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Lifelong, central corticotropin-releasing factor (CRF) overexpression is associated with individual differences in cocaine-induced conditioned place preference

Maki Kasahara [a,1], Lucianne Groenink [b,c], Elisabeth Y. Bijlsma [b,c], Berend Olivier [b,c,d], Zoltán Sarnyai [a,e,f,g,h,*]

[a] Department of Pharmacology, University of Cambridge, Tennis Court Road, Cambridge CB1 2PD, United Kingdom
[b] Department of Pharmacology, Utrecht Institute of Pharmaceutical Sciences, Utrecht University, The Netherlands
[c] Rudolf Magnus Institute of Neuroscience, Utrecht University, The Netherlands
[d] Department of Psychiatry, Yale University, New Haven, CT, USA
[e] Discipline of Physiology and Pharmacology, Faculty of Medicine, Health and Molecular Sciences, James Cook University, Townsville, QLD 4811, Australia
[f] Australian Institute of Tropical Health and Medicine, James Cook University, Townsville, QLD, Australia
[g] Comparative Genome Centre, James Cook University, Townsville, QLD, Australia
[h] Centre for Biodiscovery and Molecular Development of Therapeutics, James Cook University, Townsville, QLD, Australia

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ABSTRACT

Stress, through corticotropin-releasing factor (CRF), influences all aspects of cocaine addiction. Earlier studies suggest that individual differences in responsivity to stress affect susceptibility to develop addiction. We have previously found that CRF over-expression alters individual differences in behavioural responses to novelty stress in mice. Therefore, we hypothesised that post-natal, long-term over-expression of brain CRF may alter the rewarding effects of cocaine in a manner that is sensitive to individual differences. In this study we specifically investigated cocaine-induced conditioned place preference (CPP) in transgenic mice over-expressing CRF (CRF-OE) and in wild-type (WT) littermates after determining their individual locomotor and emotional responsivity to inescapable novelty. CRF-OE mice showed decreased overall locomotor activity and increased anxiety-like behaviour in response to novelty compared to WT mice. Low behavioural reactivity to novelty (LR) was associated with heightened anxiety-like behaviour in CRF-OE, but not in WT, mice. WT and CRF-OE mice developed CPP equally to both low (5 mg/kg) and high (20 mg/kg) doses of cocaine. However, LR CRF-OE mice expressed significantly stronger cocaine CPP than transgenic mice with high locomotor response to novelty (HR). In WT mice, on the other hand, stronger CPP induced by 20 mg/kg of cocaine was found in the HR animals. Furthermore, there was a strong negative correlation between locomotor reactivity to novelty and CPP in CRF-OE, but not in WT, mice. Collectively, these results suggest that long-term, post-natal CRF over-expression increases the rewarding effects of cocaine in individuals with high emotional response to stress.

1. Introduction

CRF is a 41-amino acid peptide released from neurons in the brain that contribute to the behavioural, hormonal and autonomic response to stress (Heinrichs and Koob, 2004). Acute, central administration of CRF mimics effects of stress and CRF receptor antagonists can prevent stress-induced behavioural responses (Heinrichs and Koob, 2004). Activity of the brain CRF system, as the principal mediator of the biological stress response, has been consistently implicated in different aspects of psychostimulant addiction, including acute behavioural and neuroendocrine effects, reward/reinforcement, withdrawal and relapse (Corominas et al., 2010; Koob, 2010; Sarnyai et al., 2001). For example, blockade of endogenous CRF signalling by an antiserum or a receptor antagonist inhibits cocaine-induced corticosterone response (Sarnyai et al., 1992a), locomotor hyperactivity (Sarnyai et al., 1992b), amphetamine-induced behavioural sensitisation (Cole et al., 1990), cocaine-induced CPP (Lu et al., 2003), cocaine self-administration (Goeders and Guerin, 2000) and behavioural

* Corresponding author at: Discipline of Physiology and Pharmacology, Faculty of Medicine, Health and Molecular Sciences, James Cook University, Townsville 4811, Australia. Tel.: +61 7 4781 6992; fax: +61 7 4779 1526.
E-mail address: zoltan.sarnyai@jcu.edu.au (Z. Sarnyai).
[1] Present address: Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden.

