Involvement of the endogenous opioid system in the psychopharmacological actions of ethanol: the role of acetaldehyde

Laura Font*, Miguel Á. Luján and Raúl Pastor

Area de Psicobiología, Universitat Jaume I, Castellón, Spain

Significant evidence implicates the endogenous opioid system (EOS) (opioid peptides and receptors) in the mechanisms underlying the psychopharmacological effects of ethanol. Ethanol modulates opiodergeric signaling and function at different levels, including biosynthesis, release, and degradation of opioid peptides, as well as binding of endogenous ligands to opioid receptors. The role of β-endorphin and μ-opioid receptors (OR) have been suggested to be of particular importance in mediating some of the behavioral effects of ethanol, including psychomotor stimulation and sensitization, consumption and conditioned place preference (CPP). Ethanol increases the release of β-endorphin from the hypothalamic arcuate nucleus (NArc), which can modulate activity of other neurotransmitter systems such as mesolimbic dopamine (DA). The precise mechanism by which ethanol induces a release of β-endorphin, thereby inducing behavioral responses, remains to be elucidated. The present review summarizes accumulative data suggesting that the first metabolite of ethanol, the psychoactive compound acetaldehyde, could participate in such mechanism. Two lines of research involving acetaldehyde are reviewed: (1) implications of the formation of acetaldehyde in brain areas such as the NArc, with high expression of ethanol metabolizing enzymes and presence of cell bodies of endorphinic neurons and (2) the formation of condensation products between DA and acetaldehyde such as salsolinol, which exerts its actions via OR.

Keywords: ethanol, acetaldehyde, endogenous opioid system, salsolinol, behavior, animal

ETHANOL AND THE OPIOID SYSTEM

Evidence indicates that ethanol modulates the activity of different components of the endogenous opioid system (EOS), with a large body of data supporting the implication of opioid ligands and receptors in the mediation of some of the psychopharmacological effects of ethanol.

THE ENDOGENOUS OPIOID SYSTEM AT A GLANCE

The opioid peptide precursors proopiomelanocortin (POMC), proenkephalin (PENK) or prodynorphin (PDYN) (Kieffer and Gavériaux-Ruff, 2002) are the source for the respective peptides β-endorphin, enkephalin, and dynorphin (Nylander and Roman, 2012). These endogenous ligands activate G-protein-coupled μ-, δ-, and κ-opioid receptors (OR) (μ-OR, δ-OR and κ-OR), which differ in their affinities and response profiles (Evans et al., 1992; Knapp et al., 1995; Kieffer and Evans, 2009). β-endorphin presents higher affinity for μ- than δ-, and reduced affinity for κ-OR (Roth-Deri et al., 2008; Trigo et al., 2010). Enkephalin binding to δ-OR is greater than that for μ-OR (Khachaturian et al., 1985; Raynor et al., 1994; Akil et al., 1998) and dynorphin shows specific affinity for κ-OR (Chavkin et al., 1982; Simon, 1991; Roth-Deri et al., 2008; Trigo et al., 2010). Ethanol can modulate opioidergic transmission at different levels, including synthesis, release, and degradation of opioid peptides, and binding of endogenous ligands to OR (for a review see, Méndez and Morales-Mulia, 2008). Since β-endorphin signaling has been specially implicated in the behavioral effects of ethanol, the present review will focus on the effects of ethanol on this component of the EOS. In this regard, although OR and ligands are widely distributed through the brain, there are important neuroanatomical determinants related to β-endorphin distribution that are worth highlighting. β-endorphin-synthesizing cell bodies are primarily located in the hypothalamic arcuate nucleus (NArc) (Chronwall, 1985). Important brain regions for drug-induced effects such as the nucleus accumbens (NAcc) are under tonic control of β-endorphin innervations from the NAcc (Chronwall, 1985; Khachaturian et al., 1985; Spanagel et al., 1992; Gianoulakis, 2001). These NAcc β-endorphin projections exert this control through the direct activation of OR located at the NAcc and by an indirect pathway via OR in the ventral tegmental area (VTA), which in turn modulate NAcc activity via VTA-NAcc dopamine (DA) neurons (Mansour et al., 1988; Di Chiara and North, 1992; Spanagel et al., 1992).

ETHANOL-INDUCED MODULATION OF β-ENDORPHINIC NEUROTRANSMISSION

Acute administration of ethanol induces the release of β-endorphin; an effect found in hypothalamic cell cultures and
tissue preparations (Gianoulakis, 1990; Boyadjieva and Sarkar, 1994; de Waele et al., 1994; Reddy et al., 1995; De et al., 2002). Ethanol also produces in vivo increases in β-endorphin content at the level of the hypothalamus (Schulz et al., 1980; Patel and Pohorecky, 1989), NAcβ (Anwer and Soliman, 1995; Olive et al., 2001; Marinelli et al., 2003a), midbrain including the VTA (Rasmussen et al., 1998; Jarjour et al., 2009) and the central amygdala (CeA) (Lam et al., 2008). Some studies, however, have found inconsistent results, probably related to procedural and methodological differences (Seizinger et al., 1983; Popp and Erickson, 1998; Rasmussen et al., 1998; Leriche and Méndez, 2010). Increased levels of enkephalin in the hypothalamus (Schulz et al., 1980; Seizinger et al., 1983; Milton et al., 1991) and NAcβ (Marinelli et al., 2003b) have also been found after acute ethanol.

Long-term exposure to ethanol primarily induces a decrease in POMC expression (Boyadjieva and Sarkar, 1997; Rasmussen et al., 2002; Oswald and Wand, 2004) and in hypothalamic β-endorphin release and levels (Boyadjieva and Sarkar, 1994; Oswald and Wand, 2004). A limited number of studies reported an increase in biosynthesis of POMC and POMC mRNA expression (Seizinger et al., 1984; Gianoulakis et al., 1988) as well as an initial increase followed by a gradual return to normal levels (Wand, 1990). Also, some authors found an increase or no effect on β-endorphin release (Boyadjieva and Sarkar, 1994; Oswald and Wand, 2004). Discrepancies might be attributable to the method of ethanol administration, ethanol dose, time course of drug exposure, administration route and differences in the development of tolerance. Also, it has been observed that alcohol-induced changes depend on the brain region investigated as well as the species and strain of animals used (Gianoulakis, 2001; Méndez and Morales-Mulia, 2008).

**EVIDENCE OF BEHAVIORAL EFFECTS OF ETHANOL MEDIATED BY THE ENDOGENOUS OPIOD SYSTEM**

Given that β-endorphin, and also enkephalin, activate μ-OR, extensive research has investigated the role of μ-OR in the behavioral effects of ethanol (Gianoulakis, 1993; Herz, 1997; Sanchis-Segura et al., 2000; Thorsell, 2013). Here we will focus on the involvement of these components of the EOS in several behavioral effects of ethanol, including psychomotor stimulation and sensitization, consumption, and associative learning (with a special focus on conditioned place preference (CPP)).

