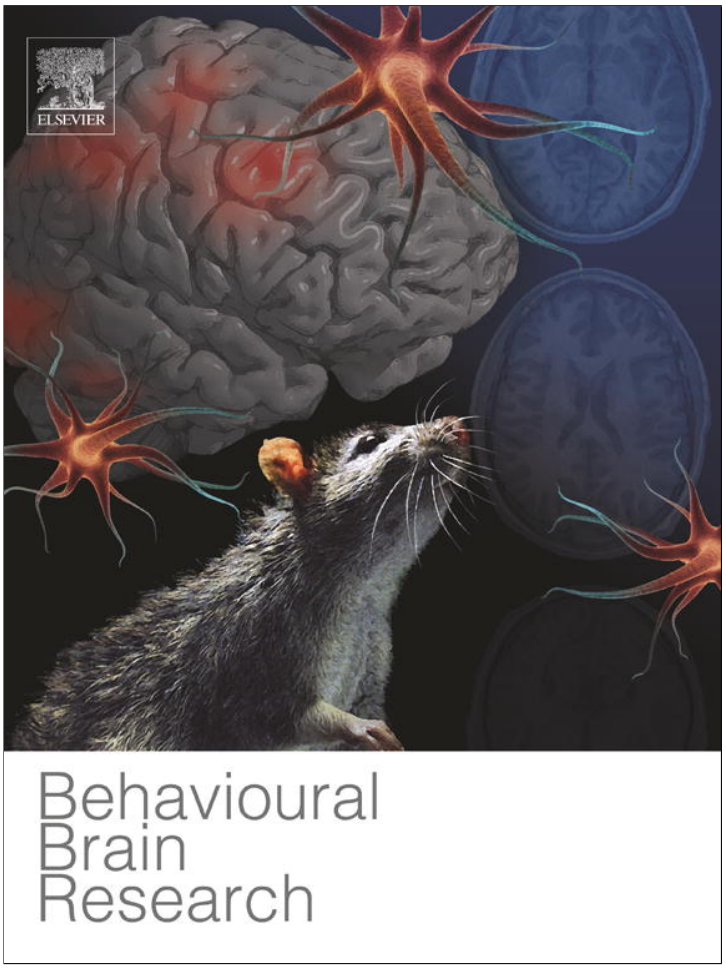


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Short communication

# Perinatal protein deprivation facilitates accumbal ERK phosphorylation in cocaine-sensitized adult rats

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## HIGHLIGHTS

- Only D-animals exhibited behavioral sensitization to the lowest cocaine dose (5 mg/kg).
- Pretreatment with cocaine 10 mg/kg induced behavioral sensitization in C- and D-animals.
- In the NAc core only D-rats showed a significant pERK2 increase with the lowest dose of cocaine.
- C-rats with 10 mg/kg showed an increase in pERK2 levels from WD 7 while D-rats showed this on WD 4.
- Undernutrition facilitates molecular processes involved in neuroplasticity during withdrawal.

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## ABSTRACT

In previous studies we described that perinatal protein deprivation facilitates the development and expression of behavioral sensitization to cocaine. In this research, we explored whether the increased reactivity observed in deprived (D) versus control (C) rats is also evident during drug-free withdrawal periods. Considering that activation of the extracellular signal-regulated protein kinase (ERK) is suggested to be involved in cocaine-induced behavioral sensitization, we study the effects of perinatal protein deprivation on phosphorylated ERK2 (pERK2) protein levels in the NAc (core and shell) during different drug-free withdrawal periods. To induce behavioral sensitization, C- and D-rats received a daily injection of cocaine (5–10 mg/kg, i.p.) for 7 days and locomotor activity was performed on days 1 and 7. Cocaine-sensitized animals were left drug-free and pERK2 was assessed on withdrawal days (WD) 1, 4, 7 and 21. In the NAc core, cocaine induced ERK signaling pathway activation in a dose-dependent manner, and only D-rats showed a significant increase in pERK2 protein levels with the lowest dose of cocaine (5 mg/kg). Moreover, sensitized C-rats with 10 mg/kg showed an increase in pERK2 levels from WD7 while D-rats showed this activation on WD4, which remained increased on WD7 and 21. In contrast, in the NAc shell, only sensitized D-rats with cocaine 10 mg/kg showed ERK2 activation on WD21. These results suggest that perinatal protein deprivation facilitates the molecular processes involved in neuronal plasticity occurring during withdrawal.



