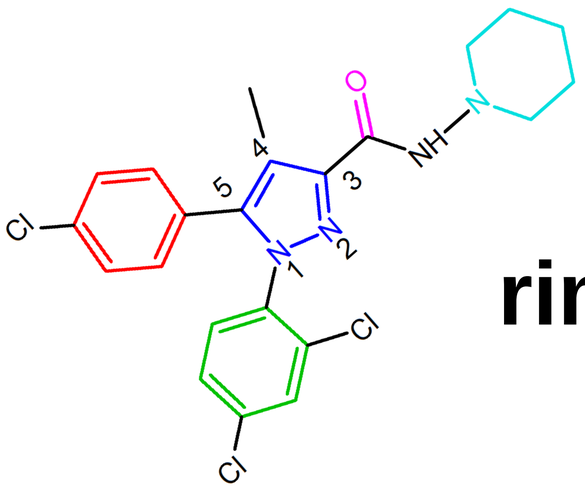


CB-1 receptor antagonist rimonabant increases striatal D2/3R availability in rats

Elsmarieke van de Giessen[1], Cleo Crunelle[2], Kora de Bruin[1], Wim van den Brink[2], Jan Booij[1]

[1]Dept. of Nuclear Medicine, [2]Dept. of Psychiatry, Academic Medical Centre, Amsterdam

Introduction

The cannabinoid 1 (CB1) receptor antagonist rimonabant (SR141716) has been shown to reduce food intake, body weight, and the rewarding properties of food and drugs. However, the underlying mechanisms of action are not entirely clear. Interactions between the cannabinoid and dopamine systems have been demonstrated. The dopamine D2 receptor (D2R) has been closely implicated in reward phenomena, and lower availability of striatal dopamine D2 receptors has been detected in both subjects with obesity and drug addiction. Therefore, the present study investigated the effects of rimonabant on dopamine D2 and D3 receptor (D2/3R) availability.

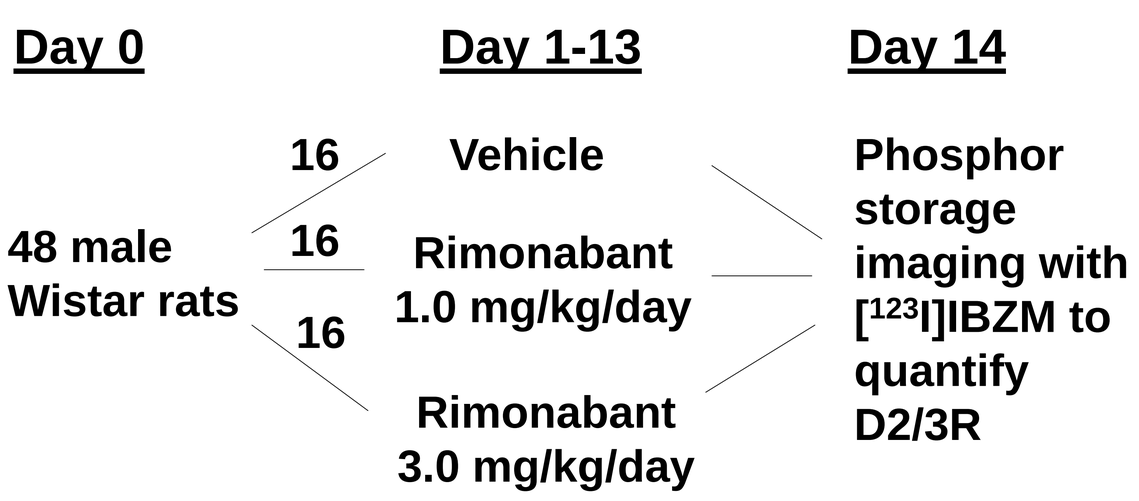
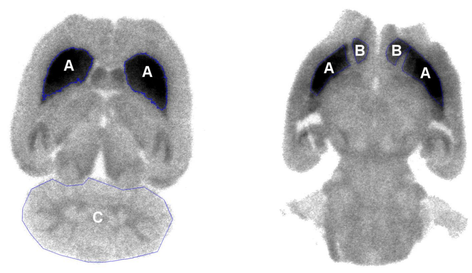


Figure 1. Study design.

Figure 2.
Examples of regions of interest: dorsal striatum (A), nucleus accumbens (B), and cerebellum (C).



Methods

Male Wistar rats (n = 48) were randomised into three equally sized groups (Fig 1) and treated for 13 consecutive days with either vehicle, rimonabant 1.0 mg/kg body weight or rimonabant 3.0 mg/kg body weight. Changes in body weight were measured. On day 14, D2/3R availability was determined in the nucleus accumbens (NAcc) and dorsal striatum (Fig 2) by ratios of striatal-to-cerebellar binding of the radiotracer [^{123}I]IBZM using storage phosphor imaging.

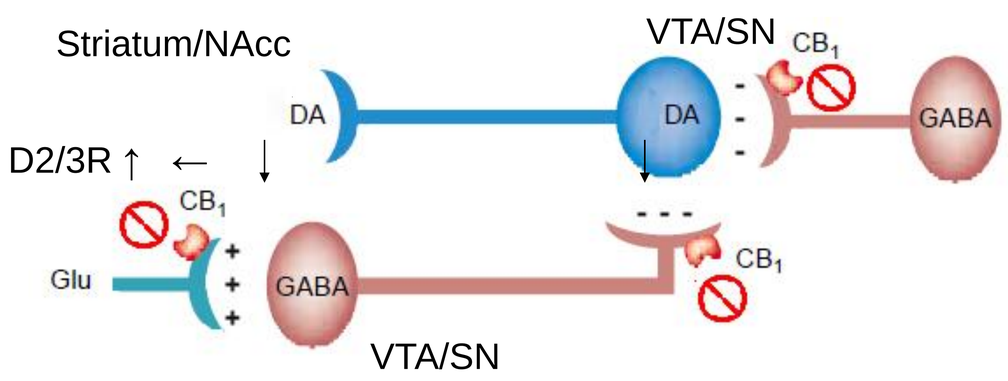


Figure 5. Potential mechanism of action
VTA = ventral tegmental area, SN = substantia nigra
Adapted from (1)