**Psychomotor stimulation and sensitization**

Increased psychomotor stimulation induced by ethanol in mice can be blocked with non-selective opioid receptor antagonists such as naloxone or naltrexone (Kianna et al., 1983; Camarini et al., 2000; Sanchis-Segura et al., 2004; Pastore et al., 2005; Pastor and Aragon, 2006). Some pharmacological strategies have suggested the existence of three so-called subtypes of μ-OR; μ₁, μ₂, and, μ₃ (Pasternak, 2001a,b; Cadet et al., 2003) and several studies have shown that μ₁ OR, μ₂ OR, and μ₃ OR are involved in the motor stimulant effects of ethanol in adult mice (Pastor et al., 2005), and also in rats during early development (Arias et al., 2010; Pautassi et al., 2012). Other studies conducted in mice have suggested that this involvement of μ-OR in ethanol stimulation is debatable (Cunningham et al., 1998; Gevaerd et al., 1999; Holstein et al., 2005). Consistent with the EOS involvement, however, a lesion of the NAcβ produces a decrease in ethanol-induced stimulation in mice (Sanchis-Segura et al., 2000), and knockout mice deficient in β-endorphin showed attenuated ethanol-induced stimulation (Dempsey and Grisel, 2012). Also, in rats, naltrexone prevents activation produced by ethanol when locally administered in the NAcβ (Pastor and Aragon, 2008) and intra-VTA blockade of the μ-OR using either naltrexone or the irreversible and selective μ-OR antagonist β-funaltrexamine reduces ethanol-induced locomotor stimulation (Sánchez-Catalán et al., 2009). Additionally, chronic naltrexone, which upregulates μ-OR (Unterwald et al., 1998; Lesscher et al., 2003), enhances the stimulant effects of ethanol in mice (Sanchis-Segura et al., 2004).

A critical role of the EOS in the motor sensitizing effects of ethanol has also been proposed (Camarini et al., 2000; Miquel et al., 2003; Pastor and Aragon, 2006). Unspecific OR antagonism prevents development (Camarini et al., 2000) but not expression (Abrahao et al., 2008) of ethanol-induced locomotor sensitization. μ-OR are particularly involved in ethanol sensitization (Camarini et al., 2000), without a clear role of any of the μ-OR subtypes in mediating this process; μ₁/₂ -OR antagonism slowed down, but did not block development of sensitization (Pastor and Aragon, 2006). Facilitation of ethanol-induced sensitization found after a period of voluntary alcohol consumption in mice was also seen to be absent in μ-OR deficient CXBK mice (Tarragón et al., 2012). The involvement of μ-OR in ethanol sensitization might be related to ethanol-induced increases in β-endorphin release as a recent study demonstrated that β-endorphin-deficient mice do not show locomotor sensitization to ethanol (Dempsey and Grisel, 2012). Also, animals with selective lesions of the NAcβ show prevented sensitization to ethanol (Miquel et al., 2003; Pastor et al., 2011). Altogether these data suggest that opioids and specifically β-endorphins, via μ-OR, might be critical mediators of ethanol-induced neuroplasticity underlying psychomotor sensitization.

**Ethanol consumption**

Numerous studies conducted during the last few decades showed that systemic, as well as local administration of opioid antagonists decrease ethanol consumption under a variety of schedules in different animal species (for reviews see Herz, 1997; Gianoulakis, 2001; Oswald and Wand, 2004; Modesto-Lowe and Fritz, 2005). These conclusions have also been supported by the use of OR knockout mouse models (Roberts et al., 2000; Méndez and Morales-Mulia, 2008). This strong pre-clinical basis has lead to the use of opioid antagonists in alcoholism pharmacotherapy (O’Malley et al., 1992). In rodents, the use of non-selective, as well as selective μ-OR antagonists proved to be effective at reducing ethanol consumption (Méndez and Morales-Mulia, 2008). However, the effects of these manipulations have been seen to be, in some cases, non-specific; fat, saccharin, sucrose and water intake were also reduced by these manipulations (Krishnan-Sarin et al., 1995; Nielsen et al., 2008; Rao et al., 2008; Simms et al., 2008; Corwin and Wojnicki, 2009; Wong et al., 2009). These data are compatible with the interpre-
tation that OR, and especially μ-OR might be a key mediator of the processing of positive reinforcement, both at emotional and motivational levels (Herz, 1997; Pecina and Berridge, 2005).

In general, data obtained with κ-OR or δ-OR manipulations are less conclusive. A recent review of the literature indicates that κ-OR stimulation generally antagonizes the reinforcing effects of alcohol whereas κ-OR blockade has no consistent effect (Wee and Koob, 2010). Dynorphin/κ-OR system appears to be involved in the negative reinforcing effects of ethanol by producing an aversive effect rather than by directly modulating the rewarding mechanism of ethanol (Wee and Koob, 2010; Walker et al., 2012). However, under an alcohol dependent-state, antagonism of κ-OR results effective in decreasing ethanol voluntary consumption (Wee and Koob, 2010; Walker et al., 2012). It has been reported that blockade of δ-OR either attenuates (Lê et al., 1993; Froehlich, 1995; Krishnan-Sarin et al., 1995; June et al., 1999; Hyytiä and Kianamna, 2001; Ciccocioppo et al., 2002), increases (Margolis et al., 2008) or has no effect on ethanol intake (Ingman et al., 2003). These discrepancies may be related to dynamic changes in δ-OR efficacy during ethanol exposure (Margolis et al., 2008). All these data support the participation of the POMC and PENK systems in maintaining alcohol consumption (Froehlich et al., 1991; Vengeliene et al., 2008).

**Associative learning and conditioned place preference**

It has been suggested that the EOS participates in the underlying mechanisms mediating conditioned effects induced by abused drugs, including ethanol. This implication is supported by two groups of experiments. On one hand, evidence indicates that OR antagonists attenuate cue-induced reinstatement of previously extinguished responding for ethanol self-administration (Lê et al., 1999; Ciccocioppo et al., 2002, 2003; Liu and Weiss, 2002; Burattini et al., 2006; Dayas et al., 2007; Marinelli et al., 2009), which suggests a role of EOS in cue-induced incentive motivational effects influencing ethanol-seeking behavior. This interpretation is consistent with clinical data showing that opioid antagonists increase abstinence duration periods in alcohol abusers (O’Malley et al., 1992), probably by reducing cue-induced seeking behavior. On the other hand, pretreatment with opioid receptor antagonism, while not influencing the acquisition of ethanol-induced CPP, reduces the expression and facilitates the extinction of this drug-free conditioned response (Bormann and Cunningham, 1997; Middaugh and Bandy, 2000; Kuzmin et al., 2003; Pastor et al., 2011). Mice lacking μ-OR also showed attenuated ethanol CPP (Hall et al., 2001). Further studies have suggested that expression of ethanol-induced CPP depends on OR located in the VTA, CeA, as well as anterior cingulated cortex (Bechtolt and Cunningham, 2005; Bie et al., 2009; Gremel et al., 2011). Additionally, a neurotoxic lesion of the β-endorphin neurons of the NArc, showed a facilitated extinction of ethanol-induced CPP (Pastor et al., 2011), β-endorphin and μ-OR appear to be therefore critically involved in the mechanisms underlying ethanol CPP. As Cunningham and collaborators have suggested, it is possible that altered opioid signaling might in turn alter conditioned motivation that normally maintains cue-induced seeking behavior during CPP testing (Cunningham et al., 1998). It is interesting to mention that pharmacological blockade of δ-OR with naltrindole in the CeA reduces expression of CPP induced by ethanol in rats (Bie et al., 2009). Activation of κ-OR has been shown to blunt acquisition of ethanol CPP (Logrip et al., 2009). Supporting these results, κ-OR knockout mice also showed enhanced ethanol CPP (Femenía and Manzanares, 2012).