## 1. Introduction

Perinatal protein deprivation produces dramatic damage to the developing brain. Coinciding with the brain growth spurt period, malnutrition induces biochemical, anatomical, morphological and behavioral alterations that persist in the adult individual even after a nutritional recovery period [1].

In humans, prenatal exposure to severe famine has been associated with an increased risk for the occurrence of affective disorders and addiction [2]. Enhanced reactivity to drugs of abuse has been demonstrated in animal models of early malnutrition, with undernourished rats showing increased response to drug effects in their adult life. Thus, repeated administration of amphetamine, cocaine or morphine facilitated the development of behavioral sensitization and cross-sensitization [3–8]. Similarly, the rewarding effects of cocaine and morphine were increased in deprived rats (D-rats), correlated with increased delta Fos-B protein in different areas of the reward circuitry [6,7].

Behavioral sensitization, characterized by increased locomotor activity in response to repeated administration of different drugs of abuse, has been associated to drug craving and drug-seeking behavior, both characteristic of addictive processes [9]. The extracellular signal-regulated protein kinase (ERK), a member of mitogen-activated protein kinase MAPK, has a critical role in the development, but not in the expression of cocaine sensitization [10]. Moreover, ERK is involved in other aspects of the

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addictive process such as reward, as well as the mechanism underlying learning and memory [11,12]. In addition, drug craving is assumed to progressively increase over the first week of abstinence and remains high over extended periods [13] and activation of the ERK signaling pathway is one of the mechanisms involved in this incubation process [14].

Considering that deprived animals showed facilitation in the development and expression of behavioral sensitization to cocaine, the present study aimed to investigate whether early nutritional insult induced an altered response in processes occurring during withdrawal times. For this purpose, we measured pERK2 levels in the core and shell nucleus accumbens (NAc) of cocaine sensitized D- and C-animals, at different withdrawal days.

## 2. Experimental procedures

### 2.1. Animals

A protein deprivation schedule described by Borghese et al. [15] was used, with minor modifications. Briefly, pregnant rats (Wistar strain, from our own colony) were divided into two groups on the 14th day of pregnancy and fed isocaloric diets containing 24% and 8% casein for control (C) and deprived (D) rats, respectively. Litters from both groups were culled to eight pups. After weaning at 30 days, when the deprivation period was ended, both groups were fed on balanced standard chow (Gepsa feeds, Pilar Group, Argentina) for at least 40 days prior to assays (nutritional recovery period). Animals were maintained at 22 ± 2 °C in a light/dark cycle (light on at 07:00 h) with food and water available ad libitum. All experimental groups were composed of male animals from different litters, in order to avoid sibling replication. Animals used were maintained and the studies conducted in accordance with the NIH Guide for the Care and Use of Laboratory Animals (National Research Council, USA, 2010). All efforts were made to minimize both animal suffering and the number of animals used.

### 2.2. Drugs

Cocaine hydrochloride (Laboratorio Verardo, Buenos Aires, Argentina) was dissolved in 0.9% saline and injected i.p. in a volume of 1 ml/kg of body weight. Drug dose is expressed in terms of the salt.

### 2.3. Locomotor activity

To evaluate locomotor activity, Plexiglas cages (28.5 cm × 46 cm × 20 cm), equipped with two parallel horizontal photocell beams located 3 cm above the floor and spaced evenly along the longitudinal axis, were used. Interruption of two successive beams resulted in a photocell count. Activity counts were automatically recorded by computer every 10 min. All animals were tested between 9:00 and 18:00 h in the light phase of the light/dark cycle, under tenuous light and white noise to minimize the influence of surrounding sounds.

The protocol to induce behavioral sensitization to cocaine was performed according to Kim and Kim [16] with minor modifications. Different groups of C- and D-rats received daily cocaine (5 or 10 mg/kg) or saline (1 ml/kg) injections during 7 days. To evaluate behavioral sensitization, locomotor activity was measured on day 1 and on day 7. Animals were removed from the homecage, and submitted to a double test of 1 h each. The first test was performed after saline administration to obtain the baseline activity, and the second after cocaine or saline injection. The criterion for behavioral sensitization was a greater than 20% increase in locomotor activity on day 7 relative to day 1, and only those animals were used for the immunoblotting experiments.

