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ScienceDirect
European Psychiatry 22 (2007) 267–275
EUROPEAN PSYCHIATRY
http://france.elsevier.com/direct/EURPSY/

Review

Antipsychotic efficacy: Relationship to optimal D_2-receptor occupancy

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Received 3 August 2006; received in revised form 19 January 2007; accepted 12 February 2007
Available online 6 April 2007

Abstract

Clinically important differences exist between antipsychotic agents and formulations in terms of safety and tolerability. Features of the biochemical interaction between the antipsychotic and the D_2-receptor may underlie these differences. This article reviews current information on the relationship between antipsychotic receptor occupancy and clinical response. A literature search was performed using the keywords 'antipsychotic or neuroleptic', 'receptor' and 'occupancy' and 'dopamine' and 'D_2' supplemented by the authors' knowledge of the literature. Imaging and clinical data have generally supported the hypotheses that optimal D_2-receptor occupancy in the striatum lies in a 'therapeutic window' between ~65 and ~80%, however, pharmacokinetic and pharmacodynamic properties of a drug should also be taken into account to fully evaluate its therapeutic effects. Additional research, perhaps in preclinical models, is needed to establish D_2-receptor occupancy in various regions of the brain and the optimal duration of D_2-receptor blockade in order to maximise efficacy and tolerability profiles of atypical antipsychotics and thereby improve treatment outcomes for patients with schizophrenia.

Keywords: Antipsychotic; Atypical; Dopamine; Receptor; Occupancy; Extrapyramidal symptoms

1. Introduction

An increasing body of evidence from positron emission tomography (PET) studies suggests that there are relationships between the clinical response and side effects observed with antipsychotic therapy, and factors such as antipsychotic dose and receptor occupancy in different regions of the brain. In particular, antipsychotic occupancy of dopamine D_2-receptors has been the focus of extensive research. Blockade of cortical and limbic dopamine D_2-receptors is thought to mediate both clinical response to antipsychotics and the occurrence of adverse events. D_2-receptor-related adverse events are mediated via blockade of striatal and tuberoinfundibular D_2-receptors, which are associated with extrapyramidal symptoms (EPS) [69] and prolactin elevation [9], respectively. Side effects and poor clinical response are of concern since they can lead to discontinuation of study medication, subsequent patient relapse and, thus, contribute to suboptimal treatment outcomes.

Several systematic reviews concur in suggesting that the newer atypical antipsychotics achieve comparable efficacy accompanied by a lower incidence of EPS [11,56] when compared with conventional agents. Indeed, data from randomized clinical trials of aripiprazole [34,41], ziprasidone [7,31], risperidone [48], quetiapine [28] and olanzapine [75] have shown these agents provide comparable or superior efficacy and improved tolerability profiles compared with haloperidol. It is noteworthy, however, that some of the atypical agents are associated with increased incidences of metabolic side effects, including weight gain and dyslipidemia [1]. The recent CATIE study demonstrated that the conventional agent perphenazine,

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doi:10.1016/j.eurpsy.2007.02.005

had similar discontinuation rates as the atypical agents olanzapine, quetiapine, risperidone and ziprasidone [46] and, as such, further studies are needed to fully evaluate the potential advantages in terms of the efficacy and safety profile of atypical agents compared with conventional agents. Moreover, several studies have reported clinical benefits of reduced relapse after switching from orally administered antipsychotic to long-acting formulations [14,59].

Although clinical efficacy and incidence of side effects might differ between oral immediate-release and long-acting formulations of conventional and atypical antipsychotics, these therapies share D_2-receptor blockade as the primary mechanism of antipsychotic action. It is, therefore, possible that several aspects might combine in determining the final pharmacological effects produced by the D_2-receptor blockade. Among them, three features of the biochemical interaction between the antipsychotic agent and the D_2-receptor might be particularly relevant for the clinical outcome: (1) the level (thresholds) of D_2-receptor occupancy; (2) the dissociation (affinity) of the drug to the D_2-receptor; and (3) the availability of the drug to the receptor over time.

