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RAPID REPORT

GENETIC DIFFERENCES IN HIPPOCAMPAL SYNAPTIC PLASTICITY

S. PRAKASH,[a] E. AMBROSIO,[b] L. F. ALGUACIL[a1] AND N. DEL OLMO[a*]

[a]*Departamento de Farmacología, Tecnología y Desarrollo Farmacéutico, Facultad de Farmacia, Universidad San Pablo CEU, Urb. Montepríncipe, Boadilla del Monte, 28668 Madrid, Spain*

[b]*Departamento de Psicobiología, Facultad de Psicología, UNED, 28040 Madrid, Spain*

Abstract—Synaptic plasticity is considered a physiological substrate for learning and memory [Lynch MA (2004) Long-term potentiation and memory. Physiol Rev 84:87–136] that contributes to maladaptive learning in drug addiction [Schoenbaum G, Roesch MR, Stalnaker TA (2006) Orbitofrontal cortex, decision-making and drug addiction. Trends Neurosci 29:116–124]. Many studies have revealed that drug addiction has a strong hereditary component [Kosten TA, Ambrosio E (2002) HPA axis function and drug addictive behaviors: insights from studies with Lewis and Fischer 344 inbred rats. Psychoneuroendocrinology 27:35–69; Uhl GR (2004) Molecular genetic underpinnings of human substance abuse vulnerability: likely contributions to understanding addiction as a mnemonic process. Neuropharmacology 47 (Suppl 1):140–147], however the contribution of the genetic background to drug-induced changes in synaptic plasticity has been scarcely studied. The present study reports on an analysis of long-term potentiation (LTP) and depotentiation in Lewis (LEW) and Fischer-344 (F344) rats, two inbred rat strains that show different proneness to drugs of abuse and are considered an experimental model of genetic vulnerability to addiction [Kosten TA, Ambrosio E (2002) HPA axis function and drug addictive behaviors: insights from studies with Lewis and Fischer 344 inbred rats. Psychoneuroendocrinology 27:35–69]. The induction of saturated-LTP was similar in LEW and F344 rats treated with saline or cocaine. However, only slices from LEW saline-treated rats showed the reversal of LTP; thus, the depotentiation of saturated-LTP was not observed in cocaine-injected LEW rats and in F344 animals (treated either with cocaine or saline). These results suggest significant differences in hippocampal synaptic plasticity between Lewis and Fischer 344 rats.
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Key words: LTP, cocaine, hippocampus, depotentiation, Fisher-344, Lewis.

Neuronal plasticity supporting memory processes involves phenomena such as long-term potentiation (LTP) (Bliss and Collingridge, 1993), long-term depression (LTD) (Dudek and Bear, 1992) and depotentiation (Staubli and Lynch, 1990), which are supposed to represent the cellular mechanisms underlying information storage in the mammalian brain (Heynen et al., 1996). Numerous studies have described prominent effects of drug abuse on the brain circuits involved in memory and learning (Berke and Hyman, 2000; Robbins and Everitt, 1999). Accordingly, cocaine appears to facilitate the induction and maintenance of different forms of LTP in some areas of the brain including hippocampus (Huang et al., 2007a; Liu et al., 2005; Thompson et al., 2004; del Olmo et al., 2006). Moreover, it has been demonstrated that cocaine exposure modulates other processes such as LTD in the nucleus accumbens (Martin et al., 2006) and prefrontal cortex (Huang et al., 2007b).

LTP is a flexible event that can be erased by subsequent low frequency stimulation (LFS) in the hippocampus (Bashir and Collingridge, 1994; Huang et al., 2001). It is considered that under physiological conditions the reversal of hippocampal LTP might be considered the one of the mechanisms behind forgetting (Huang and Hsu, 2001). Moreover, cocaine administration to rats altered their capacity to undergo depotentiation after the application of LFS to corticostriatal terminals (Centonze et al., 2006).

