INTRODUCTION

Many reports suggest the involvement of the endogenous opioid system as a relevant part of the neurobiological mechanisms that are functionally involved in the reinforcement of drinking behaviour and development of alcohol dependence. In particular, findings showing that alcohol-induced dopamine release can be blocked by opioid antagonists implicate opioidergic activity as an intermediary in the process (Benjamin et al., 1993; Gonzales and Weiss, 1998). Available data suggest that alcohol increases opioid neurotransmission and that this activation is part of the mechanism responsible for the reinforcing effects of alcohol (Gianoulakis, 1996; Ulm et al., 1995). Furthermore, a number of studies suggest that alterations in gene expression of opioid peptides may determine the vulnerability to alcohol dependence (Oswald and Wand, 2004) and the therapeutic efficacy of antigraving drugs.

A summary of facts relating alcohol intake, development of alcohol dependence and genetic vulnerability to alcohol with endogenous opioid and cannabinoid receptor systems are depicted in Fig. 1. As shown, excessive alcohol consumption is a complex, multifactorial problem that includes not only the alteration of neurochemical elements in the brain but also a number of psychosocial conditions that may possibly favour the development of problems related to alcohol intake, which has been observed in dependent subjects. From these conditions (left part of Fig. 1), several personality traits such as high impulsivity, low self-esteem and sensation-seeking behaviour may contribute greatly to enhance vulnerability to alcohol dependence. In addition, a number of psychiatric disorders (phobias, attention-deficit hyperactive disorder or affective disorders) may also modify the effects of alcohol, enhancing its reinforcing properties and leading towards the progression to alcohol dependence. Although psychological traits and psychiatric conditions play a major role in the development, treatment and relapse of alcoholism, the findings of neurochemical alterations reported in a number of preclinical studies have allowed the identification of potential targets involved in the development, treatment and reinstatement of alcohol seeking behaviour.

It is well known that alcohol intake increases the release of opioid peptides and subsequently increases gene expression in mesencephalic brain areas related to reinforcement and reward, such as the nucleus accumbens or the ventral part of caudate-putamen. In these regions, alcohol-induced opioid release stimulates dopamine neurons by acting directly on the nucleus accumbens and by disinhibiting GABA mesencephalic neurons projecting into the dopamine tegmental area (Spanagel and Weiss, 1999). Alterations in dopamine neurons in the terminals (nucleus accumbens, cortex) and/or cell bodies (ventral tegmental area) of mesolimbic and mesocortical systems lead to loss of a neurochemical homeostatic control, contributing to the development of relapse and facilitating the progression to alcohol dependence. Differences in opioid functional activity have also been associated with a distinct vulnerability to drugs of abuse in animal models of drug dependence. Indeed, the examination of basal opioid gene expression has revealed that lower opioid activity in the areas involved in motivation and reward of rats that were selected for their high preference for alcohol appears to be related to increased vulnerability to alcohol dependence (Nylander et al., 1994). In preclinical studies, blockade of opioid...
receptors with the non-selective receptor antagonist naltrexone decreases alcohol intake in alcohol-preferring rats and reduces the alcohol-induced increase in opioidergic activity (Cowen and Lawrence, 2001), thereby inhibiting, at least in part, the reinforcing properties of alcohol.

In recent years, several reports have suggested a close interaction between the endogenous cannabinoid system and alcohol consumption. It has been suggested that ethanol, using neuronal cells, increases the release of the endogenous cannabinoid ligands arachidonylethanolamide (AEA) and 2-arachidonylglycerol (2-AG) (Basavarajappa and Hungund, 1999a; Basavarajappa et al., 2000, 2003). The increase in ligand release may continuously activate the receptor, potentially down-regulating the cannabinoid CB1 receptor, after chronic ethanol administration, as shown recently (Basavarajappa et al., 1998; Basavarajappa and Hungund, 1999b; Ortiz et al., 2004a). On the other hand, although it remains to be clarified, the administration of low doses of cannabinoid agonists enhances ethanol intake and this effect appears to be dependent upon the conditions of the experimental paradigm (Gallate and McGregor, 1999; Colombo et al., 2002). Conversely, several authors suggest that the administration of cannabinoid receptor antagonists reduces ethanol intake in rodents (Arnone et al., 1997; Colombo et al., 1998). Several mechanisms may participate in reducing ethanol intake in rats treated with the cannabinoid antagonist. First, as shown in Fig. 1, the blockade of cannabinoid CB1 receptors may impede the increase in opioid release induced by ethanol. Second, cannabinoid receptor antagonists may reduce the ethanol-induced increase in mesencephalic dopamine neurons or block the disinhibition of GABAergic neurons (for review see Piomelli, 2003) that, in turn, results in the activation of dopamine neurons. This represents hypothetically distinct mechanisms by which the use of cannabinoid antagonists may be effective in reducing ethanol intake.

