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Research Report

Innate BDNF expression is associated with ethanol intake in alcohol-preferring AA and alcohol-avoiding ANA rats

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ABSTRACT

We have shown recently that acute administration of ethanol modulates the expression of brain-derived neurotrophic factor (BDNF) in several rat brain areas known to be involved in the development of addiction to ethanol and other drugs of abuse, suggesting that BDNF may be a factor contributing to the neuroadaptive changes set in motion by ethanol exposure. The purpose of the present study was to further clarify the role of BDNF in reinforcement from ethanol and in the development of addiction to ethanol by specifying the effect of acute administration of ethanol (1.5 or 3.0 g/kg i.p.) on the expression profile of BDNF mRNA in the ventral tegmental area and in the terminal areas of the mesolimbic dopamine pathway in the brain of alcohol-preferring AA and alcohol-avoiding ANA rats, selected for high and low voluntary ethanol intake, respectively. The level of BDNF mRNA expression was higher in the amygdala and ventral tegmental area of AA than in those of ANA rats, and there was a trend for a higher level in the nucleus accumbens. In the amygdala and hippocampus, a biphasic change in the BDNF mRNA levels was detected: the levels were decreased at 3 and 6 h but increased above the basal levels at 24 h. Furthermore, there was a difference between the AA and ANA lines in the effect of ethanol, the ANA rats showing an increase in BDNF mRNA levels while such a change was not seen in AA rats. These findings suggest that the innate levels of BDNF expression may play a role in the mediation of the reinforcing effects of ethanol and in the control of ethanol intake.

Abbreviations: AA rat, alcohol-preferring AA (Alko Alcohol) rat; ANA rat, alcohol-avoiding ANA (Alcohol Non-Alcohol) rat; BDNF, brain-derived neurotrophic factor; GABA, gamma-aminobutyric acid; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; MAPK, mitogen-activated protein kinase; NP rat, alcohol nonpreferring NP rat; P rat, alcohol-preferring P rat; pCREB, phosphorylated cAMP response element-binding protein; RT-qPCR, real-time quantitative polymerase chain reaction; VTA, ventral tegmental area

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1. Introduction

Brain-derived neurotrophic factor (BDNF) is one of the most abundant neurotrophic factors widely expressed in the adult mammalian brain (Lewin and Barde, 1996; Hofer et al., 1990) and, as with most neurotrophins, it is a key player in neuronal survival, development and plasticity (Schuman, 1999; Goggi et al., 2002; Chao, 2003; Lipsky and Marini, 2007). The involvement of BDNF in several psychiatric and neurological conditions has been well established (Nestler et al., 2002; Shirayama et al., 2002; Bramham and Messaoudi, 2005; Autry and Monteggia, 2012) as well as its contribution to the reinforcing effects and neuroadaptive changes set in motion by drugs of abuse (Russo et al., 2009; Ghitza et al., 2010).

The addictive properties of drugs are generally believed to be based on their reinforcing effects. The mesolimbic dopamine pathway is suggested to be the primary neural substrate for reinforcement from ethanol and other substances of abuse, and has a role in their self-administration (Koob et al., 1998; Wise, 1998). Cell bodies of the mesolimbic dopamine neurons are located in the ventral tegmental area and their axons project to the nuclei of the forebrain (Koob, 1992; Chick and Erickson, 1996). It has been demonstrated that essentially all mesencephalic dopaminergic neurons express BDNF (Numan and Seroogy, 1999).

Several studies have shown that BDNF plays a role in the reinforcing effects of psychostimulants and opiates (Ghitza et al., 2010; McGinty et al., 2010). There are also data suggesting that BDNF may act as an endogenous regulator of ethanol intake. It has been found that the expression of endogenous BDNF is related to the levels of ethanol intake and is altered by exposure to ethanol (Hensler et al., 2003; McGough et al., 2004; Kerns et al., 2005; Raivio et al., 2012), and that the basal BDNF levels in the nucleus accumbens differ between rat lines showing different preference to ethanol (Yan et al., 2005). Furthermore, clinical studies have provided evidence that BDNF may be one factor underlying genetic vulnerability to alcohol dependence (Matsushita et al., 2004; Keun-Ho et al., 2007).

We showed recently in Wistar rats that acute ethanol administration modulates the expression profile of BDNF in a temporal manner in several brain regions associated with the development of addiction to ethanol and other drugs of abuse (Raivio et al., 2012). In the present study we wanted to clarify further the role of the expression of BDNF in reinforcement from ethanol by exploring the effects of acute administration of ethanol on the expression of BDNF mRNA in the ventral tegmental area as well as in the projection areas of the dopamine pathway of alcohol-preferring Alko Alcohol (AA) and alcohol-avoiding Alko Non-Alcohol (ANA) lines of rats selected for high and low voluntary ethanol intake, respectively (Eriksson, 1968). The lines represent two non-overlapping phenotypic distributions of voluntary ethanol consumption. The utility of selected lines for unraveling the biological factors underlying the predisposition for high and low ethanol intake is based on the assumption that in the high-drinking line, the selection pressure applied gradually leads to enrichment of alleles promoting ethanol intake, while the alleles accumulated in the low-drinking line have opposite effects. The most common strategy for probing the mechanisms behind regulation of ethanol intake is the comparison of various central neurotransmitter systems in the selected lines. Therefore, examination of neurobiological differences between the lines – either in naïve animals or in their response to ethanol – is supposed to reveal the nature of interaction between the innate predisposition and ethanol exposure, and will help to identify the neuronal mechanisms underlying ethanol intake and abuse (Kiianmaa et al., 1992; Sommer et al., 2006). The present data complement the earlier work done in respect to the role of BDNF in the control of ethanol intake, and provide new information on the role of BDNF in the different levels of intake of ethanol in the two rat lines.

2. Results

2.1. *Blood ethanol concentrations*

The ethanol doses resulted in blood ethanol concentrations as shown in Table 1. The blood ethanol concentrations were similar between comparable groups in the dose response study and in the time course study. Blood ethanol concentrations were similar between the AA and ANA lines in respective groups.

2.2. *Effect of ethanol on BDNF expression*

2.2.1. *Basal levels*

There was a significant difference in the basal levels of BDNF mRNA expression between the AA and ANA lines in several brain parts [$F(4,473)=5.48$, $p=0.3\times10^{-3}$, for the interaction between effects of rat line and brain region; $F(4,473)=5.48$,

Table 1 – The concentration of ethanol in the blood of alcohol-preferring AA and alcohol-avoiding ANA rats after administration of ethanol 1.5 or 3 g/kg i.p.

Ethanol	Time point				
Dose g/kg	Rat line	90 min	3 h	6 h	24 h
1.5	AA	n/a	16.4±1.4	n/a	n/a
	ANA	n/a	18.0±0.8	n/a	n/a
3	AA	74.9±1.3	64.4±1.0	38.4±1.6	1.7±0.4
	ANA	77.9±0.8	63.6±0.8	37.0±1.1	2.0±0.6

The samples were collected from the animals both in the dose response and time course studies. Values (mean±SEM) are given in mM; $n=9$–20.