### 2.4. Western blotting

After the sensitization expression phase, animals were submitted to 1, 4, 7 or 21 days of drug-free withdrawal periods, according to the experimental schedule. On the corresponding day, saline- or cocaine-pretreated rats were carried to the room, where they were injected and left for a few minutes before being sequentially sacrificed in a separate room. Groups of naive C- and D-rats were processed in the same way. Their brains were quickly removed and the NAc (core and shell) were dissected from coronal brain slices obtained with an ice-cold brain slicer (Fig. 2C).

Brain samples and Western blot determinations were performed according to Maldonado et al. [17] with minor modifications. Briefly, pools of bilateral NAc (core and shell) tissue punches from two animals were merged to obtain enough material for cellular fractionation. Tissue punches were homogenized in RIPA buffer [150 mM NaCl, 0.1% Triton X-100, 0.5% sodium deoxycholate, 0.1% sodium dodecylsulphate (SDS), 50 mM Tris, pH 7.5] containing protease inhibitors (10 μg/ml aprotinin, 1 μl/ml leupeptin, 1 μg/ml pepstatin A and 100 μg/ml phenylmethylsulfonyl fluoride) and phosphatase inhibitor (1 mM $Na_3VO_4$, sodium orthovanadate). Samples were centrifuged at 10,000 × *g* for 10 min at 4 °C. The supernatants were combined with 1/3 volume of Laemmli buffer (2% SDS, 20% glycerol, 10% β-mercaptoethanol, 0.01% bromophenol blue, 125 mM Tris, pH 6.8), boiled at 100 °C for 5 min and stored at −20 °C until use. Aliquots of the supernatant were used for total protein quantification using Bio-Rad Bradford Protein Assay Kit (Hercules, CA, USA).

Protein samples (30 μg/lane) from homogenates were electrophoretically separated in 10% SDS-PAGE gel and subsequently blotted to polyvinylidene fluoride membrane (Bio-Rad). Blots were blocked with 5% skim milk in TBS buffer (50 mM Tris–HCl, pH 7.5, 150 mM NaCl and 0.1% Tween 20) during 30 min at room temperature. Specific monoclonal antibodies against phospho-ERK1/2 MAPK at $Thr^{202}$ and $Tyr^{204}$ (anti-rabbit, 1:1000; Cell Signaling Technologies), ERK1/2 MAPK (anti-mouse, 1:2500, Cell Signaling) and α-tubulin (anti-mouse, 1:2000, Sigma–Aldrich) were used to probe the blots. Primary antibodies were detected with a secondary antibody anti-rabbit conjugated to horseradish peroxidase (1:2500, Cell Signaling) followed by enhanced chemiluminescence (ECL) on X-ray film. Phospho-ERK1/2 antibody on the membrane was stripped with NaOH 1 M, for 10 min, before being