D2/3R availability dorsal striatum

D2/3R availability NAcc

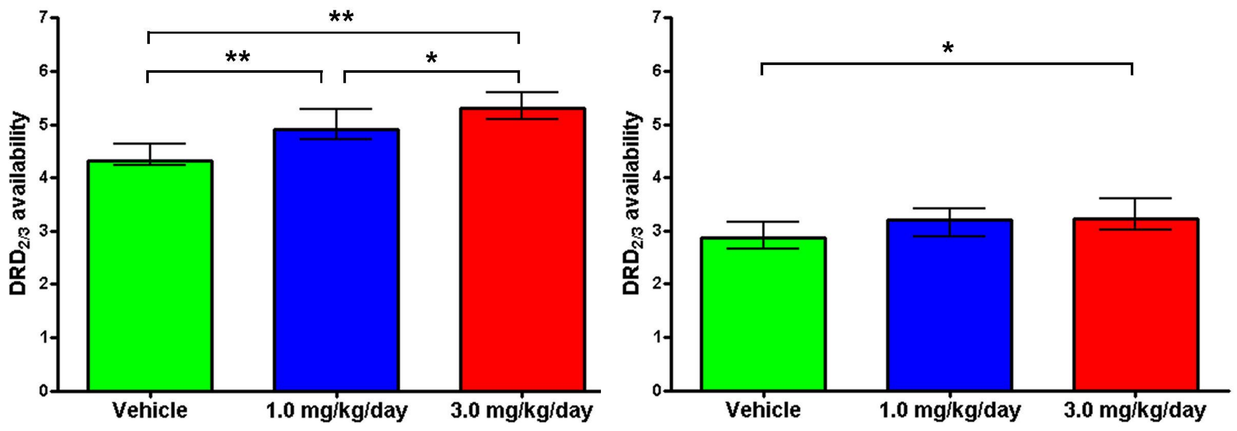
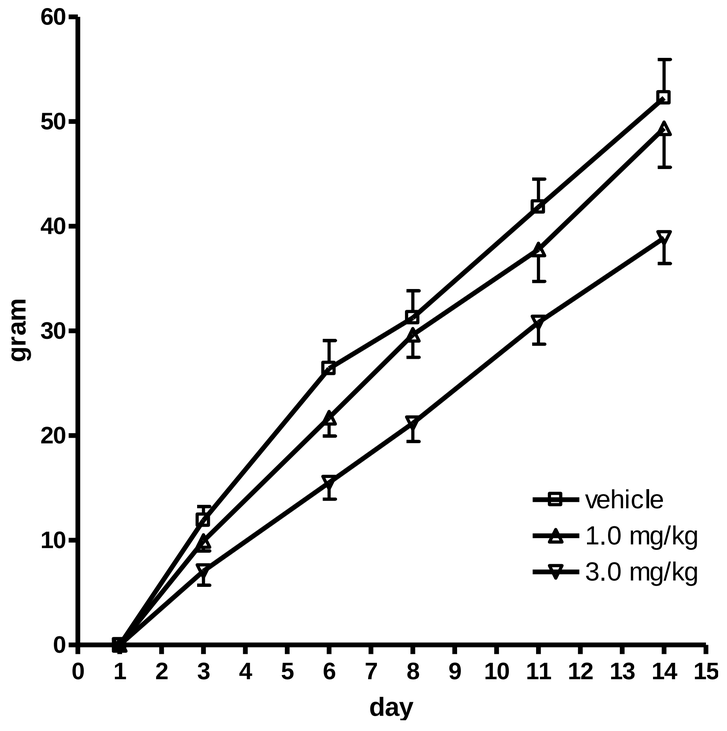


*Figure 3. D2/3R availability for dorsal striatum and nucleus accumbens (NAcc) after chronic rimonabant treatment. Median + interquartile range. * p < 0.05, ** p < 0.01*

Results

Rimonabant dose-dependently increased the D2/3R availability in the dorsal striatum (rimonabant 3.0 mg/kg vs vehicle: p = 0.001; rimonabant 1.0 mg/kg vs vehicle: p = 0.006). In the ventral striatum, only the highest dose of rimonabant (3.0 mg/kg/day) statistically significantly increased DRD2/3 availability (p = 0.016; Fig 3). In addition, high-dose rimonabant (3.0 mg/kg/day) significantly decreased body weight gain during the treatment period (p = 0.003; Fig 4).

Figure 4. Cumulative weight gain curves.



Conclusion and discussion

Chronic treatment with rimonabant significantly increased DRD2/3 receptor availability in dorsal striatum and nucleus accumbens.

The potential mechanism of action is by reduction of the GABAergic inhibiting signal on de dopaminergic neurons in the ventral tegmental area and substantia nigra. Subsequently, dopamine release in the striatum is reduced and D2/3R increased (Fig 5; 1,2).

Upregulation of striatal D2/3R availability may be a mechanism by which CB1 receptor antagonists alter the rewarding and motivational properties of food and drugs, as well as their intake (3).

References

1. Schlicker et al. 2001 *Trends Pharmacol Sci* 22:565-72.

2. Lupica and Riegel. 2005 *Neuropharmacology* 48:1105-1116.

3. Nader et al. 2006 *Nat Neurosc* 9:1050-1056.

Disclosure

No potential conflict of interest.