**ACETALDEHYDE: A PSYCHOACTIVE METABOLITE**

The specific mechanism by which ethanol modulates the activity of the EOS remains to be understood. Evidence indicates that one possible mechanism might involve the role of acetaldehyde, the first metabolite of ethanol (Miquel et al., 2003; Sanchis-Segura et al., 2005b; Pastor and Aragon, 2008). Acetaldehyde is a psychoactive compound that produces behavioral and neurochemical effects suggested to mediate at least some of the effects of ethanol. Acetaldehyde is self-administered orally (Peana et al., 2010, 2012; Cacace et al., 2012) and directly into the brain (Brown et al., 1979; McBride et al., 2002; Rodd-Henricks et al., 2002; Peana et al., 2011). Its administration induces CPP (Smith et al., 1984; Quertemont and De Witte, 2001; Peana et al., 2009; Spina et al., 2010) as well as behavioral stimulation and sensitization when centrally administered (Arizzi et al., 2003; Correa et al., 2003a,b, 2009; Rood et al., 2005; Arizzi-LaFrance et al., 2006; Sánchez-Catalán et al., 2009). The oxidation of ethanol to acetaldehyde in the brain is essentially mediated by the catalase-H2O2 system (Aragon et al., 1992a; Gill et al., 1992). Reduced brain catalase activity, which have been seen to decrease ethanol-derived central acetaldehyde formation in brain tissue preparations (Hamby-Mason et al., 1997) and in the brain of free-moving rats (Jamal et al., 2007), decreases ethanol consumption (Aragón and Amit, 1992; Koechling and Amit, 1994; Correa et al., 2004; Karahanian et al., 2011), ethanol-induced locomotor stimulation (Aragon et al., 1992b; Correa et al., 1999b, 2004; Sanchis-Segura et al., 1999a,b,c; Pastor et al., 2002; Pastor and Aragon, 2008), the anxiolytic effects of alcohol (Correa et al., 2008) and modulates ethanol-induced CPP (Font et al., 2008). Strategies aimed at increasing the production of brain acetaldehyde via an enhancement in activity of the enzymatic catalase system have also been used. These manipulations produced an increase in the motor stimulant properties of ethanol in mice (Correa et al., 1999a; 2000; Pastor et al., 2002). Other ethanol-induced effects such as taste aversion (Aragón et al., 1985) and social memory recognition have also been seen to be modulated by changes in brain catalase (Manrique et al., 2005).

Apart from brain catalase manipulation, the direct inactivation of acetaldehyde has also been shown to reduce ethanol effects, including drinking (Font et al., 2006a) and alcohol-induced relapse drinking (Orrico et al., 2013), CPP (Font et al., 2006b; Peana et al., 2008) and motor stimulation (Font et al., 2005; Martí-Prats et al., 2010; Pautassi et al., 2011).

**ACETALDEHYDE-INDUCED CHANGES IN THE OPIOIDERIC NEUROTRANSMISSION**

The NArc, the main site of β-endorphin synthesis in the brain, is one of areas with the highest levels of catalase expression (Moreno et al., 1995; Zimatkin and Lindros, 1996) and lower levels of the acetaldehyde-degrading enzyme aldehyde dehydroge-
nase (Zimakin et al., 1992). Therefore, it has been thus suggested that catalase-dependent formation of acetaldehyde into the NArc might mediate ethanol-induced increases in the release of β-endorphin from the NArc in turn activating OR at the level of the VTA/NAcb to stimulate behavioral and neurophysiological actions (Sanchis-Segura et al., 2005a; Pastor and Aragon, 2008). Supporting this hypothesis, several authors (Reddy and Sarkar, 1993; Pastorcic et al., 1994; Reddy et al., 1995) have demonstrated that ethanol-induced increases in hypothalamic β-endorphin release are, indeed, mediated by acetaldehyde (Reddy and Sarkar, 1993; Pastorcic et al., 1994; Reddy et al., 1995). Hypothalamic cell cultures exposed to ethanol (12.5–100 μM) led to the formation of acetaldehyde (8–24 μM) and similar concentrations of acetaldehyde (12.5–50 μM) were able to stimulate β-endorphin release when tested in the absence of ethanol (Reddy and Sarkar, 1993; Pastorcic et al., 1994). Moreover, pretreatment of hypothalamic cell cultures with catalase inhibitors caused dose-dependent decreases in ethanol-stimulated β-endorphin secretion (Reddy et al., 1995).

Another line of research linking the EOS and acetaldehyde is the investigation of the actions of salsolinol (for a review see Hipólito et al., 2012), the condensation product of DA and acetaldehyde. Salsolinol has been shown to alter enkephalin-receptor site binding (Lucchi et al., 1982) and other OR an effect that is blocked by naltrexone (Fertel et al., 1980). Interestingly, intra-NAC administration of salsolinol increases DA levels when microinjected in the core and decreases DA levels if the administration is in the NAC shell (Hipólito et al., 2009) in a similar way to μ- and δ-OR agonists (Hipólito et al., 2008). It has been demonstrated that μ-OR receptors exert a tonic modulatory control over activity of the DA system (Di Chiara and North, 1992; Devine et al., 1993). Thus, one possible mechanism by which salsolinol exerts its effects on the OR could be disinhibiting DA neurons in the VTA. Upholding this hypothesis, intra-posterior VTA administration of salsolinol induced locomotor stimulation and sensitization in rats; stimulation (but not sensitization) was prevented by μ-OR antagonism. Finally, Sanchis-Segura et al. (2005b) demonstrated that administration of a catalase inhibitor directly into the NArc is sufficient to prevent the effects of ethanol on rat locomotion. Conversely, locomotor stimulation induced by ethanol injected directly into the NArc, was prevented by catalase inhibition or naltrexone, indicating a link between the behavioral effects of a reduction in acetaldehyde formation and the antagonism of μ-OR (Pastor and Aragon, 2008). The NArc, therefore, may represent a critical site to link two independent but related hypotheses: (1) the hypothesis proposing that acetaldehyde may mediate some of the psychopharmacological actions attributed to ethanol (Aragon et al., 1992a; Smith et al., 1997; Quertemont et al., 2005; Correa et al., 2012) and (2) the hypothesis that suggests that the β-endorphin/δ-OR system participate in the reinforcing and psychomotor effects of ethanol (Stinus et al., 1980; Herz, 1997; Gianoulakis, 2001; Sanchis-Segura et al., 2005b; Pastor and Aragon, 2008). Early findings also suggested a role of the opioidergic system in mediating CPP induced by salsolinol in rats (Matsuzawa et al., 2000). Antagonism of μ-OR attenuated CPP induced by salsolinol when achieved under fear stress (Matsuzawa et al., 2000). Moreover, intra-posterior VTA administration of salsolinol, that produced CPP in rats, also produced an increase in DA in the NAc that was suppressed by β-funaltrexamine administration (Hipólito et al., 2011).