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effects of cocaine withdrawal (Basso et al., 1999; Sarnyai et al., 1995) as well as stress-induced reinstatement of cocaine seeking (Shalev et al., 2010 for review). Therefore, we hypothesised that chronic over-activity of brain CRF may affect the individual's sensitivity to the rewarding effects of the psychostimulant cocaine.

Although many people experiment with drugs at some point in their lives, far fewer develop substance use disorders. The existence of marked individual differences in behavioural responsiveness to novel, stressful stimuli has been recently recognised (Blanchard et al., 2009). In a series of seminal studies Piazza and co-workers have shown that outbred Sprague-Dawley rats which are characterised as 'high-responders' (HR) on the basis of their locomotor response to a novel environment fundamentally differ from 'low-responders' (LR) in a number of behavioural and physiological indices related to stress pathology, such as stress-induced corticosterone response, propensity to self-administer drugs of abuse, cognitive function in later life and brain neurochemistry (Dellu et al., 1993, 1994; Piazza et al., 1989). The role of individual differences in cocaine-induced CPP is less conclusive, with some studies finding no association (Erb and Parker, 1994; Gong et al., 1996), and others finding a negative association (Brabant et al., 2005; Shimosato and Watanabe, 2003) between locomotor response in a novel environment and the magnitude of CPP. HR and LR rodents differ in other behavioural and molecular indices as well. For example, LR animals are more anxious and express higher levels of CRF mRNA in the central nucleus of amygdala than HR animals (Kabbaj et al., 2000). Therefore, we hypothesised that CRF over-expression may influence individual differences in susceptibility to the rewarding effects of cocaine.

The primary aim of the present study was to investigate the effects of post-natal, life-long brain CRF over-expression on the sensitivity to the rewarding effects of cocaine by using the CPP procedure. We specifically investigated individual differences in locomotor and anxiety-like response to environmental novelty, and their relationship to cocaine-induced CPP. The results will be discussed in relation to the behavioural response to novelty and the rewarding properties of cocaine under the influence of heightened brain CRF expression in mice.

2. Materials and methods

2.1. Subjects

CRF-OE mice were generated as previously described (Dirks et al., 2002) to yield founder animals which gave rise to a line (CRF-OE 2122 line) that was further bred at the local breeding facilities (Central Laboratory Animal Institute, Utrecht University, The Netherlands) and used for the present study. Breeding consisted of mating between transgenic male and C57BL/6J female mice. Tail DNA from offsprings, extracted with High Pure PCR Template Preparation Kit (Boehringer, Mannheim, Germany), was screened using PCR with transgene specific primers. The forward primers were specific for rat CRF and the reverse primers originated from the Thy-1 promoter, thus excluding the possibility that the endogenous CRF and Thy-1 genes were amplified. Total of 20 male C57BL/6J WT (18–35 weeks old) and 20 male CRF-OE (16–34 weeks old) mice were used for these experiments. Mice were housed (n=2–3 per cage) in plastic cages ($12 \times 22 \times 15$ cm^3, Techniplast, Bugugiatte, Italy) enriched with bedding (EnviroDri®, BMI, Helmond, The Netherlands), a piece of PVC tubing (diameter 5 cm) and nesting material at constant room temperature (21 ± 2 °C) and relative humidity (40–50%). Standard rodent food pellets (Special Diet Services Ltd., Essex, U.K.) and tap water was freely available. Animals were maintained on a 12 h light–12 h dark cycle (lights on from 6:00 a.m. until 6:00 p.m.). All experimental procedures were conducted during the light phase of the cycle, between 9:00 a.m. and 4:30 p.m. All studies and procedures were approved by the ethical committee on animal experiments of the Faculties of Pharmacy, Biology, and Chemistry of Utrecht University, The Netherlands, according to the Dutch law for animal experimentation and the Declaration of Helsinki.

2.2. Cocaine conditioned place preference

2.2.1. Apparatus

A Plexiglas three-compartment conditioned place preference (CPP) chamber was placed in a sound-attenuated room to allow recording of undisturbed behaviour. The two larger, outer compartments (17.5 cm × 20 cm × 20 cm) were separated by a central compartment (7 cm × 20 cm × 20 cm) and differed in both visual and tactile cues. One compartment had white walls and sand-coloured rough grained floor ('light' compartment) and another had black walls and blue smooth rubber floor ('dark' compartment). The central compartment had grey walls and a Plexiglas floor, and allowed free movement between the two outer compartments, unless barred by removal Plexiglas partitions, which were of the same colour as the walls of the central compartment. These partitions were designed to restrict travel between the two outer compartments during conditioning sessions. The entire experiment was video-recorded.