Taking into account that the administration of cannabinoid receptor agonists enhances endogenous opioid activity (Corchero et al., 1997a,b; Manzanares et al., 1999), differences in endogenous cannabinoid and opioid function may suggest a distinct vulnerability to ethanol consumption and/or dependence. Therefore, it is tempting to speculate that animals with low opioid expression and more vulnerability to ethanol may have impaired cannabinoid receptor function in key regions of the brain related to motivation and reward.  

In the present review, we examined some of the effects of ethanol on opioid and cannabinoid receptor systems in the brain in relation to chronic consumption, genetic vulnerability towards high preference for ethanol and the pharmacological response to opioid and cannabinoid receptor antagonists in relation to ethanol consumption.

**ROLE OF OPIOID SYSTEM ON ETHANOL INTAKE, VULNERABILITY AND DEPENDENCE**

**Opioid receptors**

Consumption of ethanol in animal models of ethanol dependence modifies the expression and function of opioid receptors. However, in several reports a great variability has been detected that appears to depend on the method used to induce ethanol dependence, the region examined and/or the strain of rats or mice used (Gianoulakis, 2001; Oswald and Wand, 2004). For instance, prolonged (30 days) ethanol...
consumption increases the binding of mu-opioid receptors in the caudate putamen of Sardinian rats (Fadda et al., 1999) but downregulates these receptors in the nucleus accumbens and caudate-putamen of Wistar rats (Turchan et al., 1999). Similarly, Chen and Lawrence (2000) have shown that chronic (50 days) voluntary ethanol intake inhibits DAMGO-stimulated $[^{35}\text{S}]\text{GTP}\gamma\text{S}$ binding in the nucleus accumbens, caudate-putamen, and lateral septum in Fawn-Hooded ethanol-prefering rats. In contrast, Sim-Selley et al. (2002) have reported that mu-opioid-stimulated $[^{35}\text{S}]\text{GTP}\gamma\text{S}$ binding was lower in the prefrontal cortex of brains from ethanol self-administering Long Evans rats, although voluntary ethanol intake showed no effect on mu-opioid function in the cingulate cortex, caudate-putamen, nucleus accumbens, amygdala, hypothalamus, thalamus, and locus coeruleus compared with sucrose self-administering rats. These results taken together suggest that alterations in the mu-opioid receptor may be related to the duration and level of ethanol consumption, the regions of the brain examined and pattern of ethanol intake (Table 1).

The development of gene knockout technique has further strengthened the evidence supporting the key role of opioid receptors in ethanol dependence. Indeed, Roberts et al. (2000) have reported that mice deficient in mu-opioid receptor do not self-administer ethanol. Similarly, delta-opioid receptor knockout mice displayed a greater preference for ethanol and consumed more ethanol than wild-type mice, suggesting that a decrease in delta-receptor activity may be associated with increased ethanol-intake behaviour (Roberts et al., 2001).

### Opioid peptides

It is well established that ethanol induces the release of opioid peptides, which interact with brain nuclei closely involved in reward and positive reinforcement systems (Jamensky and Gianoulakis, 1997; Koob et al., 1998). Acute ethanol administration increases endorphin and enkephalin gene expression in discrete regions of the brain and increases the release of these peptides in the brain and pituitary of rodents (Schulz et al., 1980; Gianoulakis and Barcomb, 1987; Patel and Pohorecky, 1989; Anwer and Soliman, 1995; Li et al., 1998; Rasmussen et al., 1998; Oliva et al., 2002a, 2003a) (Table 2).