**EVIDENCE OF BEHAVIORAL EFFECTS OF ACETALDEHYDE MEDIATED BY THE ENDOGENOUS OPIOID SYSTEM**

Whereas accumulating evidence indicates that the EOS participates in the behavioral effects of ethanol, only few studies have studied the involvement of this system in acetaldehyde effects. Self-administration of acetaldehyde appears to be mediated by the EOS; high doses of naltrexone reduced intravenous acetaldehyde self-administration in rats, and naltrexone reduced the maintenance, the deprivation effect, and operant break points of acetaldehyde voluntary consumption (Myers et al., 1984; Peana et al., 2011). Treatment with naltroxone, a specific μ-OR antagonist reduces maintenance of acetaldehyde oral self-administration (Peana et al., 2011). Blockade of μ-OR using either naltrexone or the irreversible and selective μ-OR antagonist β-funaltrexamine suppress the locomotor stimulation effect of acetaldehyde when microinjected into the rat posterior VTA (Sánchez-Catalán et al., 2009). Additionally, Hipólito et al. (2010) have provided data supporting the hypothesis that acetaldehyde may mediate the actions of ethanol through a mechanism dependent on μ-OR activation. These authors showed that intraperitoneal injections of salsolinol induced locomotor stimulation and sensitization in rats; stimulation (but not sensitization) was prevented by μ-OR antagonism. Finally, Sanchis-Segura et al. (2005b) demonstrated that administration of a catalase inhibitor directly into the NArc is sufficient to prevent the effects of ethanol on rat locomotion. Conversely, locomotor stimulation induced by ethanol injected directly into the NArc, was prevented by catalase inhibition or naltrexone, indicating a link between the behavioral effects of a reduction in acetaldehyde formation and the antagonism of μ-OR (Pastor and Aragon, 2008). The NArc, therefore, may represent a critical site to link two independent but related hypotheses: (1) the hypothesis proposing that acetaldehyde may mediate some of the psychopharmacological actions attributed to ethanol (Aragon et al., 1992a; Smith et al., 1997; Quertemont et al., 2005; Correa et al., 2012) and (2) the hypothesis that suggests that the β-endorphin/δ-OR system participate in the reinforcing and psychomotor effects of ethanol (Stinus et al., 1980; Herz, 1997; Gianoulakis, 2001; Sanchis-Segura et al., 2005b; Pastor and Aragon, 2008). Early findings also suggested a role of the opioidergic system in mediating CPP induced by salsolinol in rats (Matsuzawa et al., 2000). Antagonism of μ-OR attenuated CPP induced by salsolinol when achieved under fear stress (Matsuzawa et al., 2000). Moreover, intra-posterior VTA administration of salsolinol, that produced CPP in rats, also produced an increase in DA in the NAc that was suppressed by β-funaltrexamine administration (Hipólito et al., 2011).

**SUMMARY AND PERSPECTIVES**

In the present review we have summarized consistent results indicating that the EOS, and particularly β-endorphin and μ-OR, are critically involved in the psychopharmacological effects of ethanol. Additionally, we have reviewed a large body of data that indicates that the first metabolite of ethanol, acetaldehyde, might be responsible for the activation of β-endorphin release and μ-OR signaling after ethanol administration. There are two main lines of research suggesting a link between acetaldehyde and the EOS: (1) formation of acetaldehyde in brain areas such as the NArc, with high expression of ethanol metabolizing enzymes and presence of cell bodies of endorphinic neurons and (2) the formation of condensation products between DA and acetaldehyde such as salsolinol, which exerts its actions via μ-OR. To a certain degree both lines of research show important incompatibility. The fact that the lesions of the NArc are sufficient to block ethanol-induced behaviors challenge the putative role of salsolinol formed in other non-hypothalamic areas. Future studies will need to explore how to reconcile those two sets of data, and to clarify what is sufficient and/or necessary for acetaldehyde to induce behavioral responses mediated by the EOS. Finally, it is interesting to mention that most of the data suggesting a role of the EOS in acetaldehyde-induced behavioral effects have been linked to acetaldehyde-induced changes in the opioid system that are suggested to impact behavior via modulation of the DA system (Peana et al., 2011). Ethanol as well...
as acetaldehyde activate firing of dopaminergic neurons in the VTA (Foddaï et al., 2004; Diana et al., 2008) and stimulate DA transmission in the NAc (Melis et al., 2007; Enrico et al., 2009; Sirca et al., 2011), effects that are prevented by D-penicillamine, a sequestering agent of acetaldehyde (Enrico et al., 2009). A recent study demonstrates that in rats, ethanol and acetaldehyde induce via DA D1 receptors, ERK phosphorylation in the NAc and extended amygdala (Vinci et al., 2010). This effect is blocked by D-penicillamine and by naltrexone, suggesting that the opiodergic modulation of the reinforcing properties of acetaldehyde could be mediated by the dopaminergic system (Vinci et al., 2010; Peana et al., 2011). There are other effects such as ethanol-induced CPP, ethanol drinking in some non-operant conditions and even ethanol-induced sensitization that appear to have a less straightforward involvement of DA signaling (Risinger et al., 1992; Broadbent et al., 1995; Spina et al., 2010; Young et al., 2013). Future research will need to investigate DA-dependent and independent mechanisms by which acetaldehyde might induce behavioral responses via its modulation of the EOS.

ACKNOWLEDGMENTS

This work was supported by grants from Fundación Bancaixa (P1-1A2011-05), Spain.

REFERENCES

Abrahao, K. P., Quadros, I. M., and Souza-Formigoni, M. L. (2008). Morphine attenuates the expression of sensitization to ethanol, but opioid antagonists do not. Neurosci. 136, 857–864. doi: 10.1016/j.neuroscience.2008.08.012

Akil, H., Owens, C., Gutstein, H., Taylor, L., Curran, E., and Watson, S. (1998). Endogenous opioids: overview and current issues. Drug Alcohol Depend. 51, 127–140. doi: 10.1016/s0376-8716(98)00071-4

Anwex, J., and Soliman, M. R. (1993). Ethanol-induced alterations in beta-endorphin levels in specific rat brain regions: modulation by adenosine agonist and antagonist. Pharmacol. 51, 364–369. doi: 10.1159/000139348

Aragon, C. M., and Amit, Z. (1992). The effect of 3-aminoo-1,2,4-triazole on voluntary ethanol consumption: evidence for brain catalase involve-

ment in the mechanism of action. Neuropharmacol. 31, 709–712. doi: 10.1016/0028-3908(92)90150-n

Aragon, C. M., Pesold, C. N., and Amit, Z. (1992b). Ethanol-induced motor activity in normal and cata-
asem mice. Alcohol 9, 207–211. doi: 10.1016/0741-8329(92)90055-f

Aragon, C. M., Rogan, F., and Amit, Z. (1992a). Ethanol metabolism in rat brain homogenates by a catalase-

H2O2 system. Biochem. Pharmacol. 44, 93–98. doi: 10.1016/0006-

2952(92)90042-h

Aragon, C. M., Spivak, K., and Amit, Z. (1985). Blockade of ethanol induced conditioned taste aversion by 3-aminoo-1,2,4-triazole: evidence for catalase mediated synthesis of acetaldehyde in rat brain. Life Sci. 37, 2077–2084. doi: 10.1016/0022-

3205(85)90579-x

Arias, C., Molina, J. C., and Spear, N. E. (2010). Differential role of mu, delta and kappa opioid receptors in ethanol-mediated locomotor activation and ethanol intake in preweaning rats. Physiol. Behav. 99, 348–354. doi: 10.1016/j.physbeh.2009.11.012

Ariazi, M. N., Correa, M., Betz, A. I., Wisniecki, A., and Salamone, J. D. (2003). Behavioral effects of intra-

ventricular injections of low doses of ethanol, acetaldehyde, and acetate in rats: studies with low and high rate operant sched-

ules. Behav. Brain Res. 147, 203–210. doi: 10.1016/j.