2.2.2. Preconditioning session: novelty-induced activity

Prior to any drug treatments, mice were habituated to experimenter handling for a minimum of 5 days. WT and CRF-OE mice were randomly assigned to each group with respect to cocaine dose and compartment pairing. In a preconditioning session animals were placed into the centre compartment and then allowed to freely explore and habituate to all the compartments of CPP chamber for 20 min on two consecutive days. The activity was scored by counting the frequency of entries into each compartment, visually on a PC screen connected to the video camera that was used to record the experiment. The time spent in each compartment was also recorded, while watching the video recording of the experiment at a later time. The locomotor activity, as measured by the total number of entries made into all compartments during the first day of preconditioning, was regarded as an index for locomotor response to the novel environment. Upon the completion of the CPP experiment, subjects were retrospectively assigned to low-responder (LR) and high-responder (HR) groups, which showed locomotor activity during the first preconditioning session being below and above, respectively, the median value in each genotype (WT: 121.5 ± 5.9; CRF-OE: 79.0 ± 5.5). Anxiety-like behaviour expressed upon the first exposure to the CPP apparatus was measured as described by Shimosato and Watanabe (2003). This approach is similar to the traditional 'light–dark box' in that it takes advantage of the contrasting 'dark' vs 'light' compartments of the apparatus and the animals' propensity to enter more often and spend more time in the 'dark' compartment over the 'light' compartment when anxiety-like behaviour increases. Anxiety was quantified by calculating the ratio of 'dark' compartment entry and time over number of entries into and time spent in the other, 'light', compartments.

2.2.3. Conditioning sessions

Conditioning phase started 24 h after the second habituation and took place over a period of 8 days. Each conditioning session lasted for 20 min. During the conditioning phase, the partitions were closed to restrict access of the mice from an outer compartment to the other compartments. For the two cocaine treatment groups, cocaine (cocaine–hydrochloride; 5 mg/kg and 20 mg/kg)

was administered by intraperitoneal (i.p.) injection immediately before placing the mice into one of the two previously assigned outer compartments ('light' or 'dark'). On the alternate days the same mice were injected with saline and immediately placed into the outer compartment on the opposite side from the previous days for 20 min. Therefore, across the conditioning session, subjects received cocaine or saline four times each. The alternate sides of the body were chosen for i.p. injection each day. For the saline groups, mice were given i.p. injection of 0.9% NaCl in the same pattern and were placed into alternate ('light' or 'dark') compartments on each day. Between conditioning sessions, the walls and floors of the CPP chamber were cleaned with 70% ethanol and allowed to dry completely to ensure the absence of olfactory cues.

2.2.4. Test session: CPP score

On the test day, 24 h after the last conditioning session in which all the subjects were treated with saline (i.e. 48 h after the last cocaine administration), mice were tested for their place preference. No injection was given on the test day. The experiment on test day was video-recorded and the time mice spent in each compartment was measured and used to calculate the degree of place preference. Cocaine CPP was measured as the amount of time spent in the drug-paired chamber on the test day relative to the amount of time spent in the drug-paired chamber during the baseline session for each individual animal (CPP score—difference from baseline in sec) (9). During scoring, the scorer was blind to the genotype and the treatment of the animals.

2.3. Statistical analysis

The degree of ambulatory activity displayed during the preconditioning habituation session was used as a measure of the novelty-induced locomotion. To test whether an animal's locomotor response to a novel environment predicts its sensitivity to the rewarding effects of cocaine, the CPP scores of LR and HR animals were analysed separately and compared within and across genotypes. Activity scores on the first exposure to the place conditioning apparatus were correlated with the scores of place preference using regression analysis. Data were analysed using *t*-test to compare WT and CRF-OE mice in their initial response to the novel CPP environment and analysis of variance (ANOVA) for analysing the CPP data and the effects of individual differences in response to novelty on anxiety-like behaviour and CPP. ANOVA was followed by Fisher's post-hoc test for paired comparisons. Differences were considered significant when $p < 0.05$. Data are presented as mean ± SEM. Correlation analyses using simple linear regression method were also performed between the measure of locomotor reactivity to novelty and the measures of CPP. The statistical analyses were performed by using StatView software (SAS Institute, North Carolina, USA).