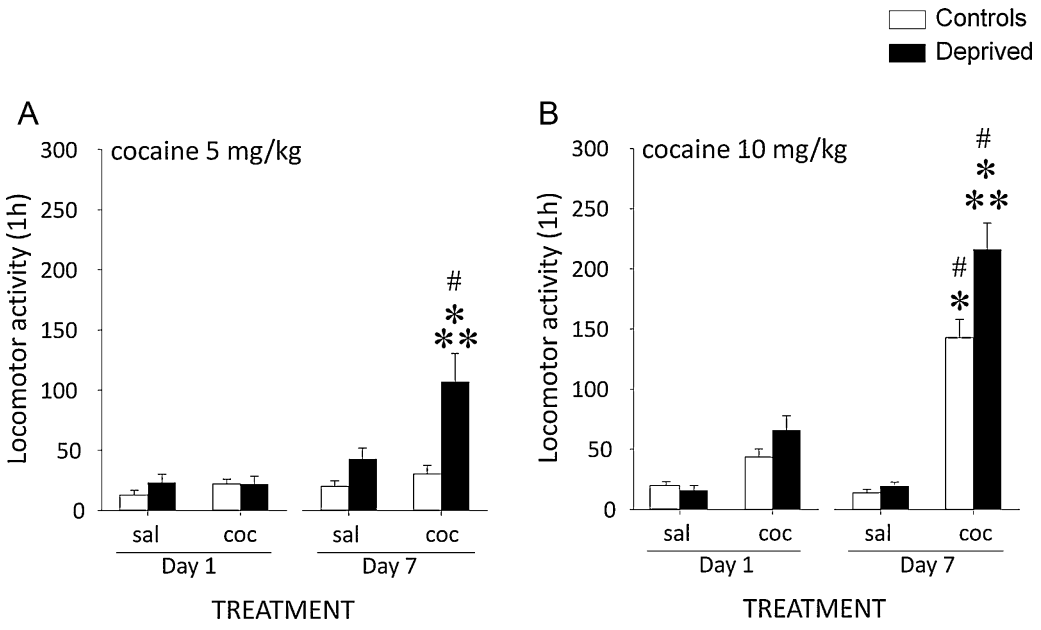


**Fig. 1.** Effect of perinatal protein deprivation on cocaine-induced behavioral sensitization. Animals received a daily injection of cocaine 5 mg/kg or 10 mg/kg; (A) and (B) respectively or saline solution during seven days and locomotor activity was evaluated on days 1 and 7. Bars represent the total activity evaluated during 1 h ± SEM. #$P < 0.05$ vs. day 1; *$P < 0.05$ vs. their respective group treated with saline, **$P < 0.05$ represent significant difference between C- and D-animals under the same experimental conditions.

washed 3 times for 5 min with TTBS and reprobed with total ERK1/2 antibody. The resulting film samples were scanned and analyzed with an image analysis program (GelPro32 Analyzer) and the data were normalized with the total signal of each plot. Only film exposures that were in linear range of the ECL reaction were used for quantification analysis, with data being presented as the ratio of phospho-ERK2/tubulin and total ERK2/tubulin. Although the antibody used in these experiments recognized both ERK1 and ERK2 isoforms, only ERK2 was quantified, considering that it has been more implicated in addictive processes than ERK1 [18]. Phospho-ERK1/2 or total ERK1/2 levels were examined on the same gel and normalized to α-tubulin protein levels.

α-tubulin was used instead of total ERK2 as control protein to avoid misleading results, because total ERK2 levels in deprived animals may be different from control rats.

### 2.5. Statistics

Data are presented as mean ± S.E.M. Differences in behavioral scores were analyzed using two-way ANOVA with time as the repeated measure. Western blotting data were analyzed using two-way factorial ANOVA. Post hoc comparisons were made using Newman-Keuls test, with values of $P < 0.05$ considered as statistically significant.

## 3. Results

### 3.1. Effect of perinatal protein deprivation on cocaine-induced behavioral sensitization

Fig. 1A shows the locomotor behavioral scores obtained in rats pre-exposed to cocaine (5 mg/kg) or saline. Analysis of the data revealed a significant interaction (diet × treatment × day, $F_{1,27} = 9.55$ $P < 0.05$). Newman- Keuls test showed that treatment with the lowest cocaine dose induced behavioral sensitization only in D-rats, with significantly higher activity levels on day 7 than at day 1 ($P < 0.001$). Moreover, D-rats had significantly higher activity levels than C-rats ($P < 0.001$). Saline pre-treatment did not modify locomotor activity in C- or D-rats and no differences between C- and D-groups were detected. On the other hand, treatment with cocaine 10 mg/kg induced sensitization in both C- and D-rats, but locomotor response to cocaine was significantly higher in the D- than the C-group ($P < 0.001$) (Fig. 1B). Behavioral sensitization induced in our paradigm is context-independent since seven-day test locomotor activity did not increase after the initial saline injection in C- or D- cocaine-pretreated rats compared to C and D- saline-pretreated animals (data not shown).

### 3.2. Effect of cocaine pre-treatment and drug-free withdrawal day on pERK2 protein levels in nucleus accumbens (core and shell)

Total ERK2 levels remained unchanged in the NAc core and shell in both C- and D-groups at all withdrawal time points, cocaine doses and treatments analyzed (Figure 2B, 3B, 4B).

