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DISSERTATION TITLE:	*The contribution of 6-acetylmorphine to heroin-induced effects: Studies of pharmacokinetics, behavior and immunotherapeutic intervention using a monoclonal antibody in mice*

I dette arbeidet har vi studert betydningen av heroins første nedbrytningsprodukt, 6-acetylmorfin (6-AM), for heroins ruseffekter. Ved å kombinere atferdstester i mus med farmakokinetisk analyse og bruk av et antistoff rettet mot 6-AM, viser vi at 6-AM spiller en viktig rolle for virkningen av heroin. Videre viser vi at antistoffet mot 6-AM kan beskytte mot heroins kort- og langtidseffekter, og muligens ha terapeutisk potensiale.

Heroin is one of the most addictive drugs of abuse, but heroin itself is considered an inactive prodrug which acts mainly through its metabolites. The work of this doctoral thesis highlights the role of heroin's first active metabolite, 6-acetylmorphine (6-AM), in heroin-induced effects. This was done by combining animal behavior with pharmacokinetic analyses, and by using an antibody specifically targeting 6-AM in the blood. The pharmacological potential of the 6-AM-specific antibody was also evaluated. First, we show that 6-AM is essential for the immediate heroin effect, and for heroin reward and sensitization, suggesting that 6-AM plays an important role in the development of heroin addiction. We found that heroin induced stronger rewarding effects than injected 6-AM, most likely because it provides faster delivery of 6-AM to the brain. Next, we found that even small amounts of heroin administered during pregnancy can cause long-term effects in the offspring. Female mice exposed to heroin during fetal life were hyperactive and more sensitive to heroin in adolescence compared with non-exposed offspring. Finally, we show that the antibody targeting 6-AM can protect the fetus against heroin exposure. When pregnant animals were treated with antibody before heroin injection, the long-term effects in the offspring were successfully prevented. Antibody treatment also protected against heroin-induced behavior in adult mice. The protection offered by this 6-AM-specific antibody underpins the crucial role of 6-AM in heroin-induced effects, and shows that immunotherapy against heroin is dependent on sequestering 6-AM in the bloodstream. Immunotherapy against heroin may have potential as future treatment of specific patient groups, such as pregnant heroin users or people who are susceptible to relapse. By understanding the individual contribution of the heroin metabolites, we may be one step closer to understand the mechanisms underlying

heroin effects, and to develop new strategies to treat heroin addiction.