3. Results

3.1. Exposure to the novel environment

Upon first exposure to the novel CPP environment CRF-OE mice showed lower locomotor activity than WT littermates ($t=6.309$, df=38, $p < 0.0001$; Fig. 1A). CRF-OE mice preferred to enter more frequently ($t=-2.591$, df=38, $p=0.014$, Fig. 1B) and to spend more time in the 'dark' compartment over the 'light' compartments than the WT animals ($t=-3.206$, df=38, $p=0.003$). We then analysed the animals' preference toward the 'dark' compartment (anxiety-like behaviour) in relation to their individual differences in locomotor responsivity to novelty, e.g. LR and HR mice were analysed separately. For the ratio of 'dark' entries, ANOVA revealed a significant Genotype × Individual Difference interaction ($F_{1,35}=6.182$, $p=0.018$). Preference toward the 'dark' compartment, as measured by the number of entries into the 'dark' over the other, 'light', compartments, was higher in LR CRF-OE mice than in HR mice of the same genotype and than in LR and HR WT mice (Fig. 2A). For the ratio of 'dark' times, ANOVA revealed a significant Genotype × Individual Difference interaction ($F_{1,35}=5.237$, $p=0.028$). Preference toward the 'dark' compartment, as measured by time spent in 'dark' over the other compartments, was significantly higher in LR CRF-OE mice than in HR mice of the same genotype and than in LR and HR WT mice (Fig. 2B).

3.2. Cocaine CPP

WT and CRF-OE mice developed cocaine CPP in a similar manner to both low (5 mg/kg) and high (20 mg/kg) doses of cocaine (Genotype $F_{1,2}=0.055$, $p=0.816$; Treatment: $F_{1,2}=8.467$, $p=0.001$; Genotype × Treatment interaction: $F_{2,34}=0.092$, $p=0.913$; Fig. 3E). WT and CRF-OE mice spent equal time in both the saline- and drug-paired compartments on the preconditioning day (Fig. 3A and B). On the test day, both WT and CRF-OE mice spent equal time in the saline-paired compartment (Fig. 3C). However, there was an almost significant treatment effect ($F_{1,2}=2.898$, $p=0.069$) on the time spent in the cocaine-paired compartment (Fig. 3D).

3.3. Individual differences in novelty response and cocaine CPP

We analysed cocaine CPP in LR and HR WT and CRF-OE mice and found a significant Genotype × Individual Differences

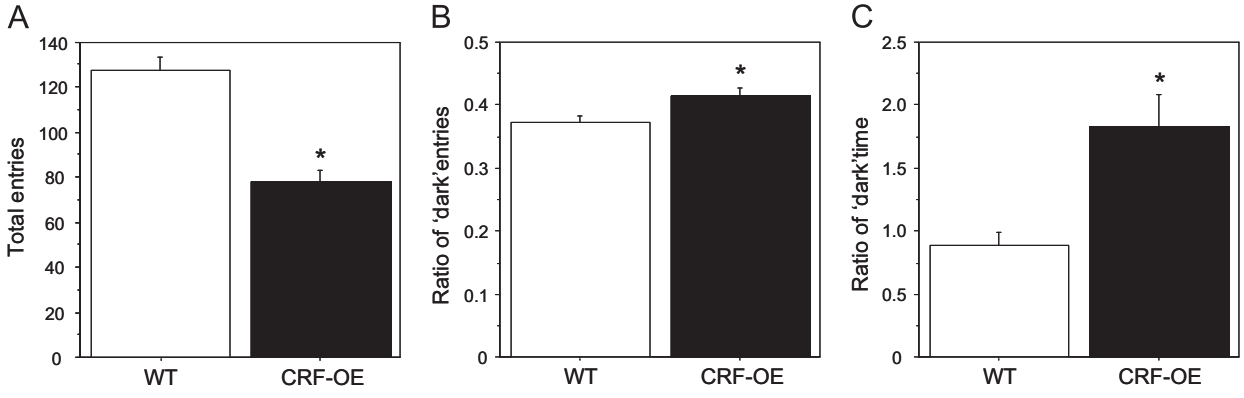

Fig. 1. Activity (A) and anxiety-like behaviour (B, C) of wild-type (WT) and CRF-OE mice in the novel CPP apparatus. Open bar, WT; closed bar, CRF-OE; *$p < 0.05$.