#### 3.2.1. Nucleus accumbens core

Following cocaine 5 mg/kg, no difference was found between groups on WD1. However, on WD7, only D-rats showed a significant increase in pERK2 levels ($P < 0.0005$ vs. naive/saline D-group). In addition, a significant effect of diet was found ($F_{4,45} = 3.15$, $P < 0.05$), resulting mainly from differences between cocaine-pretreated C- and D-rats ($P < 0.05$, Fig. 2A). Moreover, in the animals sensitized with cocaine 10 mg/kg, the C-group showed a significant increase in pERK2 levels on WD7 and WD21 ($P < 0.05$) whereas D-group pERK2 protein levels significantly increased as from WD4 ($P < 0.01$, Fig. 3A).

#### 3.2.2. Nucleus accumbens shell

Cocaine withdrawal did not alter pERK2 levels in the NAc shell of C- and D-rats pretreated with the lowest dose of cocaine ($F_{4,59} = 0.62$, N.S; data not shown). However, in the D-group pretreated with cocaine 10 mg/kg, a significant increase in pERK2 protein levels was found on WD21 ($F_{4,45} = 3.15$, $P < 0.05$, Fig. 4A).

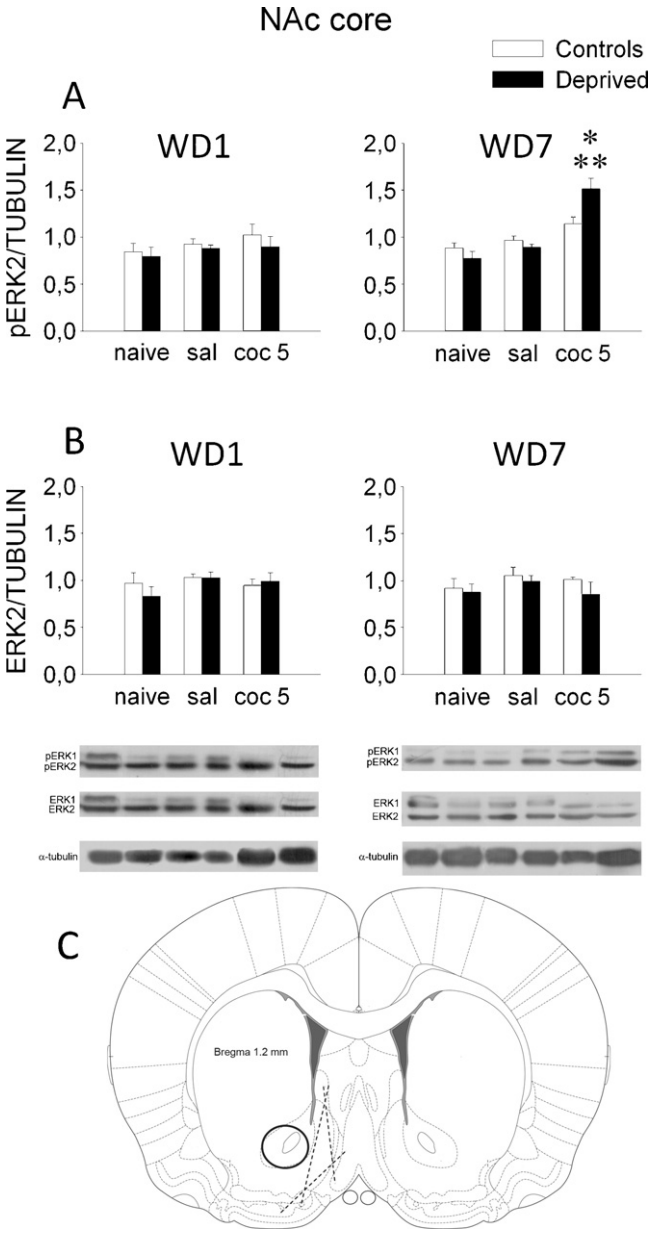


**Fig. 2.** Perinatal protein deprivation facilitates ERK2 phosphorylation in the NAc core of cocaine-pretreated animals following withdrawal. Animals pre-exposed to daily IP injections of cocaine (5 mg/kg) or saline for 7 days were sacrificed at WD1 or WD7, and pERK2 (A) and ERK2 (B) levels evaluated. Bars represent mean relative optical density ± S.E.M of at least four independent determinations obtained from a pool of two rat dissections each.*$P < 0.05$ vs. their respective naïve or saline-treated group, **$P < 0.05$ represent significant difference between C- and D-animals under the same experimental conditions. (C) The area inside the circle represents the NAc core and the area inside the triangle NAc shell. This rat coronal section scheme is from Paxinos and Watson's atlas (2007).