On the other hand, prolonged ethanol administration may decrease the release of endogenous opioid peptides. For instance, chronic ethanol administration decreased pro-opiomelanocortin gene expression in the forebrain (Oliva et al., 2002b; Rasmussen et al., 2002) and in the pituitary gland (Patel and Pohorecky, 1989; Oliva et al., 2002b) of rats and β-endorphin release in cultured hypothalamic neurons (Boyadjieva and Sarkar, 1994). However, Cowen and Lawrence (2001) have shown that ethanol consumption increases preproenkephalin mRNA in central and intercalated nuclei of the amygdala but decreases preproenkephalin mRNA in the nucleus accumbens and olfactory tubercle. These authors suggest that alterations in opioid peptide release and/or gene expression are dependent on the regions of the brain examined and the duration of ethanol consumption (Table 2).

The role of opioid peptide release and opioid gene expression has also been investigated in relation to increased vulnerability to ethanol dependence. Several studies have shown that basal opioid activity differs between ethanol-prefering and non-prefering strains of rodents. Selectively bred AA (ethanol-prefering) rats present a higher hypothalamic basal pro-opiomelanocortin gene expression compared with ANA (ethanol-avoiding) rats (Marinelli et al., 2000) and more sensitivity to ethanol consumption in selectively bred, ethanol-prefering P rats compared with ethanol-avoiding NP rats (Krishnan-Sarin et al., 1998) as well as in ethanol-prefering C57BL/6 mice compared with ethanol non-prefering DBA/2 mice (Jamensky and Gianoulakis, 1999).

Met-enkephalin and Leu-enkephalin peptide levels were lower in the nucleus accumbens of AA compared with ANA rats (Nylander et al., 1994), whereas a more intense proenkephalin expression was reported in the prefrontal cortex of AA compared with ANA rats (Marinelli et al., 2000). Despite a number of studies that examined the basal functional activity of opioid receptors in selectively bred rats with a high preference for ethanol consumption, the results remain inconclusive. It has been shown that the density of opioid receptors in various regions of the brain is lower, higher or similar in ethanol-prefering compared with non-prefering rats (McBride et al., 1998; Marinelli et al., 2000).

Our laboratory has determined opioid functional activity in naive ethanol-prefering Fawn-Hooded rats and ethanol non-prefering Wistar rats. The Fawn-Hooded strain of rat shows a high preference for ethanol intake (10% v/v) in a two-bottle free-choice situation (Rezvani et al., 1990; Ortiz et al., 2004b) that may be related, at least in part, to decreased brain opioid function (Cowen et al., 1998; Rezvani et al., 2002). Indeed, as depicted in Fig. 2, we have observed lower mu-opioid receptor-stimulated $[^{35}\text{S}]\text{GTP}\gamma\text{S}$-binding autoradiography in the caudate-putamen and cingulate cortex, lower proenkephalin gene expression in the caudate-putamen and nucleus accumbens, and lower pro-opiomelanocortin gene expression in the arcuate nucleus of Fawn-Hooded compared with Wistar rats. Therefore, the results of this study, in agreement with previous reports, strongly support the hypothesis that the basal functional activity of the opioid system plays a critical role in the vulnerability to ethanol intake.

### Table 1. DAMGO-stimulated $[^{35}\text{S}]\text{GTP}\gamma\text{S}$ binding in different brain regions of several rat strains after chronic ethanol consumption

<table>
<thead>
<tr>
<th>Animals</th>
<th>Brain regions</th>
<th>$[^{35}\text{S}]\text{GTP}\gamma\text{S}$ binding</th>
<th>Ethanol administration</th>
<th>References</th>
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<tr>
<td>Sardinian</td>
<td>CPu, Acc</td>
<td>↑</td>
<td>Two-bottle choice paradigm</td>
<td>Fadda et al., (1999)</td>
</tr>
<tr>
<td>Wistar</td>
<td>CPu, Acc</td>
<td>↓</td>
<td>Two-bottle choice paradigm</td>
<td>Turchan et al., (1999)</td>
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<tr>
<td>Fawn-Hooded</td>
<td>CPu, Acc, Lateral Septum</td>
<td>↑</td>
<td>Two-bottle choice paradigm</td>
<td>Chen and Lawrence, (2000)</td>
</tr>
<tr>
<td>Long Evans</td>
<td>PF cortex Cg, CPu, Acc, Ce, hyp, thalamus, LC</td>
<td>↓</td>
<td>Ethanol self-administration</td>
<td>Sim-Selley et al., (2002)</td>
</tr>
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</table>