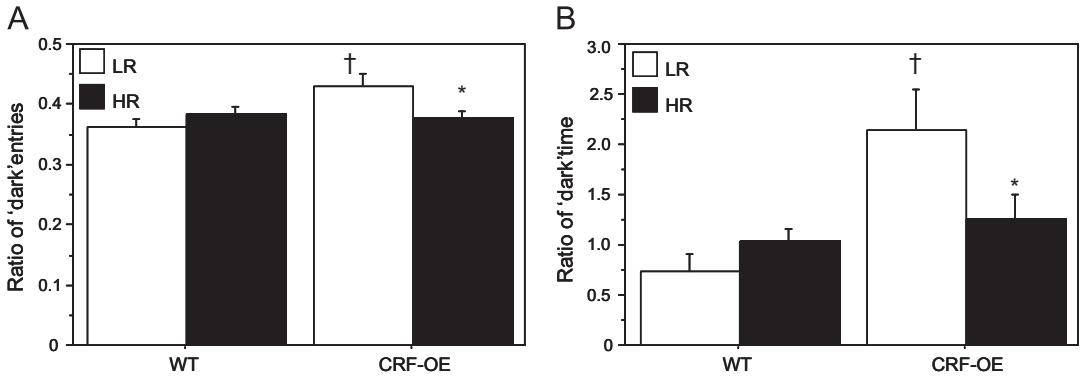

Fig. 2. Anxiety-like behaviour in low-responder (LR, open bars) and high-responder (HR, closed bars) WT and CRF-OE mice in response to novel CPP apparatus. *$p < 0.05$ vs HR of the same genotype; †$p < 0.05$ vs WT LR mice.