The importance of genetic differences in the proneness to become addicted to drugs has recently been highlighted in both human subjects (Uhl, 2004) and animals (Kosten and Ambrosio, 2002), especially in Fischer 344 (F344) and Lewis (LEW) rat strains (Kosten and Ambrosio, 2002). Indeed, it is commonly accepted that LEW rats are more sensitive to cocaine addiction and relapse, while F344 animals seem to be more resistant to the extinction of drug-seeking behaviors (Kosten et al., 1997). In the attempt to clarify the genetic differences in synaptic plasticity in animals that show a different behavior after drugs of abuse, we studied the effects of chronic cocaine administration on the reversal of hippocampal LTP in LEW and F344 rats in order to discern the genetic contribution to synaptic plasticity that supports the learning and memory processes.

EXPERIMENTAL PROCEDURES

Adult male LEW and F344 rats (200–220 g, Harlan, Spain) were administered i.p. injections of either saline (0.9% NaCl) or cocaine chlorhydrate (15 mg/kg) for seven consecutive days. Saline- and cocaine-treated rats were sacrificed by decapitation 24 h after the last i.p. injection. Their brains were removed immediately and placed in bubbled (95% O_2 and 5% CO_2) and ice cold Krebs–Ringer bicarbonate (KRB) solution containing (in mM): 109 NaCl, 2.5 KCl, 1 KH_2PO_4, 1.3 $MgSO_4$, 2.5 $CaCl_2$, 26.2 $NaHCO_3$ and 11 glucose. As described previously (del Olmo et al., 2000, 2003), transverse slices

[1] Present address: Translational Research Unit on Eating Disorders and Obesity, Ciudad Real General Hospital, Spain.
*Corresponding author. Tel: +34-91-3724752; fax: +34-91-3510475.
E-mail address: nolmo@ceu.es (N. Del Olmo).
Abbreviations: fEPSP, field excitatory postsynaptic potential; F344, Fischer 344; HFS, high frequency stimulation; KRB, Krebs–Ringer bicarbonate; LEW, Lewis; LFS, low frequency stimulation; LTD, long-term depression; LTP, long-term potentiation.

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(400 μm) of each hippocampus were cut with a manual tissue chopper and placed in a humidified interface chamber at room temperature (20–25 °C). After a 2-h incubation period, the slices were transferred to the submersion recording chamber which was continuously perfused with standard KRB solution at a rate of 1.8–2 ml/min. Field excitatory postsynaptic potentials (fEPSPs) were recorded for 100 min in the CA1 stratum radiatum with tungsten electrodes (1 MΩ) and evoked by stimulating Schaffer collateral–commisural fibers with biphasic electrical pulses (30–70 μA; 100 μs; 0.033 or 0.066 Hz) delivered through bipolar tungsten insulated microelectrodes (0.5 MΩ) every 15 s. Stimulus strength was adjusted to evoke a response of 30%–40% of maximal fEPSP slope. The recording electrode was connected to an AI-402 amplifier (Axon Instruments, USA) plugged into a CyberAmp 380 signal conditioner (Axon Instruments). Electrical pulses were supplied by a Master 8 pulse generator (AMPI, Israel). Evoked responses were digitalized at 25–50 Hz using a Digidata 1322 A (Axon Instruments) and stored on a Pentium IV IBM compatible computer using pCLAMP 9.0 software (Axon Instruments).

After obtaining stable synaptic responses for at least 20 min (baseline period), the pathway was tetanized with three 100 Hz pulses for 1 s and of 100 μs duration every 20 s (high frequency stimulation, HFS). After a 20 min period of LTP stabilization, low frequency stimulation (LFS) pulses were applied to induce depotentiation. LFS involved a train of 900 pulses of 1 Hz/1 s (15 min). The synaptic strength was assessed by measuring the initial slope of the fEPSP, as analyzed with pCLAMP 9.0 software. The data were normalized with respect to the mean values of the responses obtained from each animal during the 20 min baseline period. A single slice from each separate animal was considered as $n=1$. All electrophysiological experiments were carried out at 31–32 °C and all the chemicals used in these studies were obtained from Sigma (Madrid, Spain).

All the animals used in this study were maintained in accordance with European Union Laboratory Animal Care Rules (86/609/ECC directive) and the protocols were approved by the Animal Research Committee of USP-CEU. All efforts were made to minimize the number of animals used and their suffering. For this reason, we always worked with the minimum number of animals which will provide us with scientifically meaningful data.