## 4. Discussion

Environmental insults that occur in coincidence with CNS ontogenesis induce deleterious effects on the development process, and have profound influences on a wide range of adult behaviors [19]. Thus, and in agreement with our findings, certain early life experiences (such as prenatal stress, maternal deprivation, neonatal isolation, and environmental cues), social or physical stress and food restriction can make an individual more vulnerable to develop drug addiction or to relapse into drug seeking (see review [20]).

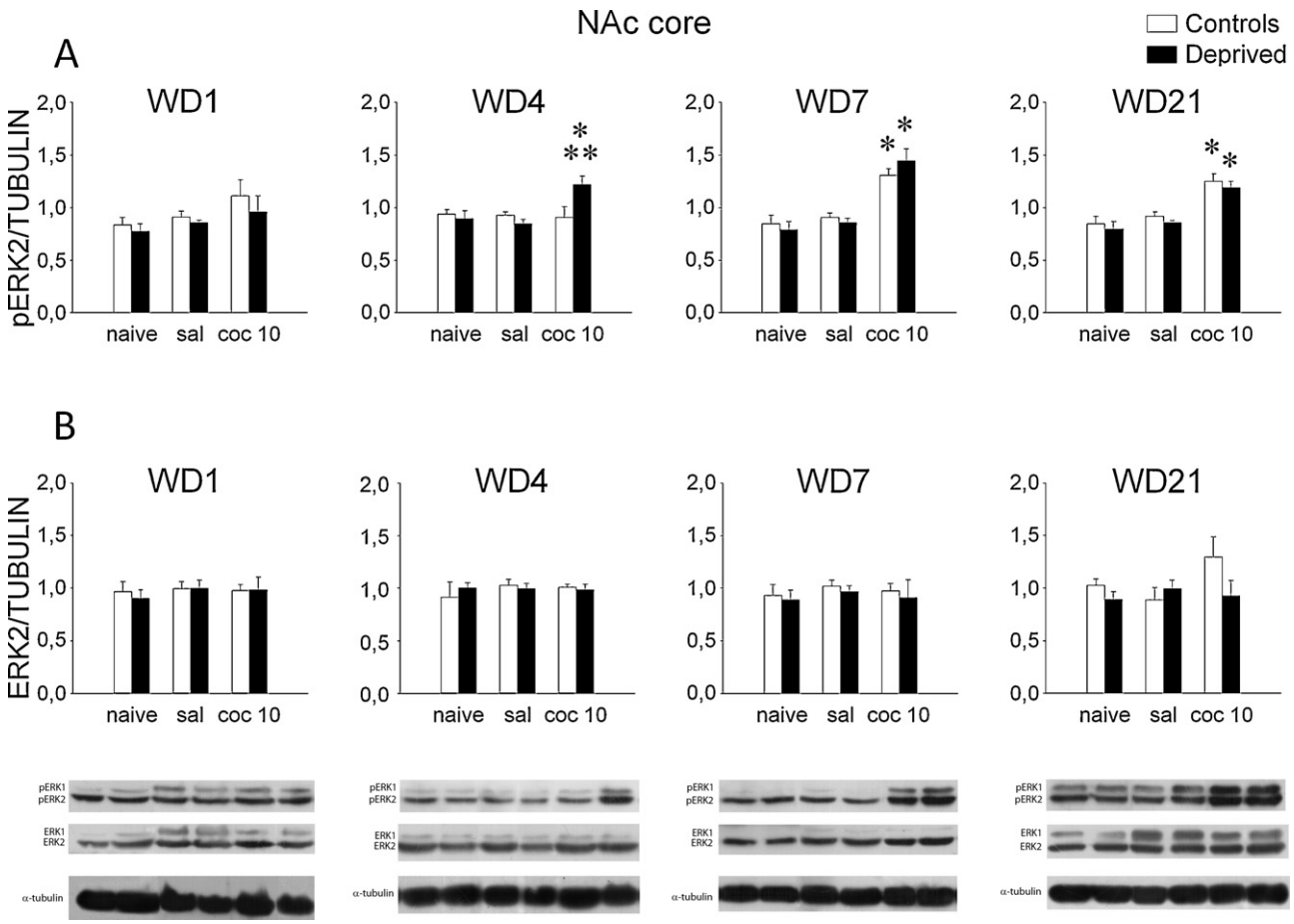


**Fig. 3.** Perinatal protein deprivation facilitates ERK2 phosphorylation in the NAc core of cocaine-sensitized animals during drug-free withdrawal period. Animals pre-exposed to daily IP injections of cocaine (10 mg/kg) or saline for 7 days were sacrificed at WD1, WD4, WD7 or WD21, and pERK2 (A) and ERK2 (B) levels evaluated. Bars represent the mean relative optical density ± S.E.M. of at least four independent determinations obtained from a pool of two rat dissections each. $^{*}P < 0.05$ vs. their respective naïve or saline-treated group, $^{**}P < 0.05$ represent significant difference between C- and D-animals under the same experimental conditions.

Perinatal malnutrition brings about permanent alterations in different neuronal pathways that may account for the altered reactivity to diverse pharmacological treatments. The present study demonstrated that early nutritional insult increases the reactivity of adult animals not only to cocaine-induced behavioral sensitization but also to processes during the drug-free withdrawal period that are involved in drug-induced neuronal plasticity.

It is well established that behavioral sensitization contributes to the development of drug craving. Similarly, some drug-induced brain neuroadaptations progressively increase after withdrawal, leading to enhanced response to drug cues and drug-seeking behavior [21,22]. As ERK has been implicated in cocaine-induced behavioral sensitization and incubation of drug craving, considering the important participation of the NAc in the expression of sensitization, the present work studied the effects of perinatal protein deprivation on pERK2 protein levels in NAc (core and shell) following different withdrawal times in animals sensitized to cocaine (5–10 mg/kg).