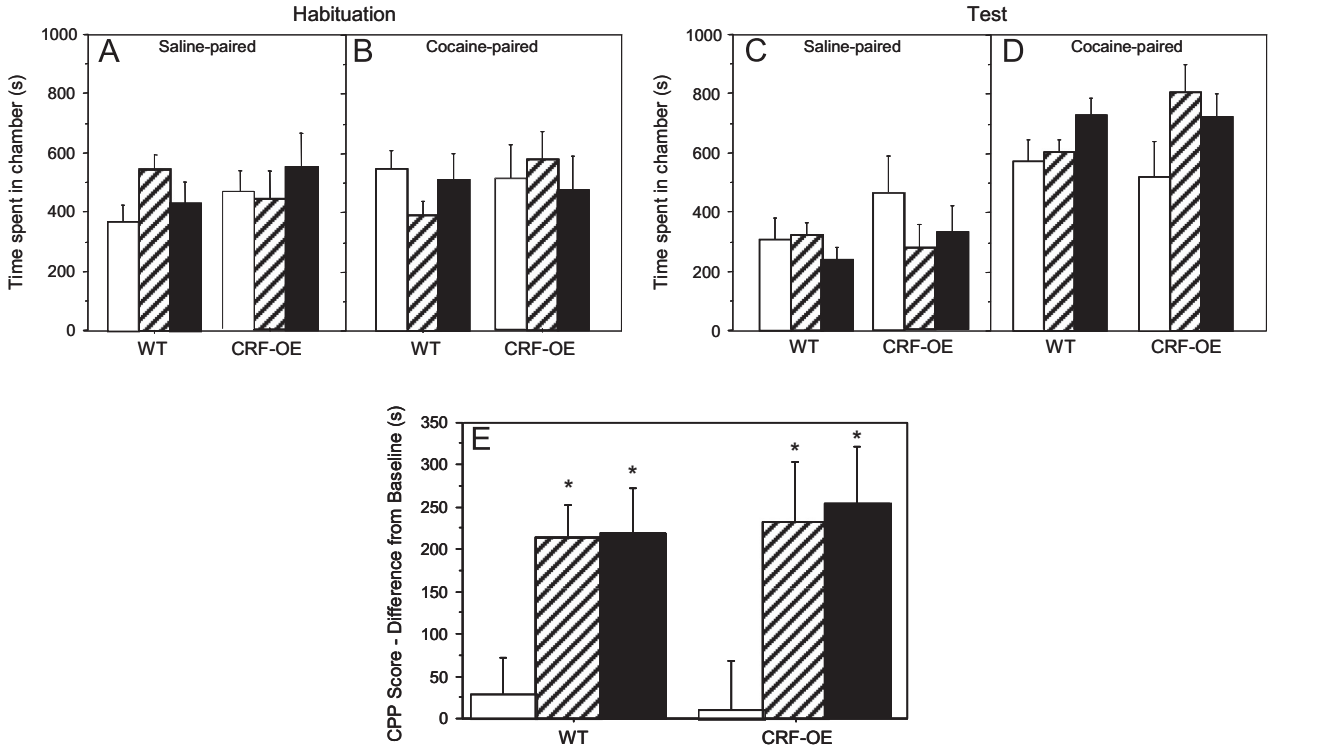

Fig. 3. Cocaine-induced CPP in WT and CRF-OE mice. (A, B) Total time spent in the saline-paired (A) and cocaine-paired (B) chambers during the habituation session. (C, D) Total time spent in the saline-paired (C) and cocaine-paired (D) chambers during the test session. (E) Change from baseline preference (CPP score) for the cocaine-paired chamber. Open bars, saline; hatched bars, 5 mg/kg cocaine; closed bars, 20 mg/kg cocaine. *$p < 0.05$ vs saline.

($F_{1,20} = 17.968$; $p = 0.0004$) and a Genotype × Dose × Individual Differences ($F_{1,20} = 6.677$; $p = 0.012$) interactions. Post-hoc analysis revealed higher CPP scores in HR than in LR WT mice treated with 20 mg/kg of cocaine ($p < 0.005$). However, in CRF-OE mice, LR animals showed higher CPP scores upon treatment with both low (5 mg/kg) and high (20 mg/kg) doses of cocaine, compared to HR transgenic mice ($p < 0.05$ and $p < 0.01$, respectively). In addition, CPP scores induced by 20 mg/kg cocaine were higher ($p < 0.001$) in LR transgenic mice than in LR WT animals (Fig. 4A). Furthermore, there was a significant negative correlation between initial locomotor response to the novel environment on the preconditioning session and cocaine-induced CPP in CRF-OE mice ($R = -0.6$, $p < 0.05$). No such relationship was found in the WT animals (Fig. 4B).

4. Discussion

We found that, in line with our previous results, CRF-OE mice show anxiety-like behaviour in a novel environment, which was more pronounced in LR mice. Furthermore, we showed that although CRF-OE mice develop cocaine-induced CPP similar to WT controls, individual differences in behavioural reactivity to novelty affected sensitivity to the rewarding effect of cocaine in CRF-OE and WT mice differently. CRF-OE mice that showed low response to environmental novelty exhibited more robust CPP than HR transgenic mice, while the reverse was found for WT animals place conditioned for the higher dose of cocaine.

CRF-OE mice were less active than WT animals in the novel environment of the CPP apparatus and showed higher preference