The averaged values of the initial slope of the fEPSP were analyzed by a repeated measure ANOVA. Unpaired *t*-tests were performed to assess specific group differences in the average fEPSP measured during five consecutive minutes at different times of the recording assay. In all cases, statistical differences were considered significant if the probability of error was less than 5%. All calculations were performed using the SPSS statistical package 15.0 version.

RESULTS

The main objective of this work was to compare the effect of passive chronic cocaine administration on LTP in LEW and F344 rats. Hence, we first examined induction and the

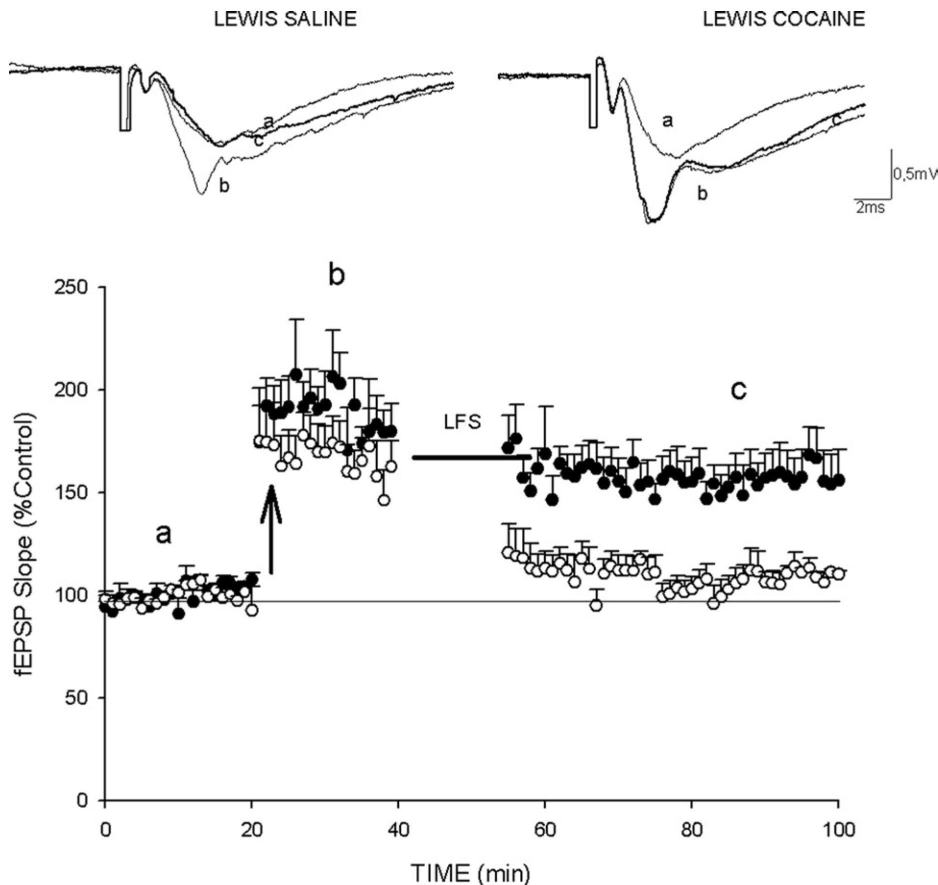

Fig. 1. Effect of chronic cocaine administration on LTP and depotentiation in LEW rats. The symbols represent the fEPSP slope values from CA1 hippocampal slices. After a basal 20 min period, three trains of HFS (indicated by the arrow) were applied to slices from cocaine (filled circles, $n=11$) and saline (open circles, $n=10$) treated animals. Following a 20 min stabilization period after LTP, a train of LFS was applied (indicated by the horizontal black line). The upper traces are the averages ($n=4$) of the fEPSPs recorded during the basal period (a, thin trace), after HFS (b, thin trace) and after LFS (c, thick trace) in both saline (left) and cocaine (right) treated animals. Scale bars=0.5 mV, 2 ms.

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