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# The cannabinoid receptor antagonist SR 141716 prevents acquisition of drinking behavior in alcohol-preferring rats

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**Abstract**

The cannabinoid $CB_1$ receptor antagonist, *N*-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-3-pyrazole-carboxamide) (SR 141716); 0.3–3 mg/kg, i.p., twice daily for 10 days), prevented the acquisition of alcohol drinking behavior in rats genetically selected for alcohol preference (Sardinian alcohol-preferring (sP) rats), having the free choice between alcohol (10%, v/v) and water. The results suggest that activation of cannabinoid $CB_1$ receptors is essential for the acquisition of alcohol drinking behavior in animals with a genetically determined alcohol preference. 

*Keywords:* Cannabinoid $CB_1$ receptor antagonist; Alcohol intake; Sardinian alcohol-preferring (sP) rat

The cannabinoid $CB_1$ receptor antagonist, *N*-piperidino-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-3-pyrazole-carboxamide (SR 141716), has been found to reduce voluntary alcohol intake in alcohol-consuming C57BL/6 mice (Arnone et al., 1997), selectively bred Sardinian alcohol-preferring (sP) rats (Colombo et al., 1998) and alcohol self-administering Long Evans rats (Freedland et al., 2001). Further, SR 141716 reduced the break-point for alcohol intake and the probability of response requirement completion for alcohol in operant procedures using Wistar (Gallate and McGregor, 1999) and Long Evans (Freedland et al., 2001) rats. These findings suggest that cannabinoid $CB_1$ receptors are involved in the reinforcing properties of alcohol. The above studies tested SR 141716 in "alcohol-experienced" animals, in which alcohol use was already established before the administration of SR 141716. The present investigation aimed at assessing the effect of SR 141716 on the acquisition of alcohol drinking behavior in rats alcohol-naive at the time of the start of the study.

Male sP rats, 75 days old at the start of the study, were used. Rats were individually housed in an animal facility with inverted 12:12-h light–dark cycle and standard environmental conditions. The rats were habituated to handling and i.p. injection. The rats were divided into four groups ($n = 9–10$) matched for body weight. Throughout the duration of the experiment, alcohol was offered in a free-choice regimen between the alcohol solution (10%, v/v) and water. The position of the alcohol and water bottles was alternated daily. Alcohol presentation was initiated at the start of the dark phase. Rats received their first treatment, SR 141716 (Sanofi-Synthelabo, Montpellier, France; 0.3, 1 and 3 mg/kg, i.p., suspended in 1 ml/kg saline with 0.1% Tween 80), or vehicle, 30 min before alcohol presentation. Subsequent treatments were given twice daily, 6 h apart during the dark phase, for 10 days. Alcohol, water and food intakes were monitored once daily immediately before the dark phase throughout the 10 days of treatment and for an additional 20 days after termination of treatment. Food pellets were always available. Data concerning daily alcohol, water, total fluid and food intake during the 10-day treatment period and the 20-day post-treatment period were evaluated separately by two-way (treatment; days) analyses of variance with repeated measures on days.

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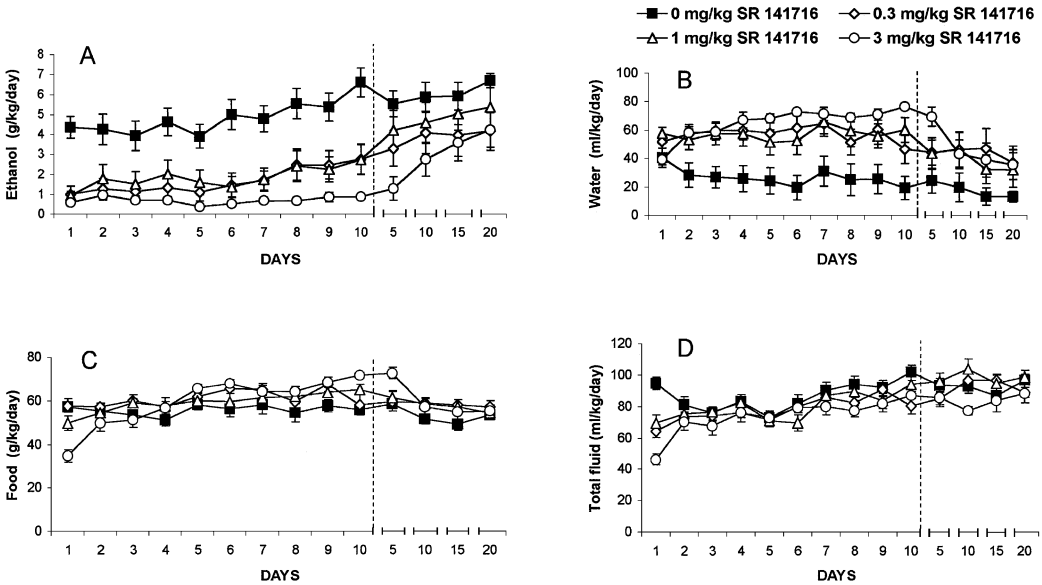