Studies have demonstrated that the atypical antipsychotics generally have a much lower affinity for D_2-receptors than the older, conventional antipsychotic agents [63–65]. Moreover, several authors have highlighted that D_2-receptor occupancy and dissociation rates are an important consideration, although few studies have really addressed the question of optimal duration of D_2-receptor occupancy. Finally, the recent introduction of a long-acting atypical antipsychotic indicates that clinical benefits, in terms of relapse prevention and therapy outcome, might occur when this pharmacological strategy is adopted.

Thus, although it can be postulated that a favourable equilibrium exists between D_2-receptor occupancy, dissociation of the drug from the D_2-receptor and availability of the drug to the receptor, further work is required to study these pharmacological aspects in detail, with regard to the potential clinical benefit and impact on the development of new antipsychotic agents.

This article will examine the available information with regard to the relationship between antipsychotic receptor occupancy and clinical response and side effects. The contribution of different aspects of the antipsychotic–receptor interaction (occupancy thresholds, dissociation and availability over time) will also be reviewed.

2. Methods

A literature search was performed using the keywords 'antipsychotic or neuroleptic', 'receptor' and 'occupancy' and 'dopamine' and 'D_2'. Additional articles were included based on the authors' knowledge of the literature and after reviewing the reference lists of retrieved articles. Abstract books from recent congresses were also reviewed.

2.1. D_2-receptor occupancy thresholds

In light of the clinical relevance of combining optimal therapeutic efficacy with a low incidence of side effects, several studies have investigated whether the different pharmacological effects induced by antipsychotic drugs could be related to progressively exceeding threshold limits of D_2-receptor occupancy.

Using basal ganglia as an index of the D_2-receptor occupancy induced by antipsychotic drugs in the brain, imaging studies suggest that a D_2-receptor occupancy of greater than 65% is necessary for an antipsychotic effect to be observed, regardless of the type of drug [37,61]. In addition, preclinical and human studies have shown that EPS are observed if striatal D_2-receptor occupancy exceeds around 80%, as the access of endogenous dopamine to the receptors within this region is substantially reduced, leading to a relative increase in cholinergic activity that impairs motor function [12,37,68,69]. Using [^{11}C]-raclopride PET, it has been demonstrated that patients with schizophrenia receiving therapeutic stable doses of conventional antipsychotics and experiencing EPS have an average D_2-receptor occupancy within the striatum of 82%, compared with 74% in patients who did not experience EPS while receiving these agents (Table 1) [22].

These results have been confirmed using [^{123}I]-IBZM SPECT, with the highest EPS rates observed in patients treated with haloperidol (mean D_2-receptor occupancy of 85%) compared with lower mean D_2-receptor occupancy of 20–74% and lower rates of EPS observed in patients treated with atypical agents including clozapine, olanzapine, risperidone and quetiapine (Table 1) [73]. A similar study with olanzapine has demonstrated that doses of 10–20 mg/day achieve mean D_2-receptor occupancy of around 75%, and that increasing the dose and, therefore, the D_2-receptor occupancy to >80%, produces akathisia. Furthermore, doses higher than 20 mg/day of olanzapine were also associated with an increased likelihood of prolactin elevation (Table 1) [39]. A correlation between subjective response to antipsychotic treatment and D_2-receptor occupancy has been proposed. D_2-receptor occupancy of 60–70% (as measured by [^{123}I]-IBZM SPECT) was associated with a significantly higher (i.e. more favourable) total score on the Subjective Wellbeing Under Neuroleptics Scale (SWN) [15] (Table 1). This correlation was also observed for scores on all the subscales of the SWN, and was similar for haloperidol and olanzapine [15].

These data suggest that a D_2-receptor 'occupancy window' might exist in which a drug exerts its antipsychotic activity without inducing EPS. EPS may occur when the D_2-receptor blockade involves more than 85% of the striatal D_2-receptors.

Although the D_2-receptor 'occupancy window' concept is generally accepted, its applicability requires several distinctions depending on the drug and on the pharmacological effect to be considered. Low D_2-receptor striatal occupancies have been reported following clozapine and quetiapine administration. These findings are based on scans taken 6 or 12–14 h [22,73] after the last oral dose and, therefore, allowances must be made given the rapid decline in clozapine and quetiapine D_2-receptor occupancy within 24 h of last dose [62]. Two small studies have shown that quetiapine achieves a transient striatal D_2-receptor occupation (mean 62% at peak and 14% at trough within 24 h of a once-daily dose of up to 400 mg)