



Universiteit
Leiden
The Netherlands

Vulnerability to cocaine: role of stress hormones

Jong, I.E.M. de

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Summary

Despite the powerful psychostimulant properties of cocaine, not every individual will acquire cocaine abuse after occasional use of the drug. A fundamental question in the neurobiology of addiction is therefore how these individual differences in susceptibility to drugs of abuse emerge. Evidence is accumulating that genes and adverse life experience can constitute risk factors. Especially the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system responses to stress have gained increasing attention for their role in vulnerability to psychostimulants in both humans and laboratory animals. The **objective** of this thesis was to assess the role of the end products of both stress response systems -the adrenal glucocorticoid hormones and epinephrine- in the susceptibility to the psychostimulant effects of cocaine, taking into account the *midbrain dopamine circuits*, the *genetic background* of the individual and the *context* in which the hormones operate.

Studies were designed with two inbred mouse strains (C57BL/6 and DBA/2) that can be considered a model for genetic differences in the midbrain dopamine system, the HPA-axis and susceptibility to the behavioural and reinforcing properties of psychostimulant drugs. The *context* required for the action of adrenal hormones was investigated in the DBA/2 strain that proved most susceptible to adrenal hormones in cocaine sensitivity. Adrenal hormones were manipulated by surgical removal of the adrenals (adrenalectomy: 'ADX') and subsequent hormone replacement. The sensitisation measured as an enhanced locomotor response to repeated drug exposure is thought to reflect long term neuronal adaptations underlying certain aspects of drug addiction. In addition, endocrine parameters were measured to investigate HPA-axis responsiveness to cocaine. Since the dopamine system plays a critical role in the rewarding effects of drugs of abuse, several markers of dopaminergic transmission were measured.

In **chapter 2** the C57BL/6 and DBA/2 inbred mouse strains were characterised for behavioural and endocrine responsiveness to cocaine. Whereas C57BL/6 mice showed greater locomotor responses to the first cocaine exposure, only DBA/2 mice exhibited an increase in drug responsiveness during repeated drug treatment. However, when exposed to a challenge dose of cocaine after a 5 day withdrawal interval, both strains expressed behavioural sensitisation. Therefore, the sensitisation paradigm was suitable to investigate the contribution of adrenal hormones in both strains. ADX completely prevented initiation and expression of behavioural sensitisation in the DBA/2, but not the C57BL/6 strain. Furthermore, only the DBA/2 strain displayed sensitisation of corticosterone secretion with repeated cocaine exposure, whereas the psychostimulant attenuated this endocrine measure in the C57BL/6 strain. These data indicate that the C57BL/6 and DBA/2 strains represent a model for genetic differences in behavioural and endocrine responsiveness to

cocaine. Moreover, the adrenals play an essential role in cocaine-induced behavioural sensitisation, but only in the DBA/2 strain.

In **chapter 3** it was investigated whether a neural correlate for the strain differences in behavioural responsiveness to cocaine, and susceptibility to the impact of adrenal stress hormones, can be found in the midbrain dopamine system. Whereas ADX did not affect strain differences in the basal dopamine system or the locomotor response to the first cocaine exposure, strain-dependent adaptations were observed in behavioural and neural responsiveness to cocaine. In the DBA/2 strain, sensitisation resistant ADX mice were characterised by reduced D2 binding in the nucleus accumbens core and rostral caudate putamen. Conversely, ADX prevented the cocaine-induced increase in TH and DAT mRNA expression in the substantia nigra and the decrease in D2 binding in a subdivision of the dorsal caudate putamen observed in SHAM mice. In the C57BL/6 strain, by contrast, behavioural sensitisation was independent of the adrenals and ADX only marginally affected drug-induced neuroadaptations. These results demonstrate that adrenal stress hormones affect psychostimulant sensitivity in a strain-dependent fashion, possibly through adaptations in the midbrain dopamine system. Furthermore, the DBA/2, but not the C57BL/6 strain, is vulnerable to the impact of adrenal stress hormones on cocaine sensitivity at the level of dopaminergic neurotransmission and behavioural responsiveness. This strain was therefore chosen to investigate the context-dependency of the glucocorticoid actions (**chapters 4 and 5**).

In **chapter 4**, the critical time-window for the actions of adrenal glucocorticoids was investigated in DBA/2 mice in relation to i) the stage of behavioural sensitisation to cocaine (induction vs. expression) and ii) the time of drug exposure. Administration of the glucocorticoid receptor antagonist mifepristone to sensitised animals failed to block expression of previously established behavioural sensitisation. This suggests that corticosterone plays a role during initiation of sensitisation, as appeared from the observations in the ADX mice. Intermittent corticosterone replacement 2 hours or 5 minutes prior to cocaine was ineffective in reversing the effect of ADX on behavioural sensitisation. By contrast, initiation of behavioural sensitisation was partially restored if the glucocorticoid was continuously substituted through release from a s.c. implanted pellet. These data indicate that corticosterone facilitates initiation rather than expression of behavioural sensitisation to cocaine, provided that the hormone is continuously circulating. However, because only chronic high concentrations of the hormone partially restored behavioural sensitisation, it appeared that the adrenal glucocorticoid is necessary, though not sufficient, for full sensitisation in the DBA/2 strain.

Therefore, the possible involvement of other adrenal factors was investigated in **chapter 5**. The focus was on epinephrine, the catecholamine that is rapidly released in response to both stress and psychostimulant administration. Whereas replacement with neither epinephrine nor continuous corticosterone alone was sufficient to reverse the ADX effect, co-substitution of the two adrenal hormones was sufficient to fully restore initiation and retention of behavioural sensitisation to the level observed in SHAM-operated mice. In addition, the catecholamine may play a permissive or facilitatory role in the HPA-axis sensitisation in the DBA/2 strain, since cocaine-induced *c-fos* mRNA expression in the hypothalamic PVN was potentiated in mice with a history of epinephrine replacement. Given the critical role for glucocorticoids in cocaine sensitivity of DBA/2 mice, this might be one of the mechanisms via which epinephrine facilitates behavioural sensitisation. These findings indicate that corticosterone and epinephrine act in a coordinate fashion to facilitate behavioural responsiveness to cocaine in the DBA/2 genotype.

Overall, the data presented in this thesis show that complex interactions between genes, the HPA-axis and the sympathetic nervous system contribute to the existence of individual differences in susceptibility to the psychostimulant effects of cocaine. It was demonstrated that *genetic background* determines the contribution of adrenal hormones to cocaine sensitivity. The C57BL/6 and DBA/2 strains represent a model for respectively resistance and susceptibility to the impact of adrenal hormones on cocaine-induced behavioural sensitisation and associated neuroadaptations in the brain dopamine system. Regarding the *context* required for the hormone actions, the initiation phase of sensitisation constitutes the critical *time-window*, whereas the sympathetic nervous system may signal aspects of the *physiological context*. Therefore, in susceptible individuals, not only adrenocortical but also adrenomedullary hormones, may contribute to initiation of long-term neuronal and behavioural adaptations to cocaine.