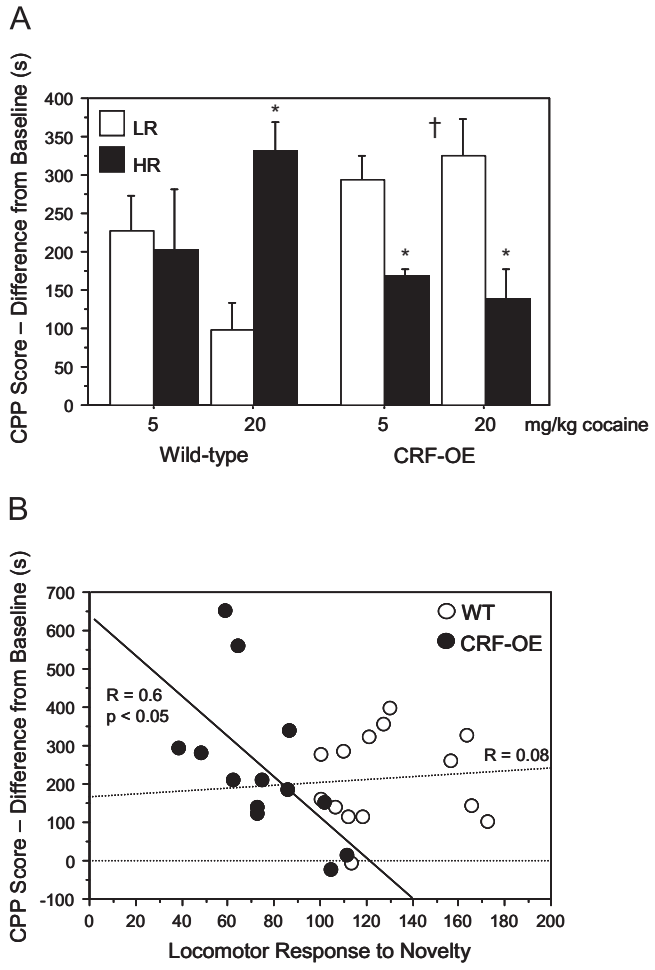

Fig. 4. Individual differences in locomotor response to environmental novelty differentially influence cocaine CPP in WT and CRF-OE mice. (A) Cocaine CPP to low (5 mg/kg) and high (20 mg/kg) of cocaine in LR vs HR WT and CRF-OE mice. Open bars, LR animals; closed bars, HR animals. $^{*}p < 0.05$ LR vs HR of the same genotype and cocaine dose; $^{\dagger}p < 0.05$ vs WT LR mice receiving 20 mg/kg of cocaine. (B) Correlation between locomotor activity during the first habituation session in the CPP apparatus and CPP scores in WT and CRF-OE mice. Open circles, WT; filled circles, CRF-OE.

to the dark than to the light compartment. This heightened anxiety-like behaviour is in agreement with our previous results in the same transgenic mouse line in the open-field (Kasahara et al., 2007) and with a series of other studies using different CRF transgenic animals (Kolber et al., 2010; Lu et al., 2008; Stenzel-Poore et al., 1994; van Gaalen et al., 2002; Vicentini et al., 2009). When animals were divided into LR and HR on the basis of their locomotor response to novelty we saw no difference in anxiety-like behaviour in WT mice. One possible explanation for the lack of such difference in WT mice could be that the background C57BL/6J strain has consistently been identified as a relatively high activity and low anxiety strain (Crawley et al., 1997; Miller et al., 2010), in which the mild novelty stress has less effect on anxiety-like behaviour than in CRF-OE mice with higher trait anxiety. In contrast, LR CRF-OE mice showed higher anxiety than HRs. It has been demonstrated in a number of behavioural paradigms measuring anxiety and exploratory behaviours in rodents that LRs show more anxiety-like behaviour than HRs (Blanchard et al., 2009).

We found significant differences in 'dark' and 'light' compartment exploration/preference in CRF-OE mice during habituation. Therefore, it is important to emphasise that there was no difference between or within the two genotypes in exploring compartments that were to be assigned to either saline- or cocaine-pairing. Cocaine-induced CPP was found in both genotypes. When mice were not differentiated according to their initial response to novelty low and high cocaine doses elicited very comparable levels of CPP in WT and CRF-OE mice. These results are similar to previous data where the same dose range of cocaine induced CPP at a comparable level in WT mice (Brabant et al., 2005; Shimosato and Watanabe, 2003; Zhang et al., 2002). However, when mice were divided into LR and HR a different pattern emerged. There was a trend among HR WT animals to show higher CPP than LR counterparts. CPP was significantly higher in LR than in HR CRF-OE mice and than in LR WTs when low and high cocaine dose data were pooled. Furthermore, we found a negative correlation between the magnitude of the locomotor response to novelty and the size of the place preference induced by cocaine in CRF-OE, but not in the WT, mice. More detailed analysis of the CPP scores in LR vs HR mice, taking low and high cocaine doses into consideration, revealed that HR WT mice develop stronger CPP to the high cocaine dose than LRs. In contrast, LR CRF-OE mice showed stronger CPP to both low and high cocaine doses than HR transgenic animals. These results indicate that CRF-OE mice may fundamentally differ from WT in their individual sensitivity to rewarding effects of cocaine.