4328(03)00158-x

Ariazi-LaFrance, M. N., Correa, M., Aragon, C. M., and Salamone, J. D. (2006). Motor stimulant effects of ethanol injected into the substantia nigra pars reticulata: importance of catalase-mediated metabolism and the role of acetaldehyde. Neuropsy-

chopharmacology 31, 997–1008. doi: 10.1038/sj.npp.1003849

Bechtholt, A. I., and Cunningham, C. L. (2005). Ethanol-induced conditioned place preference is expressed through a ventral teg-

mental area dependent mechanism. Behav. Neurosci. 119, 213–223. doi: 10.1037/0735-7044.119.1.213

Bie, B., Zhu, W., and Pan, Z. Z. (2009). Ethanol-induced delta-opioid receptor modulation of glutamate synaptic transmission and condi-

tioned place preference in central amygdala. Neuroscience 160, 348–358. doi: 10.1016/j.neuroscience.2009.02.049

Bormann, N. M., and Cunningham, C. L. (1997). The effects of nalox-

one on expression and acquisition of ethanol place conditioning in rats. Pharmacol. Biochem. Behav. 58, 975–982.

Boyadjieva, N. I., and Sarkar, D. K. (1997). Effects of ethanol on basal and postprolactin E1-induced increases in beta-endorphin release and intracellular cAMP levels in hypothalamic cells. Alcohol. Clin. Exp. Res. 21, 1003–1009. doi: 10.1111/j.1530-

2777.1997.tb04245.x

Broadbent, J., Grahame, N. J., and Cunn-

ingham, C. L. (1995). Haloperidol prevents ethanol-stimulated loco-

motor activity but fail to block sen-

sitization. Psychopharmacology 120, 475–482. doi: 10.1007/bf02245821

Brown, Z. W., Amit, Z., and Rock-

man, G. E. (1979). Intraventricular self-administration of acetaldehyde, but not ethanol, in naive laboratory rats. Psychopharmacology 64, 271–276. doi: 10.1007/bf00427509

Burattini, C., Gill, T. M., Aicardi, G., and Janak, P. H. (2006). The ethanol self-administration con-

text as a reinstatement cue: acute effects of naltrexone. Neuro-

sciences 139, 877–887. doi: 10.1016/j.

neuroscience.2006.01.009

Cacace, S., Plescia, F., Barberi, L., and Cannizzaro, C. (2012). Acetalde-

hyde oral self-administration: evidence from the operant-conflict paradigm. Alcohol. Clin. Exp. Res. 36, 1278–1287. doi: 10.1111/j.1530-

2777.2011.01725.x

Cadet, P., Manfante, K. J., and Stefano, G. B. (2003). Molecular identifica-

tion and functional expression of mu 3, a novel alternatively spliced variant of the human mu opio-

er receptor gene. J. Immunol. 170, 5118–5123.

Camarin, R., Nogueira Pires, M. L., and Calii, H. M. (2000). Involv-

ement of the opioid system in the development and expression of sensitization to the locomotor-

activating effect of ethanol. Int. J. Neuropsychopharmacol. 3, 303–309. doi: 10.1017/s14611457000211x

Chavkin, C., James, I. F., and Goldstein, A. (1982). Dynorphin is a specific endogenous ligand of the kappa opi-

oid receptor. Science 215, 413–415. doi: 10.1126/science.6120570

Chronwall, B. M. (1985). Anatomy and physiology of the neuroen-

docrine arcuate nucleus. Peptides 6 (Suppl. 2), 1–11. doi: 10.1016/0196-

7981(85)90128-7

Ciccocioppo, R., Martin-Fardon, R., and Weiss, F. (2002). Effect of selective blockade of mu(1) or delta opioid receptors on reinstate-

ment of alcohol-seeking behavior by drug-associated stimuli in rats. Psychopharmacology 168, 208–215. doi: 10.1007/s00213-

022-1380-z

Correa, M., Ariazi, M. N., Betz, A., Mingote, S., and Salamone, J. D. (2003a). Open field locomotor effects in rats after intraventricular injections of ethanol and the ethanol metabo-

lites acetaldehyde and acetate. Brain Res. Bull. 62, 197–202. doi: 10.1016/j.brainresbull.2003.09.013

Correa, M., Ariazi, M. N., Betz, A., Mingote, S., and Salamone, J. D. (2003b). Locomotor stimulant effects of intraventricular injections of low doses of ethanol in rats: acute and repeated administra-

tion. Psychopharmacology 170, 368–375. doi: 10.1007/s00213-003-

1557-0

Correa, M., Ariazi-LaFrance, M. N., and Salamone, J. D. (2009). Infu-

sions of acetaldehyde into the arcuate nucleus of the hypotha-

lamus induce motor activity in rats. Life Sci. 84, 321–327. doi: 10.1016/j.lfs.2008.12.013
Acetaldehyde and the opioid system

Font et al.

Frontiers in Behavioral Neuroscience
www.frontiersin.org

July 2013 | Volume 7 | Article 93 | 6

Correa, M., Manrique, H. M., Font, L., Esgrig, M. A., and Aragon, C. M. (2008). Reduction in the anxiolytic effects of ethanol by centrally formed acetaldehyde: the role of catalase inhibitors and acetaldehyde-sequestering agents. Psychopharmacology 200, 455–464. doi: 10.1007/s00213-008-1219-3

Correa, M., Miquel, M., and Aragon, C. M. (2000). Lead acetate potentiates brain catalase activity and enhances ethanol-induced locomotion in mice. Pharmacol. Biochem. Behav. 66, 137–142. doi: 10.1016/s0091-3057(00)0294-5

Correa, M., Miquel, M., Sanchis-Segura, C., and Aragon, C. M. (1999a). Acute lead administration potentiates ethanol-induced locomotor activity in mice: the role of brain catalase. Alcohol. Clin. Exp. Res. 23, 799–805.

Correa, M., Miquel, M., Sanchis-Segura, C., and Aragon, C. M. (1999b). Effects of chronic lead administration on ethanol-induced locomotor and brain catalase activity. Alcohol 19, 43–49. doi: 10.1016/s0741-8329(99)00023-3

Correa, M., Salamone, J. D., Segovia, K. N., Pardo, M., Longoni, R., Spina, L., et al. (2012). Piecing together the puzzle of acetaldehyde as a neuroactive agent. Neurosci. Biobehav. Rev. 36, 404–430. doi: 10.1016/j.neubiorev.2011.07.009

Correa, M., Sanchis-Segura, C., Pastor, R., and Aragon, C. M. (2004). Ethanol intake and motor sensitization: the role of brain catalase activity in mice with different genotypes. Physiol. Behav. 82, 231–40. doi: 10.1016/j.physbeh.2004.03.033

Cordero, R. L., and Wojnicki, F. H. (2009). Baclofen, raclopide, and naltrexone differentially affect intake of fat and sucrose under limited access conditions. Behav. Pharmacol. 20, 537–548. doi: 10.1097/Bph.0b013e3283313618

Cunningham, C. L., Henderson, C. M., and Bormann, N. M. (1998). Extinction of ethanol-induced conditioned place preference and conditioned place aversion: effects of naloxone. Psychopharmacology 139, 62–70. doi: 10.1007/s002130050690

Dayas, C. V., Liu, X., Simms, J. A., and Weiss, F. (2007). Distinct patterns of neural activation associated with ethanol seeking: effects of naltrexone. Biol Psychiatry 61, 979–989. doi: 10.1016/j.biopsych.2006.07.034

De, A., Boyadjieva, N., and Sarkar, D. K. (2002). Role of protein kinase C in control of ethanol-modulated beta-endorphin release from hypothalamic neurons in primary cultures.

