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Modulation of the endogenous opioid system after morphine self-administration and during its extinction: A study in Lewis and Fischer 344 rats

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Abstract

Lewis (LEW) and Fischer 344 (F344) rats show differential morphine self-administration rates. In this study, after animals of both strains self-administered morphine (1 mg/kg) or extinguished this behaviour for 3, 7 or 15 days, we measured the binding to, and functional state of μ opioid receptors (MORs) as well as proenkephalin (PENK) mRNA content in several brain regions. The results showed that in most brain areas: 1) LEW rats had less binding to MORs in basal conditions than F344 rats; 2) after morphine self-administration, either one of the strains or both (depending on the brain area) showed increased levels of binding to MORs as compared to basal groups; and 3) these binding levels in morphine self-administration animals came down in each extinction group. Moreover, F344 rats exhibited, in general, an increased functionality of MORs after morphine self-administration, as compared to basal groups, which also went down during extinction. Finally, the basal content of PENK mRNA was lower in LEW rats than in F344 rats and it decreased more after self-administration; during extinction, the levels of PENK mRNA got normalized in this strain. This differential modulation of the endogenous opioid system might be related to the different rates of morphine self-administration behavior exhibited by both inbred rat strains.

Keywords: Lewis; Fischer 344; Morphine; Self-administration; Extinction; Opioid system

Abbreviations: AID, agranular insular cortex, dorsal part; AIV, agranular insular cortex, ventral part; APT, anterior pretectal nucleus; BLA, basolateral amygdaloid nucleus, anterior part; BMP, basomedial amygdaloid nucleus, porterior part; BSTMA, bed nucleus of stria terminalis, medial division, anterior part; BSTMV, bed nucleus of the stria terminalis, medial division, ventral part; CA1, field CA1 of hippocampus; CA2, field CA2 of hippocampus; CA3, field CA3 of hippocampus; Cg1, cingulate cortex, area 1; CL, centrolateral thalamic nucleus; CP, caudate-putamen; CPDL, caudate-putamen, dorsolateral division; CPDM, caudate-putamen, dorsomedial division; CP-Matrix, caudate-putamen, matrix; CP-Patches, caudate-putamen, patches; CPVL, caudate-putamen, ventrolateral division; CPVM, caudate-putamen, ventromedial division; DEn, dorsal endopiriform nucleus; DG, dentate gyrus; DM, dorsomedial hypothalamic nucleus; G1, glomerular layer of the olfactory tubercle; La, lateral amygdala; LAVM, lateral amygdaloid nucleus, ventromedial part; LC, locus coeruleus; LDDM, laterodorsal thalamic nucleus, dorsomedial part; LDVL, laterodorsal thalamic nucleus, ventrolateral part; LGP, lateral globus pallidus; LHbM, lateral habenular nucleus, medial part; LPMR, lateral posterior thalamic nucleus, mediorostral part; LSI, lateral septal nucleus, intermediate part; LSS, lateral stripe of the striatum; LSV, lateral septal nucleus, ventral part; M1, primary motor cortex; M2, secundary motor cortex; MDC, mediodorsal thalamic nucleus, central part; MDM, mediodorsal thalamic nucleus, medial part; Me, medial amygdaloid nucleus; MGD, medial geniculate nucleus, dorsal part; MePD, medial amygdaloid nucleus, posterodorsal part; MePV, medial amygdaloid nucleus, posteroventral part; MGM, medial geniculate nucleus, medial part; MGV, medial geniculate nucleus, ventral part; NAcc-Shell, nucleus accumbens, shell division; NAcc-Core, nucleus accumbens, core division; OT, nucleus of the optic tract; PAG, periaqueductal gray; PBP, parabrachial pigmented nucleus; PIR, piriform cortex; Po, posterior thalamic nuclear group; PPT, posterior prectectal nucleus; PV, paraventricular thalamic nucleus; Re, nucleus reuniens; Rh, rhomboid thalamic nucleus; RMC, red nucleus magnocellular part; RN, raphe nucleus; RPC, red nucleus parvicellular part; SNC, substantia nigra, compact part; SNR, substantia nigra, reticular part; S1J, primary somatosensory cortex, jaw region; SuG, superficial gray layer of the superior colliculus; Tu, olfactory tubercle; VRe, nucleus reuniens, ventral part; VTA, ventral tegmental area.

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1. Introduction

Different neurochemical systems have been hypothesized to play a role in the development and maintenance of addiction to opiates as well as in relapse. Among them, the endogenous opioid system is thought to be crucial (Gerrits et al., 2003). Several experiments have been done that demonstrate this involvement, especially those using genetically modified animals. In this sense, morphine- and heroin-induced conditioned place preference were respectively abolished (Matthes et al., 1996) or did not develop (Contarino et al., 2002) in μ-opioid receptor (MOR) deficient mice. Moreover, Becker et al. (2000) found that the morphine self-administration rate significantly decreased over time in MOR-null mice when compared to their wild-type counterparts.