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Table 2. Acute and chronic effects of ethanol on opioid release and gene expression in various brain and pituitary regions of rodents

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<thead>
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<th>Acute</th>
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<td><strong>POMC</strong></td>
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<td><strong>PENK</strong></td>
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<td>VMN, PVA)</td>
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<td>(Arc, Ce)</td>
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<td><strong>β-endorphin</strong></td>
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<td>(Hyp, septum,</td>
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<td>forebrain)</td>
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<td>Met-enkephalin</td>
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<td>(CPu)</td>
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<td>= (Hyp, forebrain medulla)</td>
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POMC, pro-opiomelanocortin; PENK, proenkephalin; CPu, caudate-putamen; Acc, nucleus accumbens; Tu, olfactory tubercle; Pir, piriform cortex; Ce, central amygdala; Me, medial amygdaloid nucleus; IM, intercalated amygdaloid nucleus; VMN, ventromedial nucleus; PVA, paraventricular nucleus; Hyp, hypothalamus; Arc, arcuate nucleus; IL, intermediate lobe of the pituitary; AL, anterior lobe of pituitary; PFx, prefrontal cortex.

Fig. 2. Proenkephalin gene expression in the caudate-putamen (CPu), pro-opiomelanocortin gene expression in the arcuate nucleus (ARC), and DAMGO-stimulated [35S]GTP\(^\gamma\) binding in CPu and cingulate cortex (Ccg) of 10 Fawn-Hooded and Wistar rats. Both strains of rats received food and water ad libitum. Gene expression was measured by in situ hybridization histochemistry, using synthetic oligonucleotide probes complementary to proenkephalin (PENK) or pro-opiomelanocortin (POMC) genes labelled with \(^{35}\)S using terminal deoxytransferase as described previously (Young et al., 1986; Oliva et al., 2003). [35S]GTP\(^\gamma\) binding in CPu and cingulate cortex (Ccg) was carried out following the method described by Sim-Selley et al. (2002). Symbols represent the means and vertical lines set the ± SEM in 10 rats of both strains. *Values from proenkephalin, pro-opiomelanocortin gene expression and DAMGO-stimulated [35S]GTP\(^\gamma\) binding that are significantly different (P < 0.05, Student’s t-test) in the comparison of both strains of rats.

Representative autoradiograms of coronal brain sections at the level of CPu, Ccg and ARC in Fawn-Hooded and Wistar rats. Bar represents 1 mm.
Regulation of ethanol intake by opioid receptor agonists

The precise mechanisms underlying the reinforcing properties of ethanol remain to be determined. Nevertheless, experimental results suggest that the endogenous opioid system plays a major role in the consumption of ethanol in animals. Indeed, pharmacological manipulations of opioid receptors affect the rewarding properties of ethanol, acquisition and maintenance of its consumption. Administration of small doses of morphine plus ethanol showed a strong conditioned place preference compared with morphine or ethanol administration alone (Marglin et al., 1988). Furthermore, the potentiation of ethanol consumption induced by intracerebroventricular (Linseman and Harding, 1990) or systemic (Reid and Hunter, 1984; Hubbell et al., 1991, 1987; Stromberg et al., 1997a,b) administration of doses of morphine is due to its interaction with opioid receptors, which modulate the ethanol rewarding effects.

