Cognitive and neuropsychopharmacological processes in human drug craving
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Haloperidol Improves Biased Cognitive Processing of Drug Cues in Heroin Dependence

Drug and alcohol dependence are associated with enhanced attention for drug related stimuli. This cognitive processing bias has been suggested to be related to craving and to represent one of the core mechanisms of addition. The present study tests the hypothesis that enhanced attention for heroin cues is mediated by the dopaminergic system using a haloperidol as dopamine-antagonist. In a double blind, randomized crossover design, 18 detoxified heroin dependent patients received a single oral dose of haloperidol 2 mg and placebo. Patients performed an Emotional Stroop task under both conditions. In the haloperidol condition, patients showed less attentional bias than in the placebo condition. However, no effect on subjective craving was found. These findings provide preliminary evidence that attentional bias in heroin dependent humans is mediated by dopaminergic mechanisms.


Introduction
It has been hypothesized that activation of dopaminergic system by cues which signal reward contribute to the excessive focusing on drug related stimuli. This enhanced attentional processing of motivational relevant cues is believed to be related to craving and represents one of the core mechanisms of addiction. Although the existence of enhanced processing has been demonstrated research into the neurobiological underpinnings is scarce. Recently, some progress has been made on the neural basis of these processing biases. It has been suggested that dopaminergic neurotransmission is responsible for the increased attention towards drug related stimuli. In previous studies, 4 mg haloperidol was found to inhibit cocaine craving whereas 2 mg was shown to be able to induce modulation in selective and involuntary attention, and to result in D2 receptor occupancy of 18% and 52% after 3 and 6 hours respectively.

In the present study, the hypothesis is tested that haloperidol reduces attentional bias in heroin dependent patients, and that this reduction is related to a reduction in subjective craving.

Method
Eighteen male heroin dependent subjects (DSM-IV) were recruited from a detoxification program. All subjects were abstinent from illicit drugs for at least 2 weeks. Subjects with withdrawal symptoms, lifetime use of neuroleptic medication, psychopathology and major medical disorders were excluded. Mean age was 35.7 years (SD = 6.4). Mean age of first heroin use was 22.6 (SD = 7.0), mean years of heroin use was 8.8 (SD = 6.7), and mean number of days of heroin use in month before detoxification was 26.7 (SD = 8.6). Most subjects (n=17) had a history of additional cocaine use.

Attention for heroin cues was measured using the Emotional Stroop task assessing manual reaction times (RTs) to both drug related and neutral words with longer RTs indicating more attention. This paradigm has been successfully used to measure heroin related attention. Craving was measured by the Desire for Drug Questionnaire DDQ.

Subjects received placebo and 2mg oral haloperidol 4 hours before the measurements (spaced 72 hours apart), in random order, under double-blind conditions. The study was approved by the human rights committee. All subjects provided written informed consent. Remuneration amounted to 50 euro.
Data analysis

Reaction times (RTs) were averaged within each Word Type and Condition for each subject, and were analyzed using a 2 (Word Type) x 2 (Condition) repeated measures ANOVA. Post-hoc pair-wise comparisons were made using two-tailed t-tests. Differences between placebo and haloperidol in craving were analyzed using a paired t-test.

Figure 1. Mean responding times (in milliseconds) on neutral and heroin words by medication condition (n=18).

Results

RTs in the haloperidol condition were significantly shorter than in the placebo condition (F=4.50, df=1, 17, p=.049). No significant main effect was found for Word Type (F=2.10, df=1, 17, p=.165). In addition, no interaction effect between Word Type and Condition was observed (F=.67, df=1, 17, p=.429). However, in a post-hoc analysis, the effect of haloperidol on RTs was significant for heroin related words (t=2.13, df=17, p=.048), but not for neutral words (t=1.69, df=17, p=.108) (see also figure 1). No significant effect of haloperidol on craving could be observed (t=1.13, df=15, p=.28).

Conclusion

The hypothesis that haloperidol would reduce attentional bias in heroin dependent patients suggesting an important role for dopamine in this mechanism underlying drug addiction was only partly supported: haloperidol significantly reduced RTs of drug related cues and not of neutral cues, but the interaction term of Word Type by Condition in repeated measures ANOVA was not significant probably due to substantial reductions in the RTs to both drug related and neutral cues (see figure 1). Overall selective attention was improved by haloperidol compared to placebo. One explanation of this effect is that the heroin words in the Stroop task elicit a general distracting state and a general focusing on heroin cues that results in increased overall reaction times. For example, it is known that if drug-related words are followed by neutral words, so-called "carry-over" effects appear which result in an increase in RTs to neutral words. The carry-over effect results in a general increase in RTs on the task and captures the difficulty of disengaging attention from emotional salient stimuli such as heroin cues. The present findings show faster reaction times during the haloperidol-session compared to placebo; thereby demonstrating that haloperidol attenuates this difficulty of disengaging. Another explanation could be that haloperidol normalizes a dopamine-induced disruption in attention.

We were not able to confirm the hypothesis that dopamine-antagonist reduce subjective, cue-elicited craving. This is not in accordance with a previous study of Berger et al. A possible explanation for this inconsistency is that, although low doses of haloperidol are able to modify subtle cognitive processes such as attention, this low dose may not be sufficient for modifying feelings such as craving.

There were some limitations to the present study. First, no healthy control group was used to compare with, only within-group comparisons were made. However, a previous study using the same task did show that healthy controls do not exhibit attentional bias for heroin related words. Second, the sample-size was rather small. Although the effects look robust (the effect was observed in 13 of the 18 subjects, i.e. 72 %), more studies using larger sample-sizes are needed.

In Summary, we found preliminary evidence that the enhanced attention for drug related cues, which is present in drug
dependent patients, is dopamine mediated. This evidence is consistent with the "Incentive-Sensitization" theory which claims that dopamine triggers the brain’s attention towards motivationally significant stimuli.

References