According to previous findings from our lab [5], at the lowest cocaine dose (5 mg/kg), behavioral sensitization was only induced in D-animals, and was accompanied by a corresponding p-ERK2 elevation in the NAc core on WD7. The absence of an increase at this dose of cocaine in C-rats was expected, since only sensitized animals show p-ERK2 increase during the withdrawal period [23]. Although pretreatment with cocaine 10 mg/kg induced behavioral sensitization in both groups of animals, a significant increase in ERK2 phosphorylation in D-rats was found with fewer withdrawal days (WD4) than those necessary to induce such an increase in C-animals (WD7). The present findings in C-rats match previous studies that reported a time-dependent increase in pERK2 on WD7 and WD21 in the NAc from sensitized animals that received a non-contingent cocaine administration [24,25]. Cocaine-induced ERK activation during withdrawal has also been demonstrated in animals self-administering cocaine [23]. Phospho-ERK2 increase in NAc core could be a consequence of animal exposure to the place in which cocaine was delivered since during withdrawal, drug associated cues showed a pERK increase in NAc core [11]. In the NAc shell, a significant increase in pERK2 protein levels on WD21 was found in D-rats sensitized with cocaine 10 mg/kg. The delayed increase found in this structure agrees with Pierce and Kalivas (1997) [26], who reported that changes in the NAc shell occur only after a longer drug-free period.

Our results indicate that early nutritional insult not only facilitates the development of behavioral sensitization to cocaine, but also affects the temporal development of neuroadaptive processes during withdrawal. Thus, D-animals showed a significant increase in pERK2 in the NAc core with the lower dose of cocaine used, and fewer withdrawal days were necessary to express this increase in C-rats. In addition, only D-rats showed an increase in pERK2 after a longer drug-free period in the NAc shell.

Bearing in mind the role of pERK in the incubation of craving during withdrawal [14,27], a characteristic process of addiction and its critical involvement in relapse, the facilitation of ERK2 activation in D-rats may indicate an increased propensity to relapse.