Font, L., Aragon, C. M., and Miquel, M. (2006a). Voluntary ethanol consumption decreases after the inactivation of central acetaldehyde by D-penicillamine. Behav. Brain Res. 171, 78–86. doi: 10.1016/j.bbr.2006.03.020

Font, L., Miquel, M., and Aragon, C. (2005). Prevention of ethanol induced behavioral stimulation by D-penicillamine: a sequestration agent for acetaldehyde. Alcohol. Clin. Exp. Res. 29, 1156–1164. doi: 10.1097/01.acn.0000171945.30494.af

Font, L., Miquel, M., and Aragon, C. (2006b). Ethanol-induced conditioned place preference, but not aversion, is blocked by treatment with D-penicillamine, an inactivating agent for acetaldehyde. Psychopharmacology 184, 56–64. doi: 10.1007/s00213-005-0224-z

Font, L., Miquel, M., and Aragon, C. M. (2008). Involvement of brain catalase activity in the acquisition of ethanol-induced conditioned place preference. Physiol. Behav. 93, 733–741. doi: 10.1016/j.physbeh.2007.11.026

Froehlich, J. (1995). Genetic factors in alcohol self-administration. J. Clin. Psychiatry 56(Suppl. 7), 15–23.

Froehlich, J. C., Zweifel, M., Harts, J., Lumeng, L., and Li, T. K. (1991). Importance of delta opioid receptors in maintaining high alcohol drinking. Psychopharmacology 103, 467–472. doi: 10.1007/BF02244246

Gevaerd, M. S., Sultowski, E. T., and Schenker, S., Perez, A., and Hennderon, G. L. (1997). Catalase mediates acetaldehyde formation from ethanol in fetal and neonatal rat brain. Alcohol. Clin. Exp. Res. 21, 1063–72. doi: 10.1111/j.1530-2779.1997.tb04255.x

Herz, A. (1997). Endogenous opioid systems and alcohol addiction. Psychopharmacology 129, 99–111. doi: 10.1007/s002130050169

Hipólito, L., Martí-Prats, L., Sánchez-Catalán, M. J., Polache, A., and Granero, L. (2011). Induction of conditioned place preference and dopamine release by salicolline in posterior VTA of rats: involvement of μ-opioid receptors. Neurochem. Int. 59, 559–562. doi: 10.1016/j.neuci.2011.04.014

Hipólito, L., Martí-Prats, L., Sánchez-Catalán, M. J., Granero, L., and Polache, A. (2009). Local salicolline modulates dopamine extracellular levels from rat nucleus accumbens: shell/core differences. Neuropsychopharmacology 34, 314–318. doi: 10.1038/jn.2008.52

Kuś, D., Kowalska, A., and Diethrich, R. A. (1992). Enzymatic production of acetaldehyde from ethanol in rat brain tissue. Alcohol. Clin. Exp. Res. 16, 910–915. doi: 10.1111/j.1530-0277.1992.tb01892.x

Gremel, C. M., Young, E. A., and Cunningham, C. L. (2011). Blockade of opioid receptors in anterior cingulate cortex disrupts ethanol-seeking behavior in mice. Behav. Brain Res. 219, 358–362. doi: 10.1016/j.bbr.2010.12.033

Hall, F. S., Sora, L., and Uhl, G. R. (2001). Ethanol consumption and reward are decreased in μ-opiate receptor knockout mice. Psychopharmacology 154, 43–49. doi: 10.1007/s002130050622

Hamby-Mason, R., Chen, J. J., Schenker, S. Perez, A., and Henderson, G. L. (1997). Catalase mediates acetaldehyde formation from ethanol in fetal and neonatal rat brain. Alcohol. Clin. Exp. Res. 21, 1063–72. doi: 10.1111/j.1530-2779.1997.tb04255.x

Ferré, R. H., Greenwald, J. E., Schwarz, R., Wong, L., and Bianchine, J. (1991). Opiate receptor binding and analgesic effects of the tetrahydropapaveroline. Res. Comm. Chem. Pathol. Pharmacol. 27, 116.

Feddes, M., Dosia, G., Spiga, S., and Diana, M. (2004). Acetaldehyde increases dopaminergic neuronal activity in the VTA. Neuropharmacology 29, 530–536. doi: 10.1016/s0028-3908(04)00036-2
Font et al. 2013 | Volume 7 | Article 93 | 7

Frontiers in Behavioral Neuroscience www.frontiersin.org

Hipólito, L., Sánchez-Catalán, M. J., Zornoza, T., Polache, A., and Granero, L. (2010). Locomotor stimulant effects of acute and repeated intraperitoneal injections of salsolinol in rats: role of µ-opioid receptors. Psychopharmacology 209, 1–11. doi: 10.1007/s00213-009-1751-9

Holstein, S. E., Pastor, R., Meyer, P. J., and Phillips, T. J. (2005). Naloxone does not attenuate the locomotor effects of ethanol in FAST, SLOW, or two heterogeneous stocks of mice. Psychopharmacology 182, 277–289. doi: 10.1007/s00213-005-0666-8

Hyttia, P., and Kianmäa, K. (2001). Suppression of ethanol responding by centrally administered CTOP and naltrindole in AA and Wistar rats. Alcohol. Clin. Exp. Res. 25, 23–33. doi: 10.1111/j.1530-2271.2001.tb0213x.

Ingman, K., Salvadori, S., Lazarus, L., Korpi, E. R., and Honkanen, A. (2003). Selective delta-opioid receptor antagonist N,N(CH3)2-Dmt-Tic-OH does not reduce ethanol intake in alcohol-prefering AA rats. Addict. Biol. 8, 173–179. doi: 10.1080/1355621031000171400.

Jamal, M., Ameno, K., Uekita, I., Holstein, S. E., Pastor, R., Meyer, P. J., and Gerrits, M. A. (2003). Opioid peptides from the midbrain of free-moving rats. Neuropeptides 37, 291–294. doi: 10.1016/s0893-133x(03)00033-6.

Knapp, R. J., Matlakowska, E., Collins, N., Fang, L., Wang, J. Y., Hurby, V. J., et al. (1995). Molecular biology and pharmacology of cloned opioids receptors. FASEB J. 9, 515–525.

Kochuling, U. M., and Amit, Z. (1994). Effects of 3-amino-1,2,4-triazole on brain catalase in the mediation of ethanol consumption in mice. Alcohol 11, 235–239. doi: 10.1074/jh00008-941.

