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Evidence for alcohol anti-craving properties of memantine

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Abstract

Rats consuming alcohol voluntarily for a long time show increased alcohol consumption after a phase of alcohol deprivation and this might reflect increased craving for alcohol. Administration of memantine (1-amino-3,5-dimethyl-adamantane), a clinically used uncompetitive NMDA receptor antagonist, resulted in a significant reduction of the alcohol deprivation effect without any sedative, dysphoric or stimulant side-effects. The dose of memantine used (4.8 mg/day) resulted in serum levels close to the therapeutic range in humans. These results indicate that memantine may have therapeutic potential as an anti-craving drug for alcohol.

Keywords: Alcohol; Craving; Memantine

Memantine (1-amino-3,5-dimethyl-adamantane), an uncompetitive NMDA receptor antagonist, is in clinical use for the treatment of dementia and spasticity (Kornhuber et al., 1994). There is increasing evidence that uncompetitive NMDA receptor antagonists alleviate some of the effects, including tolerance, withdrawal and sensitization phenomena, induced by drugs of abuse. In particular, the action of alcohol on the NMDA receptor complex (Hoffman and Tabakoff, 1994) led us to assume that memantine might interfere with alcohol-induced effects. Thus, memantine was tested in a recently presented long-term free choice alcohol drinking model in rats (Wolffgramm and Heyne, 1995; Spanagel et al., 1996).

Male Wistar rats (Martinsried, Germany), weighing 220–250 g at the start of the experiment, were housed individually with food, tap water, 5, 10 and 20% (v/v) alcohol solutions ad libitum for 10 months. In order to determine the basal daily alcohol intake, the 4 drinking bottles per cage, food and the animals were weighed on 4 consecutive days at 10:00 h. Daily alcohol intake, food intake, weight changes, total fluid intake, total alcohol preference and preferences for the 3 alcohol solutions offered were calculated from these measurements as described previously (Spanagel et al., 1996). After the last day of measurement the bottles containing alcohol solutions were removed from the cages leaving the animals with food and tap water ad libitum. Two weeks later, the animals were briefly anaesthetized with halothane and implanted s.c. with mini-osmotic pumps (Alzet, model No. 2ML2) delivering 5.0 μl/h. Half of the pumps had been filled with memantine (40 mg/ml) dissolved in aqua ad iniectabilia (Braun, Melsungen, Germany) and the other half with the vehicle. Pharmacokinetic studies in our laboratory with age- and weight-matched controls had indicated that this dose (4.8 mg/day) and mode of administration of memantine resulted in serum levels close to the therapeutic range in humans, i.e. 1.4 ± 0.38 μM (mean ± S.D., $n = 3$) (for methods and comparison, see Misztal et al., 1996), and without obvious side-effects. The alcohol solutions were presented again to the animals 24 h after pump implantation and bottles, food and the animals were weighed again daily.

As shown in Fig. 1, there were no differences between the vehicle and the memantine groups for basal alcohol intake before alcohol deprivation. On re-presentation of alcohol after the deprivation period, control animals showed a significant rise in alcohol intake that declined again over 3 days following alcohol re-presentation. The rise in alcohol intake was absent in the memantine group. Two-way analysis of variance with repeated measures over days after withdrawal revealed a significant effect of treatment ($F(1,16) = 10.93$, $P < 0.01$), a significant effect of days ($F(2,32) = 29.02$, $P < 0.0001$) and a significant interaction between factors ($F(2,32) = 5.07$, $P < 0.05$). The

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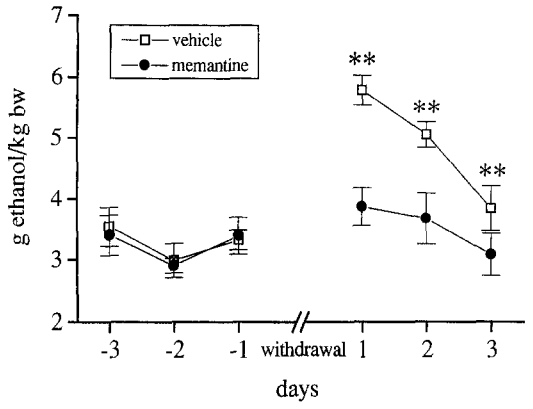

Fig. 1. Effect of memantine on increased alcohol consumption after a withdrawal period in rats consuming alcohol voluntarily for a long period. The figure shows the daily alcohol intake in g ethanol/kg body weight during the last 3 days before withdrawal of the alcohol solutions (baseline) and during the first 3 days after re-presentation of alcohol. The results are means ± S.E.M. of the results obtained in 9 rats/group. ** $P < 0.01$ vs. memantine by Newman-Keuls post-hoc test.

Newman-Keuls post-hoc test revealed that the memantine group differed from the vehicle group on the 3 post-deprivation days as shown in Fig. 1.

Analysis of the preferences for the 3 alcohol solutions revealed a significant rise in preference for the 20% solution by the control animals after alcohol deprivation ($F(1,16) = 30.36$, $P < 0.0001$) (40.2 ± 4.4% on the first post-deprivation day vs. 15.7 ± 1.3% mean basal preference) that was significantly reduced in the memantine group (29.2 ± 2.9% on the first post-deprivation day vs. 16.4 ± 1.0% mean basal preference) [interaction deprivation × treatment: $F(1,32) = 9.80$, $P < 0.01$]. There were no effects of treatment on food intake, total fluid intake or weight of the animals. Locomotor activity in an open field did not differ between the control and the memantine groups (see also Misztal et al., 1996).

The long-term alcohol drinking model used in the present study covers several aspects of alcohol addiction and proved to be a valid animal model for alcoholism, because it closely mimics human alcohol drinking behaviour (Wolffgramm and Heyne, 1995; Spanagel et al., 1996). Therefore, the relapse behaviour seen in our animals following a withdrawal period, which was described earlier as an alcohol deprivation effect (Sinclair and Senter, 1967), implies an increase in craving for alcohol (Sinclair and Li, 1989). The alcohol deprivation effect in our model was characterized by increased alcohol consumption as well as increased preference for the highest concentrated alcohol solution offered. The clinically used uncompetitive NMDA-receptor antagonist, memantine, suppressed both effects suggesting that it is a possible new anti-craving drug. Considering the lack of any signs of sedation or behavioural impairment of the rats in this study and the fact that serum levels of memantine were close to the therapeutic range, clinical studies are warranted.

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