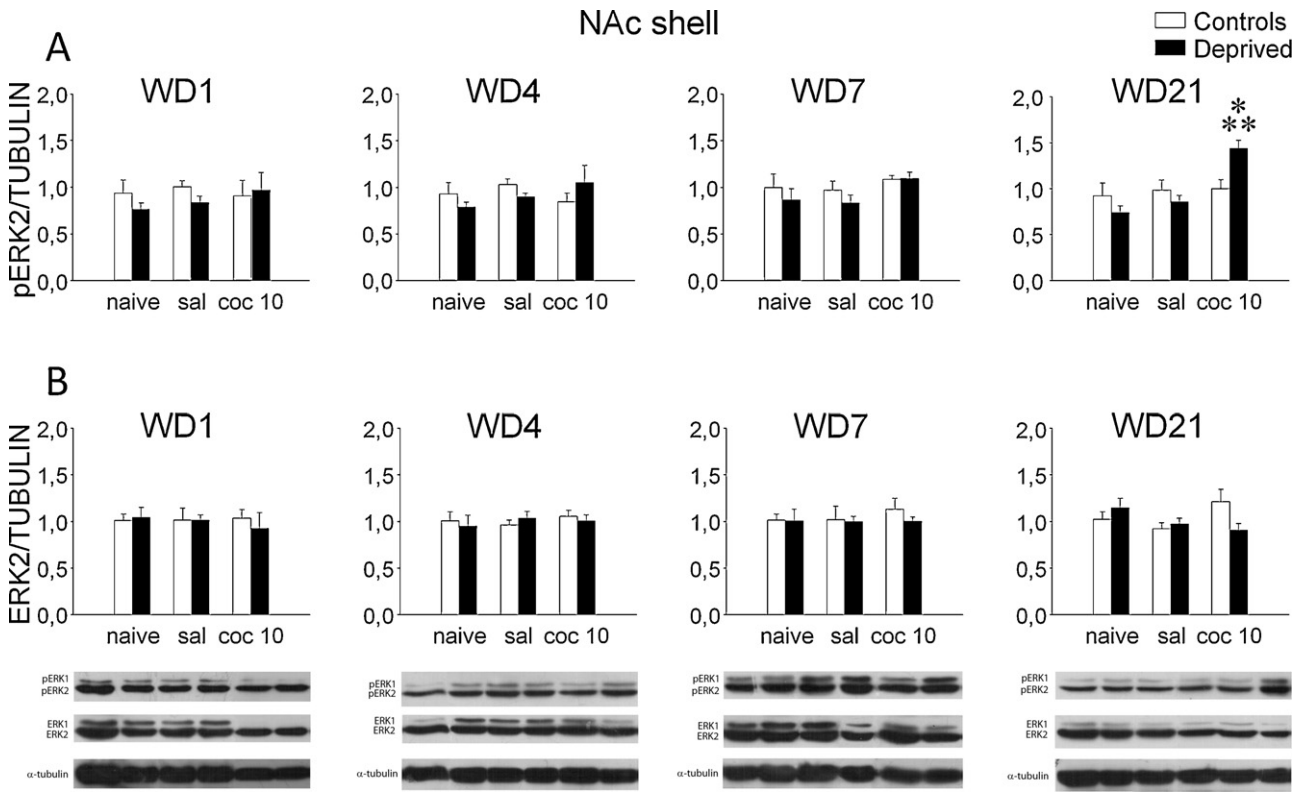


**Fig. 4.** Perinatal protein deprivation facilitates ERK2 activation in the NAc shell from cocaine-sensitized animals during drug-free withdrawal period. Animals pre-exposed to daily IP injections of cocaine (10 mg/kg) or saline for 7 days were sacrificed at WD1, WD4, WD7 or WD21, and pERK2 (A) and ERK2 (B) levels evaluated. Bars represent the mean relative optical density ± S.E.M. of at least four independent determinations obtained from a pool of two rat dissections each. $^{*}P < 0.05$ vs. their respective naive or saline-treated group, $^{**}P < 0.05$ represent significant difference between C- and D-animals under the same experimental conditions.

However, additional experiments are needed to confirm this hypothesis.

Early malnutrition and the increasing use of drugs of abuse are two major problems with great socioeconomic and public health implications in the modern world. It is very important from a health point of view to know and understand the deleterious effect of early malnutrition on vulnerability to addiction.

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