Kuzmin, A., Sandin, J., Terenius, L., and Shaham, Y. (1999). Effects of ethanol consumption and response maintained by ethanol administration on the release of corticotropin-releasing factor and opioid peptides in the paraventricular nucleus of the rat hypothalamus. J. Neurosci. 19, 435–444. doi: 10.1122/jphon.21.01.0213.

Lê, A. D., Poulos, C. X., Harding, S., Watchus, J., Juztsyz, W., and Shaham, Y. (1999). Effects of naltrexone and flunitrazepam on alcohol self-administration and reinstatement of alcohol seeking induced by priming injections of alcohol and exposure to stress. Psychopharmacology 21, 261–271. doi: 10.1007/s00213-008-0126-7.

Lê, A. D., Poulos, C. X., Quan, B., and Chow, S. (1993). The effects of selective blockade of delta and mu opiate receptors on ethanol consumption by C57BL/6 mice in a restricted access paradigm. Brain Res. 630, 330–332. doi: 10.1016/0006-8993(93)90672-z.

Leriche, M., and Méndez, M. (2010). Ethanol exposure selectively alters beta-endorphin content but not [3H]-DAMGO binding in discrete regions of the rat brain. Neuropeptides 44, 9–16. doi: 10.1016/j.npep.2009.11.009.

Lescher, H. M., Bailey, A., Burbach, J. P., Van Ree, J. M., Kitchen, L., and Gerrits, M. A. (2003). Receptor-selective changes in mu-, delta- and kappa-opioid receptors after chronic naltrexone treatment in mice. Eur. J. Neurosci. 17, 1006–1012.

Liu, X., and Weiss, F. (2002). Additive effect of stress and drug cues on reinstatement of ethanol seeking: exacerbation by history of dependence and role of concurrent activation of corticotropin-releasing factor and opioid mechanisms. J. Neurosci. 22, 7856–7861.

Logrip, M. J., Janak, P. H., and Ron, D. (2009). Blockade of ethanol reward by the kappa opioid receptor. Alcohol. Clin. Exp. Res. 43, 359–365. doi: 10.1111/j.1530-0277.2009.00642.x.

McBride, W. J., Li, T. K., Deitrich, R. A., Zimatin, S., Smith, B. R., and Rodd-Henricks, Z. (2000). Involvement of mu-opioid receptor in the salsolinol-associated place preference in rats exposed to conditioned fear stress. Alcohol. Clin. Exp. Res. 24, 366–372. doi: 10.1111/j.1530-0277.2000.00462.x.

Militz, M., Enrico, P., Peana, A. T., and Diana, M. (2007). Acetaldehyde mediates alcohol activation of the mesolimbic dopamine system. Europ. J. Neurosci. 26, 2824–33. doi: 10.1111/j.1460-9568.2007.05887.x.

Méndez, M., and Morales-Mulia, M. (2008). Role of mu and delta opioid receptors in alcohol drinking behaviour. Curr. Drug Abuse Rev. 1, 259–252. doi: 10.2174/187475710801020239.

Millo, G. W., Verhaert, P. D., and Downer, R. G. (1991). Immunofluorescent localization of dopamine-like and leucine-enkephalin-like neurons in the supraoesophageal ganglia of the American cockroach, periplaneta americana. Tissue Cell 23, 331–340. doi: 10.1016/0040-8166(91)90051-t.
Miquel, M., Font, L., Sanchis-Segura, C., and Aragon, C. M. (2003). Neonatal administration of monosodium glutamate prevents the development of ethanol but not psychostimulant-induced sensitization: a putative role of the arcuate nucleus. *Eur. J. Neurosci.* 17, 2163–2170. doi: 10.1046/j.1460-9568.2003.02646.x

Modesto-Lowe, V., and Fritz, E. M. (2005). The opioidergic-alcohol link: implications for treatment. *CNS Drugs* 19, 693–707. doi: 10.1007/120023210-20051980-00005

Moreno, S., Mugnaini, E., and Cerù, M. P. (1995). Immunocytochemical localization of catalase in the central nervous system of the rat. *J. Histochem. Cytochem.* 43, 1253–1267.

Olive, M. F., Koenig, H. N., Nannini, M. C., and Aragon, C. M. (2003). But not psychostimulant-induced monosodium glutamate pre-treatment alters the effects of ethanol on locomotor activity in the rat. *Neurosci. Lett.* 342, 125–130. doi: 10.1016/S0304-3940(03)00408-8

Olive, M. F., Koenig, H. N., Nannini, M. C., and Aragon, C. M. (2005). Role of opioid receptor subtypes in the development of ethanol-induced sensitization to ethanol. *Neuropharmacology* 43, 1253–1267.

Pasternak, G. W. (2001a). The pharmacology of mu analgesics: from patients to genes. *Neuroscientist* 7, 220–231. doi: 10.1177/107385840000700307

Pasternak, G. W. (2001b). Insights into mu opioid pharmacology the role of mu opioid receptor subtypes. *Life Sci.* 68, 2213–229. doi: 10.1016/S0023-2520(01)10086-6

Pastor, R., and Aragon, C. M. (2006). The role of opioid receptor subtypes in the development of ethanol-induced sensitization to ethanol. *Neuropharmacology* 51, 1489–1499. doi: 10.1016/j.neuropharm.2005.09.028

Peana, A. T., Assaretti, A. R., Mugurri, G., Enrico, P., and Diana, M. (2009). Reduction of ethanol-derived acetaldehyde induced motivational properties by L-cysteine. *Alcohol. Clin. Exp. Res.* 33, 43–48. doi: 10.1111/j.1530-2777.2008.00809.x

Peana, A. T., Enrico, P., Assaretti, A. R., Pulighe, E., Mugurri, G., Nieddu, M., et al. (2008). Key role of ethanol-derived acetaldehyde in the motivation properties induced by intragastric ethanol: a conditioned place preference study in the rat. *Alcohol. Clin. Exp. Res.* 32, 249–258. doi: 10.1111/j.1530-2777.2007.00574.x

Peana, A. T., Mugurri, G., and Diana, M. (2010). Acetaldehyde-reinforcing effects: a study on oral self-administration behavior. *Front. Psychiatry* 1, 1–5. doi: 10.3389/fpsyt.2010.00023

Peana, A. T., Muriggi, G., Fois, G. R., Zinelli, M., Sirca, D., and Diana, M. (2012). Effect of (L)-cysteine on acetaldehyde self-administration. *Alcohol* 46, 489–497. doi: 10.1016/j.alcohol.2011.10.004

Peana, A. T., Mugurri, G., Fois, G. R., Zinelli, M., Vinc, S., and Aquas, E. (2011). Effect of opioid receptor blocker blockade on acetaldehyde self-administration and ERK phosphorylation in the rat nucleus accumbens. *Alcohol* 45, 773–783. doi: 10.1016/j.alcohol.2011.06.003

Peñina, S., and Berridge, K. C. (2005). Hedonic hot spot in nucleus accumbens shell: where do mu-opioids cause increased hedonic impact of sweetness? *J. Neurosci.* 25, 11772–11786. doi: 10.1523/jneurosci.2329-05.2005