Fig. 1. Effect of the repeated administration of the cannabinoid $CB_1$ receptor antagonist, SR 141716, on the acquisition of alcohol drinking behavior in Sardinian alcohol-preferring (sP) rats. SR 141716 (0, 0.3, 1 and 3 mg/kg; i.p.) was injected twice daily (30 min before lights off and half-way through the dark phase) for 10 consecutive days. Alcohol (10%, v/v) and water were offered under the two-bottle, free-choice regimen with unlimited access for 24 h/day starting from the first day of treatment with SR 141716. Food pellets were always available. Alcohol, water and food intakes were monitored once a day immediately before lights off. The dashed line indicates the completion of the 10-day treatment period. Each point is the mean ± S.E.M. for $n = 9–10$ subjects.

In vehicle-treated rats, the mean alcohol intake was higher than 4 g/kg/day from the first day of exposure and rose to approximately 6 g/kg within 7–10 days. Treatment with SR 141716 prevented the acquisition of alcohol drinking [$F_{\text{treatment}}(3, 306) = 14.42$, $P = 0.000003$] (Fig. 1A); the daily alcohol intake was totally suppressed in the 3 mg/kg SR 141716-treated rats from the first day and suppression persisted throughout the 10-day treatment period. A compensatory increase in daily water intake [$F_{\text{treatment}}(3, 306) = 7.42$, $P = 0.000596$] (Fig. 1B) left the total fluid intake virtually unchanged [$F_{\text{treatment}}(3, 306) = 3.37$, $P = 0.029491$; the statistical significance was due to large differences recorded on day 1] (Fig. 1D). Food intake was not affected by SR 141716 [$F_{\text{treatment}}(3, 306) = 1.36$, $P = 0.270158$] (Fig. 1C). Moreover, after treatment completion, the alcohol intake increased very slowly, so that for rats treated with 3 mg/kg SR 141716, 20 days elapsed before their alcohol intake approached that of control rats.

These results demonstrate that the administration of SR 141716 could prevent the acquisition of alcohol drinking behavior in sP rats, suggesting that functioning of the cannabinoid $CB_1$ receptor is essential for the development of high alcohol preference and consumption in this rat line. Complete inability to self-administer alcohol has been found consistently in cannabinoid $CB_1$ receptor knockout mice (Hungund, personal communication).

Administration of SR 141716 has been found to block the acquisition, but not the expression, of cocaine- and morphine-induced conditioned place preference in rats (Chaperon et al., 1998). Interestingly, SR 141716 was much more effective to prevent acquisition of alcohol use (present study) than, as seen previously (Colombo et al., 1998), to suppress this behavior once it was established. These results support the hypothesis that the cannabinoid $CB_1$ receptor is involved in the neurobiological events underlying the acquisition to a greater extent than in those events mediating the expression of the positive reinforcing properties of abusive drugs, including alcohol.

Since SR 141716 was effective to suppress the acquisition of alcohol use at doses clinically tested under different conditions (Le Fur et al., 2001), the potential of a drug to prevent alcohol dependence and alcoholism, e.g. relapses in abstinent alcoholics, should be considered.

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