The relationship between locomotor response to novelty and vulnerability to the rewarding effects of psychostimulants has long been established (for review see Kabbaj (2006)). There is compelling evidence that rats that are more active in a novel arena exhibit enhanced self-administration compared to less active rats (Piazza et al., 1989; Pierre and Vezina, 1997). The evidence of an association between individual differences in novelty-induced locomotor response and psychomotor stimulant-induced CPP is somewhat less clear. Some studies found no association (Erb and Parker, 1994; Kosten and Miserendino, 1998), while others found negative association (Brabant et al., 2005; Mathews et al., 2010; Shimosato and Watanabe, 2003) between novelty response and CPP. These discrepant findings have been attributed to differences in species (e.g., mice vs rats), drugs (amphetamine vs cocaine) and experimental design used. Our present results add further complexity to this picture but perhaps enlighten some possible underlying behavioural mechanisms as well.

It is possible that the conflict between the anxiogenic and rewarding effects of cocaine and/or differences in emotionality/anxiety might contribute to the genotype-dependent CPP differences. In addition to its appetitive/rewarding effects cocaine induces aversive, anxiogenic effects in humans (Gawin and Ellinwood, 1988; Williamson et al., 1997) and in animals (Ettenberg and Geist, 1991; Blanchard and Blanchard, 1999). HR rats have been consistently shown to express less anxiety-like behaviour than LRs (Blanchard et al., 2009; Kabbaj et al., 2000). This may especially be pronounced in a genetically low anxiety mouse strain as the C57BL/6J used in the present study, where we saw no difference in anxiety measures between LR and HR WT mice. Therefore, it is possible that on this background the primary effect of the high dose of cocaine is rewarding rather than anxiety-inducing, hence the higher CPP scores in HR WT mice. In the CRF-OE mice, however, the level of trait anxiety is higher (Fig. 1b and c), especially in the LRs (Fig. 2). Here we found that LR CRF-OE mice, that also showed higher anxiety levels than HRs, displayed more pronounced CPP. This finding is somewhat surprising at first considering the above mentioned anxiogenic properties of cocaine. It would have been expected to see that more anxious animals would avoid the compartment of the CPP apparatus associated with cocaine, which likely increases their anxiety (David et al., 2001). Human data are conflicting in this regard showing that anxious individuals are less likely to seek stimulants (de Wit et al., 1986) but also that subjects with relatively high pre-

drug anxiety preferred amphetamine over saline during the choice test (Uhlenhuth et al., 1981). Our present data may be more consistent with the view that vulnerability to the rewarding effects of psychostimulants in anxious subjects is not immediately related to the anxiety-inducing effects of the drug. In line with our results in the anxious CRF-OE animals, recent data showed that mice with a high anxiety trait, which were also identified as LRs, exhibit high sensitivity to the rewarding properties of cocaine in the CPP paradigm (Shimosato and Watanabe, 2003).

Regardless of the exact behavioural mechanisms our data suggest that chronic CRF over-expression, either directly or indirectly through compensatory mechanisms, leads to alterations in neurobiological processes underlying individual differences in novelty response and psychostimulant reward. These findings are in line with our previous results showing that differences in open field habituation and pre-exposure response induced by CRF over-expression are related to individual differences in locomotor response to novelty (Kasahara et al., 2007). The possible role of enhanced central CRF drive in facilitated cocaine CPP in vulnerable individuals are supported by recent results that chronic stress enhances cocaine CPP in a CRF-dependent manner in mice (Kreibich et al., 2009). Furthermore, Kabbaj et al. (2000) demonstrated that LR rats have higher CRF mRNA expression in the CEA than HR animals. Our CRF-OE line has been shown to express high levels of CRF protein in the CEA (Dirks et al., 2002). However, the exact mechanism of CRF-driven differences in individual vulnerability to the rewarding effects of psychostimulants remains to be determined.

In conclusion, the present results show that long-term, post-natal CRF over-expression increases the rewarding effects of cocaine in individuals with high emotional response to stress. Recent human studies have shown that childhood traumas serve as major risk factors for substance dependence in later life, with mood and anxiety disorders in the causal path for a portion of that risk (Douglas et al., 2010). Childhood traumas have been associated with adult depression through permanently elevated central CRF activity (Heim et al., 2008). Therefore, our early post-natal onset, brain-restricted CRF over-expression model may help to better understand how early adverse events influence brain mechanisms to develop increased susceptibility to drug addiction.

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