Popp, R. L., and Erickson, C. K. (1998). The effect of an acute ethanol exposure on the rat brain POMC opioidpeptide system. *Alcoholol* 16, 139–148. doi: 10.1016/S0741-8259(98)90003-2

Quertemont, E., and De Witte, P. (2001). Conditioned stimulus preference after acetaldehyde but not ethanol injections. *Pharmacol. Biochem. Behav.* 68, 449–454. doi: 10.1016/S0091-3057(00)00486-x

Quertemont, E., Tambour, S., and Tirelli, E. (2005). The role of acetaldehyde in the neurobehavioral effects of ethanol: a comprehensive review of animal studies. *Prog. Neurobiol.* 79, 247–274. doi: 10.1016/j.pneurobio.2005.03.003

Rao, R. E., Wojnicki, F. H., Coup-land, J., Ghosh, S., and Corwin, R. L. (2008). Baclofen, raclopride, and naltrexone differentially reduce solid fat emulsion intake under limited access conditions. *Pharmacol. Biochem. Behav.* 89, 581–590. doi: 10.1016/j.pbb.2008.02.013

Rasmussen, D. D., Boldt, B. M., Wilkinson, C. W., and Mitton, D. R. (2002). Chronic daily ethanol and withdrawal: 3. Forebrain pro- opiomelanocortin gene expression and implications for dependence, relapse, and deprivation effect. *Alcohol. Clin. Exp. Res.* 26, 535–546. doi: 10.1111/j.1530-0277.2002.tb02572.x

Rasmussen, D. D., Bryant, C. A., Boldt, B. M., Colusard, E. A., Levin, N., and Wilkinson, C. W. (1998). Acute alcohol effects on opiomelanocortinergic regulation. *Alcohol. Clin. Exp. Res.* 22, 789–801. doi: 10.1111/j.1530-0277.1998.tb03870.x

Raynor, K., Kong, H., Chen, Y., Yasuda, K., Yu, L., Bell, G. L., et al. (1994). Pharmacological characterization of the cloned kappa-δ-, and mu-opioid receptors. *Mol. Pharmacol.* 45, 330–334

Reddy, B. V., and Sarkar, D. K. (1993). Effect of alcohol, acetaldehyde, and salenol on beta-endorphin secretion from the hypothalamic neurons in primary cultures. *Alcohol. Clin. Exp. Res.* 17, 1261–1267. doi: 10.1111/j.1530-0277.1993.tb05239.x

Reddy, B. V., Boyadjieva, N., and Sarkar, D. K. (1995). Effect of ethanol, propanol, butanol, and catalase enzyme blockers on beta-endorphin secretion from primary cultures of hypothalamic neurons: evidence for a mediatory role of acetaldehyde in ethanol stimulation of beta-endorphin release. *Alcohol. Clin. Exp. Res.* 19, 339–344. doi: 10.1111/j.1530-2777.1995.tb01512.x

Risinger, F. O., Dickinson, S. D., and Cunningham, C. L. (1992). Haloperidol reduces ethanol-induced motor activity stimulation but not conditioned place preference. *Psychopharmacology* 107, 453–456. doi: 10.1007/bf02245175

Roberts, A. I., McDonald, J. S., Heyser, C. J., Kieffer, B. L., Matthes,
Acetaldehyde and the opioid system

H. W., Koob, G. F., et al. (2000). Mu-opioid receptor knockout mice do not self-administer alcohol. J. Pharmacol. Exp. Ther. 293, 1002–1008.

Rodd, Z., Bell, R. L., Zhang, Y., Murphy, J. M., Goldstein, A., Zaffaroni, A., et al. (2005). Regional heterogeneity for the intracranial self-administration of alcohol and acetaldehyde within the ventral tegmental area of alcohol-prefering (P) rats: involvement of dopamine and serotonin. Neuropharmacology 30, 330–338. doi: 10.1016/s9096-8877(01)00004

Roth-Deri, I., Green-Sadan, T., Rodd, Z., Bell, R. L., Zhang, Y., Murphy, J. M., Goldstein, A., Zaffaroni, A., et al. (2005). Regional heterogeneity for the intracranial self-administration of alcohol and acetaldehyde within the ventral tegmental area of alcohol-prefering (P) rats: involvement of dopamine and serotonin. Neuropharmacology 30, 330–338.

Frontiers in Behavioral Neuroscience www.frontiersin.org

Font et al

Vinci, S., Ibba, F., Longoni, R., Spina, L., Spiga, S., and Acquas, E. (2010). Acetaldehyde elicits ERK phosphorylation in the rat nucleus accumbens and extended amygdala. Synapse 64, 916–927. doi: 10.1002/syn.20811

Walker, B. M., Valdez, G. R., McLaughlin, J. P., and Bakalini, G. (2012). Targeting dynorphin/kappa opioid receptor systems to treat alcohol abuse and dependence. Alcohol 46, 359–370. doi: 10.1016/j.alcohol.2011.10.006

Wand, G. S. (1990). Differential regulation of anterior pituitary corticosterone function is observed in vivo but not in vitro in two lines of ethanol-sensitive mice. Alcohol Clin. Exp. Res. 14, 100–106. doi: 10.1111/j.1530-2479.1990.tb00454.x

Wee, S., and Koob, G. F. (2010). The role of the dynorphin-kappa opioid system in the reinforcing effects of drugs of abuse. Psychopharmacology 210, 121–135. doi: 10.1007/s00213-010-1825-8

Wong, K. J., Wojnicki, F. H., and Corwin, R. L. (2009). Baclofen, raclopride, and naltrexone differentially affect intake of fat/sucrose mixtures under limited access conditions. Pharmacol. Biochem. Behav. 92, 528–536. doi: 10.1016/j.pbb.2009.02.002

Xie, G., Hipólito, L., Zuo, W., Polache, A., Granero, L., Krajewski, K., et al. (2012). Salsolinol stimulates dopamine neurons in slices of posterior ventral tegmental area indirectly by activating-opioid receptors. J. Pharmacol. Exp. Ther. 341, 43–50. doi: 10.1124/jpet.111.186833

Young, F. F., Donato, R. S., and Cunningham, C. L. (2013). Role of nucleus accumbens dopamine receptor subtypes in the learning and expression of alcohol-seeking behavior. Neurobiol. Learn. Mem. 106, doi: 10.1016/j.nlm.2013.05.004.[Epub ahead of print]

Zimatkina, S. M., and Lindros, K. O. (1996). Distribution of catalase in rat brain: aminergic neurons as possible targets for ethanol effects. Alcohol. Clin. Exp. Res. 20, 167–174. doi: 10.1093/oxfordjournals.alcalc.a008128

Zimatkina, S. M., Rout, U. K., Koivusalo, M., Bühler, R., and Lindros, K. O. (1992). Regional distribution of low-Km mitochondrial catalase dehydrogenase in the rat central nervous system. Alcohol. Clin. Exp. Res. 16, 1162–1167. doi: 10.1111/j.1530-2279.1992.tb00713.x
Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 03 May 2013; accepted: 10 July 2013; published online: 31 July 2013.

Citation: Font L, Luján MÁ and Pastor R (2013) Involvement of the endogenous opioid system in the psychopharmacological actions of ethanol: the role of acetaldehyde. Front. Behav. Neurosci. 7:93. doi:10.3389/fnbeh.2013.00093

Copyright © 2013 Font, Luján and Pastor. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.