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**Science may set limits to knowledge,**
**but should not set limits to imagination.**

Bertrand Russel (1872-1970)

*Voor mijn vader*

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# Preface

Not every individual who experiments with cocaine will acquire compulsive drug use. The mechanism underlying this individual difference in susceptibility to drug addiction is still poorly understood. Recent studies have identified genes and adverse life events (stress) as risk factors. The objective of this thesis is to investigate the contribution of the adrenal stress hormones glucocorticoids and epinephrine to the psychostimulant effects of cocaine in the inbred DBA/2 and C57BL/6 mouse strains. Behavioural sensitisation, measured as an enhanced locomotor response to repeated cocaine exposure, was used as a model for the long-term neural adaptations underlying certain aspects of drug addiction.

The results demonstrate that adrenal hormones play a critical role in cocaine sensitivity, which depends on genetic background because surgical removal of the adrenals or 'adrenalectomy' fully prevented cocaine sensitisation in the DBA/2, but not the C57BL/6 strain. The impact of genetic background was further emphasised by strain-specific changes in the midbrain dopamine system that mediates the rewarding effects of drugs of abuse. The effects of adrenalectomy could only be fully reversed by co-administration of glucocorticoids and epinephrine. These findings show that, depending on genetic background, adrenal stress hormones are important risk factors for vulnerability to cocaine, suggesting that pharmacological intervention in stress hormone action may have therapeutic potential in drug addiction.