ROLE OF THE CANNABINOID SYSTEM ON ETHANOL INTAKE, VULNERABILITY AND ADDICTION

Effects of ethanol intake on the cannabinoid system

The behavioural and neurochemical effects of marihuana along with ethanol have interested a great number of scientists for many years. However, not until recently have researchers been able to describe an endocannabinoid system in the brain composed of cannabinoid CB1 receptors and endogenous ligands. Similarly, the necessary pharmacological tools (cannabinoid receptor agonists and antagonists) to explore the role of this system towards the development and treatment of ethanol dependence became available only recently. The pioneering studies in this precise area were the elegant investigations conducted by Arnone et al. (1997), who described for the first time the inhibition of ethanol intake by the cannabinoid receptor antagonist SR 141716A. The results of this study were extended and confirmed by other authors (Colombo et al., 1998; Freedland et al., 2001), strengthening the involvement of the cannabinoid CB1 receptor in the pharmacotherapy of ethanol dependence. The fact that the blockade of cannabinoid CB1 receptor modulates ethanol intake led other investigators to examine the effects of ethanol on the endogenous cannabinoid system. The initial studies, which were a considerable achievement in this line of research, were the investigations carried out by Basavarajappa and Hungund (1999a,b). These authors pointed out for the first time that chronic ethanol administration downregulated cannabinoid receptors in synaptic plasma membranes of the mouse brain (Basavarajappa et al., 1998) and increased the levels of the endogenous cannabinomimetic compound anandamide and its precursor N-arachidonoylphosphatidylethanolamine in SK-N-SH cells (Basavarajappa and Hungund, 1999a). In cerebellar granule neurons, chronic ethanol exposure induced a significant increase in the levels of the endocannabinoid 2-AG (Basavarajappa et al., 2000). Confirming these studies in our laboratory (Ortiz et al., 2004a), we recently reported that chronic (52 days) forced consumption of high levels of ethanol (average ethanol intake = 5.8 ± 0.1 g of ethanol/kg/day) significantly decreased the cannabinoid CB1 receptor gene expression in rat brain areas of the rat brain such as the caudate-putamen, ventromedial nucleus of the hypothalamus, and certain fields of the hippocampus (CA1, CA2) (Fig. 3). These results provide additional support to the hypothesis that prolonged ethanol intake increases brain endocannabinoid ligands (Basavarajappa and Hungund, 1999a; Basavarajappa et al., 2000), which in turn decrease the CB1 receptor gene expression and function (Basavarajappa et al., 1998; Basavarajappa and Hungund, 1999b; Ortiz et al., 2004a).

Role of the cannabinoid system in vulnerability to ethanol intake

Coinciding evidence suggests that the CB1 receptor signalling system may play an important role in modulating ethanol-reinforcing effects and in the preference for ethanol intake behaviour. It has been demonstrated that ethanol-prefering C57BL/6J mice have a significantly lower level of CB1

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Fig. 3. Cannabinoid CB1 receptor gene expression in CPu, Ccg, hippocampal areas (CA1, CA2, CA3 and DG) and ventromedial nucleus (VMN) in control and forced-ethanol groups of rats. Rats had unlimited access to only a solution of ethanol (10% v/v) containing saccharin (0.25% w/v) or to water containing the same saccharin solution for a total period of 52 days. Columns represent the means and vertical lines + SEM of CB1 mRNA levels in 8 rats; *values from cannabinoid CB1 receptor gene expression levels in CPu, Ccg, hippocampal areas and VMN from the forced-ethanol group that differ significantly (P < 0.05) from the control group. (Reproduced from Ortiz et al., 2004a from Alcohol and Alcoholism by permission of Oxford University Press).
receptors and higher affinity for $[^3]$H]CP-55,940 than ethanol-avoiding DBA/2 mice, which do not readily consume ethanol (Hungund and Basavarajappa, 2000). Furthermore, the higher levels of CB$_1$ receptors found in DBA/2 mice are less strongly coupled to G-proteins than in C57BL/6J mice, as shown by the CB$_1$ receptor agonist (WIN-55,212-2 or HU-210 or CP-55,940)-stimulated $[^35]$S[GTP]$\gamma$S-binding assay (Basavarajappa and Hungund, 2001).