Despite the literature that suggests a key role for MORs in opiate addiction, morphine has proven to be ineffective in altering the number of surface MORs in different cell preparations (see for example Keith et al., 1996; Kramer and Simon, 2000). These results do not fit the classic model in which MORs desensitization and internalization leads to tolerance and, therefore, addiction (von Zastrow, 2004). However, there are controversial data in the literature since two studies have shown an effective internalization of MORs in nucleus accumbens (NAcc) dendrites and in striatal membranes after acute morphine (Haberstock-Debic et al., 2003, 2005).

Additionally, the importance of genetic differences in the proneness to become addicted to drugs has recently been highlighted both in humans subjects (see Uhl, 2004 and Lachman, 2006; for review) and animal models (Kosten and Ambrosio, 2002 for a review). In this respect, Fischer 344 (F344) and Lewis (LEW) inbred strains of rats have been extensively used as a model of this genetic predisposition. It has been shown that LEW rats self-administer a higher amount of several drugs of abuse than F344 rats, including opiates (see Ambrosio et al., 1995; Kosten et al., 1997; Brower et al., 2002; Suzuki et al., 1988, 1992). In this line of research, we have shown that LEW rats self-administer a higher number of morphine injections as compared to F344 rats under both fixed ratio (Ambrosio et al., 1995) and progressive ratio schedules of reinforcement (Martín et al., 1999, 2003). Moreover, this effect seems to be specifically related to morphine and not to strain-related differences in reward processing, since we did not find any difference in the acquisition of a food reinforced behavior (Martín et al., 2003). F344 and LEW rats differ in several parameters of neurotransmitter systems (Kosten and Ambrosio, 2002; Chaouloff et al., 1995; Flores et al., 1998; Selim and Bradberry, 1996), however the dissimilar pattern of opiate self-administration between both rat strains has been suggested to be related, at least in part, to strain differences in the basal opioidergic tone as well as in dopaminergic transmission. As regards this fact, we have examined the binding levels to D1 dopaminergic receptors, showing that LEW rats had higher levels of D1 binding sites compared to F344 rats in several brain regions (Martín et al., 2003). On the other hand several studies have examined the levels of endogenous opioid peptides in both rat strains in basal conditions, as well as after chronic morphine treatment and withdrawal. LEW rats showed a significantly lower level of dynorphins and they were less responsive to opiate treatments than F344 rats (Nylander et al., 1995a,b). In the same line, given the importance of proenkephalin (PENK) in opiate-related behaviors (Bodnar and Hadjimarkou, 2002) we have examined the levels of this peptide in both strains, finding that LEW rats exhibited lower levels of PENK mRNA in the caudate-putamen (CP) and NAcc when compared to F344 rats (Martín et al., 1999). Another study has characterized the specific binding of ^{3}H-DAMGO to MORs in both rat strains, showing that the density of ^{3}H-DAMGO binding sites was similar in the brain cortex and spinal cord of both strains, but ^{3}H-DAMGO affinity for MORs was lower in LEW rats (Herradon et al., 2003). Data from animal research is consistent with a study in human subjects which shows that 90% people carrying a single nucleotide polymorphism A118G in MORs were heroin abusers and exhibited a down-regulation of the preproenkephalin and preprodynorphin genes (Drakenberg et al., 2006).

Despite this body of knowledge, as far as we know, MORs levels have never been examined after morphine self-administration in these strains. Furthermore, it has been shown that LEW and F344 exhibit different withdrawal syndromes (Guitart et al., 1993) and therefore we decided to test if a differential neurochemical regulation of the opioid system occurred in both rat strains during the extinction of this behavior. These data could provide new insights into the regulation of the endogenous opioid system in addictive states as well as in drug-abstinence periods.

The aim of this work was to characterize the binding levels to and functional state of MORs in basal conditions as well as after morphine self- administration and during the extinction of this behavior. In addition, we also measured the levels of PENK gene expression by in situ hybridization histochemistry.

2. Methods

2.1. Animals

Male Fischer 344 and Lewis inbred rats (300–350 g body weight) obtained from Harlan Interfauna Ibérica, Barcelona, Spain; were used in this study. All animals were experimentally naïve, individually housed in a temperature-controlled room (23 °C) with a 12-h light-dark cycle (08:00–20:00 lights on) and given free access, unless otherwise specified, to Purina laboratory chow, and tap water prior to initiation of the experiments. Animals used in this study were maintained in facilities according to European Union Laboratory Animal Care Rules (86/609/EEC Directive).

2.2. Apparatus

Twelve operant chambers (Coulburn Instruments, USA) were used for operant food reinforced studies and morphine self-administration experiments. A lever designed to register a response when 3.0 g of force was applied was placed in the front wall of the chamber. Morphine operant data acquisition and storage were accomplished on IBM computers (Med Associates, USA).