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European Journal of Pharmacology 377 (1999) R1–R2

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Rapid communication

Clozapine pre-treatment enhances raclopride catalepsy

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Received 28 May 1999; accepted 1 June 1999

Abstract

The clinical replacement of clozapine by another antipsychotic sometimes causes extrapyramidal signs, including dystonia, to appear suddenly. The present study was done, therefore, to test whether clozapine pre-treatment of rats could affect raclopride-induced catalepsy. Clozapine, at 5 mg/kg, given 2 h before a catalepsy-threshold dose of 0.1 mg/kg raclopride, markedly enhanced raclopride-induced catalepsy in the rats. The results are compatible with earlier in vitro data where pre-exposure of human cloned dopamine D_2 receptors to clozapine resulted in an increased potency of raclopride in inhibiting the binding of [^{3}H]clozapine to the receptors. The mechanism of clozapine potentiation of raclopride action may contribute to the clinically observed post-clozapine dystonia.

Keywords: Dopamine receptor; Clozapine; Extrapyramidal sign

Clozapine is an antipsychotic drug currently recommended for psychotic patients who do not respond to traditional antipsychotic drugs (Meltzer et al., 1996), although clozapine is also used as a first-choice antipsychotic in many countries. Clozapine does not elicit extrapyramidal signs in patients or cause catalepsy in rats. Psychotic patients, however, frequently stop their antipsychotic medication or are withdrawn from it because of impending clozapine-induced agranulocytosis. Such withdrawal of clozapine frequently results in early clinical relapse of psychotic symptoms within days (Shore, 1995; Meltzer et al., 1996). Replacement of the withdrawn clozapine by another antipsychotic is usually (though not always) effective in alleviating the relapsing psychosis (Meltzer et al., 1996; Stanilla et al., 1997; Dellva et al., 1999). A number of cases have been reported, however, where a rapid emergence of extrapyramidal signs, including dystonia, occurs upon administering a replacement antipsychotic soon after clozapine withdrawal (e.g., Dickson et al. (1994) and Radford et al. (1995), both of whom used risperidone; and Shiovitz et al. (1996) who used thiothixene for one patient).

Because these extrapyramidal signs are often alleviated by benztropine, it has been thought that long-term block of acetylcholine receptors by clozapine produces cholinergic overactivity, accounting for the enhancement of extrapyramidal signs (Shiovitz et al., 1996). The rapidity with which these signs emerge, however, has not yet been explained. Moreover, it is possible that clozapine pre-treatment may have altered the properties of the dopamine receptors in the psychotic patients. In fact, during our previous work on the rapid release of radioactive clozapine from dopamine D_2 receptors (Seeman and Tallerico, 1999), we found that raclopride became much more potent in displacing [^{3}H]clozapine from these receptors if the receptors were pre-treated with clozapine. In extending these in vitro findings to rats, therefore, we examined whether clozapine pre-treatment would rapidly enhance the potency of raclopride in eliciting catalepsy, which it did. This finding is relevant to the rapid emergence of extrapyramidal signs mentioned above.

Catalepsy was measured in adult Sprague–Dawley rats (250–300 g). The animals were placed on an inclined grid (60°), and, excluding the first 30 s, the time the rat remained in the same position was measured for a maximum of 2.5 min. The catalepsy was scored from 0 to 5,

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0014-2999/99/$ - see front matter
PII: S0014-2999(99)00406-9

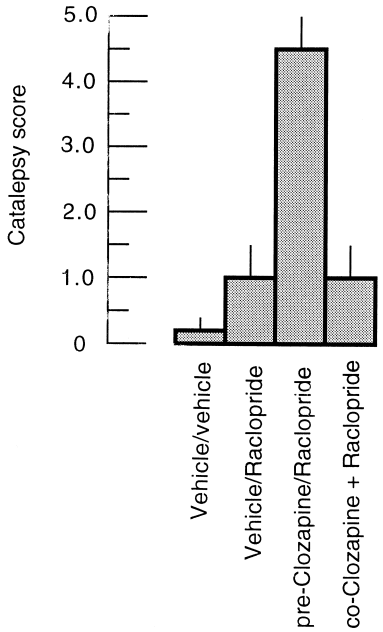

Fig. 1. Peak catalepsy occurred 1 h after raclopride injection (0.1 mg/kg i.p.). Clozapine (5 mg/kg) given 2 h before the injection of raclopride enhanced the catalepsy caused by raclopride. Twelve rats per point. Each column indicates the median ± semi-interquartile range. Statistical analysis was done by means of the Kruskal–Wallis One-way ANOVA by ranks, followed by the Mann–Whitney *U*-test for comparison between animals treated with raclopride alone and animals treated with clozapine and raclopride. $P < 0.001$, comparing pre-clozapine + raclopride vs. vehicle/raclopride.

according to the time (square root transformation) the animal remained immobile (min): 0 = 0–0.08 min, 1 = 0.09–0.35 min, 2 = 0.36–0.80 min, 3 = 0.81–1.42 min, 4 = 1.43–2.24 min, and 5 = > 2.25 min. That is, if the rat remained immobile for 2.25 min or longer, then it was scored as 5. Clozapine or the solvent vehicle was injected intraperitoneally. Raclopride, 0.1 mg/kg, which is the threshold dose for eliciting catalepsy in rats, or saline vehicle, was injected subcutaneously. The rats were either pre-treated or co-treated with 5 mg/kg clozapine. Peak catalepsy with raclopride occurred at 60 min after injection. Twelve rats were used for each dose.

At 1 h after injection, which was when peak catalepsy occurred with raclopride, a low level of catalepsy (1 unit) was elicited by either raclopride alone or by the combined injection of raclopride and clozapine (Fig. 1). However, if clozapine was injected 2 h before the injection of raclopride, the rats exhibited a marked catalepsy of 4.5 units, where 5 was the maximum possible on this scale (Fig. 1).

Considering the fact that clozapine up to 50 mg/kg does not by itself elicit catalepsy, it would not be expected that clozapine pre-treatment would enhance raclopride catalepsy. The pre-exposure of dopamine D_2 receptors to clozapine in the rat may have altered the affinity of these receptors for raclopride. Our previous work showed that the binding of [^{3}H]clozapine to the D_2 receptor was 50% inhibited by 1 nM raclopride, when competing simultaneously with [^{3}H]clozapine (Seeman and Tallerico, 1999). However, after pre-treatment for 2 h with the clinically therapeutic concentration of 250 nM clozapine, 0.1 nM raclopride was 50% effective in displacing [^{3}H]clozapine. Qualitatively, at least, the earlier in vitro data and the present catalepsy data are consistent in revealing that clozapine pre-treatment enhances raclopride potency at the dopamine D_2 receptor. It is possible, therefore, that, whatever the molecular mechanism underlying the potentiation by clozapine, that mechanism may contribute to the rapid induction of dystonic reactions in some patients when an antipsychotic is used to replace the withdrawn clozapine.

Acknowledgements

Dr. M.-L. Wadenberg was supported by a Fellowship from Eli Lilly, Canada. Supported by the Medical Research Council of Canada, the Ontario Mental Health Foundation, the National Institute on Drug Abuse, the Schizophrenia Society of Ontario, and the Stanley Foundation of the NAMI Research Institute.

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