Taking into account the idea that lower cannabinoid CB$_1$ receptor function may be associated with increased vulnerability to high ethanol preference and consumption, we recently compared the activity of cannabinoid CB$_1$ receptor (WIN-55,212-stimulated $[^35]$S[GTP]$\gamma$S-binding autoradiography, and gene expression) in ethanol-preferring Fawn-Hooded and ethanol non-preferring Wistar rats under naïve conditions (Ortiz et al., 2004b). The results of this study confirmed the presence of lower cannabinoid CB$_1$ receptor-stimulated $[^35]$S[GTP]$\gamma$S binding in cingulate cortex, caudate-putamen, nucleus accumbens, ventromedial hypothalamic nucleus, amygdaloid area, and certain fields of the hippocampus in Fawn-Hooded compared with Wistar rats (Fig. 4). The notion is further supported by the fact that the cannabinoid CB$_1$ receptor gene expression was also lower in the cingulate cortex, caudate-putamen, ventromedial hypothalamic nucleus and CA3 area of hippocampus in Fawn-Hooded compared with Wistar rats (Ortiz et al., 2004b).

The development of mice deficient in CB$_1$ receptor gene has also been critical in demonstrating that the endocannabinoid signalling acting on CB$_1$ receptors is involved in ethanol preference. It has been shown that these CB$_1^{-/-}$ mice exhibited dramatically reduced voluntary ethanol consumption (Hungund et al., 2003; Poncelet et al., 2003; Wang et al., 2003; Naassila et al., 2004).

**Regulation of ethanol intake by cannabinoid receptor agonists**

The fact that the exposure and intake of ethanol may induce alterations in the function and activity of the endocannabinoid system supports the notion that pharmacological manipulations of the cannabinoid CB$_1$ system may affect ethanol consumption. Earlier studies by McMillan and Snodgrass (1991) showed that acute administration of $\Delta^9$-tetrahydrocannabinol (THC) reduced ethanol intake in rats by 5 and 7%. However, these authors also reported that chronic administration of THC initially decreased ethanol intake and, when tolerance occurred, ethanol consumption increased, even during THC withdrawal. The hypothesis, which suggests that the activation of cannabinoid CB$_1$ receptor stimulates ethanol intake, was further confirmed by the studies of Gallate and McGregor (1999) and Colombo et al. (2002). These authors showed that acute administration of the cannabinoid CB$_1$ receptor agonists CP-55,940 or WIN-55,212...
promoted voluntary ethanol intake in Sardinian ethanol-prefering (sP) rats (Colombo et al., 2002) and increased the breakpoints for beer (Gallate and McGregor, 1999). In both studies, the increase in ethanol intake induced by CP-55,940 or WIN-55,212 was prevented by cannabinoid or opioid receptor antagonists, strongly suggesting the participation of both systems in this process.

ROLE OF CANNABINOID AND OPIOID ANTAGONISTS IN THE TREATMENT OF ETHANOL DEPENDENCE

A variety of rewarding stimuli including ethanol, enhance the activity of the endogenous opioid system (Gianoulakis, 1996). It has been hypothesized that this increase in opioid activity may explain, at least in part, the reward response produced by ethanol. Therefore, the blockade of central opioid receptors using selective and non-selective opioid antagonists may modulate the positive reinforcing properties of ethanol (Weiss et al., 1990; Franck et al., 1998) and prove effective in reducing ethanol consumption. Indeed, naltrexone, which attenuates ethanol consumption in laboratory animals (Volpicelli et al., 1986; Cowen and Lawrence, 2001; Oliva et al., 2003b) and in humans (Volpicelli et al., 1992; Kranzler et al., 1997), is a non-selective opioid antagonist approved for this clinical indication in Europe and United States.

The mechanisms by which the administration of naltrexone reduces ethanol intake have not been examined precisely. Recent reports suggest that naltrexone would render as ‘normal’, the endogenous opioid activity modified previously by prolonged ethanol consumption. Indeed, naltrexone, which reduces ethanol consumption by ~50% and that this decrease was accompanied by a reduction in proenkephalin gene expression (elevated previously by prolonged ethanol consumption) in the caudate-putamen, core and shell parts of the nucleus accumbens, and olfactory tubercle (Oliva et al., 2003b).

