naltrexone decreases alcohol consumption. Although the major mechanism is considered to be related to the inhibition of ethanol's positive reinforcement,[151] animal studies have shown that long-term opioid antagonist administration, such as naltrexone or naloxone, causes increased release of opioid peptides[152] and density of opioid receptors,[153,154] suggesting an upregulation of the endogenous opioid system; however, this would render naltrexone less effective in preventing alcohol relapse, unless additional nonopioid mechanisms are involved in achieving its long-term therapeutic efficacy. Indeed, subjects who had been taking naltrexone, when given alcohol to drink, reported an increase in the subjective ratings of sedative and unpleasant effects and a decrease in the subjective ratings of liking, best effects and desire to drink, but there was no alteration in the subjective or objective indicators of drunkenness.[155] Naltrexone has also been shown to dampen the cardiovascular responses to alcohol, which may play an important role in its therapeutic efficacy (JB Peterson, P Conrod, J Vassileva, C Gianoulakis, RO Pihl, McGill University, unpublished data, 2001). Therefore, naltrexone may act by both opioid and nonopioid mechanisms to reduce alcohol consumption. Although naltrexone may be used to treat those who are alcohol-dependent, its negative side effects decrease compliance and, as a result, decrease its effectiveness.[156]

In future studies, the effectiveness of opioid receptor antagonists selective for specific opioid receptor subclasses, as well as selective κ opioid receptor agonists, in decreasing alcohol consumption should be investigated. Considering the multifactorial nature of alcohol dependence, involving various subtypes of opioid receptors and many neurotransmitter systems, medications directed to more than one neurotransmitter system should be considered.[157] Such medications might be effective at lower doses, induce fewer side effects and thus increase compliance and treatment effectiveness.

Summary

There is increasing evidence from human and animal studies supporting a link between the endogenous opioid system and the development of alcoholism. Overactivity or hypoactivity of distinct components of the opioid system in distinct brain regions associated with reward and reinforcement may be associated with an increased vulnerability to excessive alcohol consumption exhibited by some people, as well as by animals selectively bred for alcohol preferences. The effects of endogenous opioids in controlling alcohol consumption may be either direct or through interactions with other neurotransmitter systems that have been shown be important in the control of alcohol consumption. Because of this multifactorial nature of alcohol dependence, efforts must be made to personalize treatment for each individual by trying to identify the appropriate biological, psychosocial and environmental determinant(s) contributing to the development of alcoholism. Depending on the individual patient, such treatment might include both pharmacotherapy and behavioural psychosocial therapy.[158–160]

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