The administration of cannabinoid receptor antagonists also reduces ethanol intake in a wide variety of experimental paradigms. The administration of CB1 receptor-selective antagonists such as SR-141716A, SR-147778 or AM-251 reduced voluntary ethanol consumption under the home-cage two-bottle regimen or self-administration procedures in ethanol-consuming rats and mice (Armone et al., 1997; Colombo et al., 1998; Freedland et al., 2001; Lallemand et al., 2001; Rinaldi-Carmona et al., 2004), blocked acquisition of ethanol-drinking behaviour in rats (Serra et al., 2001), decreased the motivation to consume ethanol in rats (Gallate and McGregor, 1999) and completely abolished the ethanol deprivation effect (Serra et al., 2002). However, little is known of the neurochemical mechanisms involved in this action. Since the increase of ethanol consumption induced by the cannabinoid receptor agonists CP-55,940 or WIN-55,212 can be blocked by administration of either naltrexone or SR-141716A, and cannabinoid receptor agonists increase the endogenous opioid function (for review, see Manzanares et al., 1999), it is tempting to speculate that the reduction of ethanol intake produced by administration of cannabinoid receptor antagonists may be related, as suggested previously for opioid receptor antagonists, to the ‘normalization’ of opioid peptides or opioid receptor functional activity altered by prolonged consumption of ethanol. Recent studies carried out in our laboratory revealed that the reduction of ethanol intake induced by the cannabinoid receptor antagonist AM-251 was associated with a lower decrease of [35S]GTPγs binding in the caudate-putamen and pro-opiomelanocortin gene expression in the anterior lobe of the pituitary gland compared with the reduction produced by vehicle-ethanol treated rats (Ortiz et al., unpublished results). That is, administration of AM-251 tended to normalise mu-opioid receptor binding, altered previously by continuous exposure to ethanol.

The neurochemical mechanisms involved in the reduction of ethanol intake induced by either opioid or cannabinoid receptor antagonists may not be exclusively related to alterations in opioid functional activity, and still remain to be determined. Nevertheless, the fact that both opioid and cannabinoid antagonists tend to ‘normalize’ opioid function disrupted by ethanol intake suggests a potential synergistic action between both antagonists to reduce the consumption of ethanol. Indeed, Gallate et al. (2004) reported recently that a combined low-dose treatment with opioid and cannabinoid receptor antagonists synergistically reduces the motivation to consume ethanol in rats. The mechanisms responsible for this synergistic action are still unknown and a number of preclinical studies are needed to clarify the precise nature of the interaction induced by blockade of both opioid and cannabinoid CB1 receptors. Nevertheless, although these results should be interpreted with caution, they may have an important impact in the treatment of problems related to ethanol in clinical practice. Further double-blind, placebo-controlled studies should be carried out to evaluate the outcome of combined treatment in ethanol-dependent patients.

CONCLUSIONS

The pharmacological treatment of ethanol dependence is a challenge in our society. The search for the key elements involved in the genetic differences between individuals that make them more vulnerable to ethanol dependence and the identification of targets for the design of new, potentially useful drugs to reduce ethanol intake and craving and to prevent relapse are an ongoing concern of scientists working in this field. It is now clear that opioid transmission in the brain is important in the development of ethanol dependence and possibly in dependence induced by other drugs of abuse. The best evidence of this idea is the good response of a number of ethanol-dependent patients (throughout the world) to the opioid antagonist naltrexone. The fact that cannabinoid agonists increase the release of opioids and also increase ethanol intake in preclinical studies has stimulated research on the role played by the endocannabinoid system in ethanol dependence. To date, it appears that endogenous cannabinoid ligands, cannabinoid CB1 receptor function and gene
expression are altered by ethanol consumption. Evidence from preclinical studies strongly suggests that the administration of cannabinoid receptor antagonists reduces ethanol intake. Furthermore, a synergistic action to decrease ethanol consumption has been reported between opioid and cannabinoid receptor antagonists. Although the future design and application of drugs that modulate cannabinoid receptors to improve problems related to ethanol need much more investigation, the preclinical studies discussed in this review, point to the cannabinoid receptor system as an important potential target that should be seriously considered in future studies of the pharmacological treatment of alcoholism.

REFERENCES


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