Thérapie 2008 Mai-Juin; 63 (3): 237–242
DOI: 10.2515/therapie:2008034

Markers of D_2 and D_3 Receptor Activity *in vivo*: PET Scan and Prolactin

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Text received 19 february 2008 ; accepted 28 april 2008

Keywords:
positrons emisssion tomography; dopaminergic system; extrapyramidal effect; antipsychotic drug; prolactin

Abstract – Positrons Emission Tomography (PET) allows to evaluate the dopaminergic activity of antipsychotic, by measuring post synaptic D_2 dopaminergic receptors occupancy. A good correlation was brought forward between a rate of occupancy of 80% of striatal D_2 receptors and the occurrence of extrapyramidal effects. These PET studies have also established that at least 60% D_2 receptors occupancy was predictive of clinical antipsychotic response. The PET studies in healthy volunteers can then be used to help choose doses to be tested during the clinical trials of new antipsychotic drugs. The increase in prolactin level is one other of the markers of the antagonist dopaminergic activity which concerns D_2 receptors of the pituitary gland. The example of S 33138, a potential antipsychotic, preferential D_3 *versus* D_2 receptor antagonist will be given to illustrate these data. The results of two PET studies as well as the effects on prolactin and extrapyramidal signs will be presented.

Mots clés :
tomographie par émission de positrons ; système dopaminergique ; effets extrapyramidaux ; antipsychotiques ; prolactine

Résumé – Marqueurs des récepteurs d'activité D_2 et D_3 *in vivo* : PET scan et prolactine. La tomographie par émission de positrons (PET) permet d'évaluer l'activité dopaminergique des antipsychotiques en mesurant l'occupation des récepteurs dopaminergiques D_2. Une bonne corrélation a été mise en évidence entre un taux d'occupation de 80 % des récepteurs D_2 striataux et l'apparition de signes extrapyramidaux. Ces études PET ont également établi qu'un taux d'occupation d'au moins 60 % des récepteurs D_2 était prédictif d'une bonne réponse au traitement antipsychotique. Les études PET chez le volontaire sain peuvent donc être utilisées pour aider au choix des doses à tester dans les essais cliniques de nouveaux antipsychotiques. L'augmentation du taux de prolactine est un autre marqueur de l'activité antagoniste dopaminergique qui concerne les récepteurs D_2 de l'hypophyse. L'exemple de S 33138, antipsychotique potentiel, antagoniste préférentiel des récepteurs D_3 *versus* D_2, permettra d'illustrer ces données. Les résultats de deux études PET chez le volontaire sain ainsi que les effets sur la prolactine et les signes extrapyramidaux seront présentés.

1. Introduction

In the clinical development of antipsychotics, pharmaceutical companies may have access to several markers of the dopaminergic activity of the drug such as brain receptors occupancy (using Positrons Emission Tomography (PET) tracers for specific receptors), modification of prolactin plasma level and occurrence of extrapyramidal symptoms. These markers can help to assess the pharmacodynamic properties as well as side effects of candidate compounds.

PET and SPECT (Single Photons Emission Computerized Tomography) studies have confirmed that all antipsychotics block D_2 receptors in patients, albeit to varying degrees.[1] These studies have repeatedly confirmed the existence of a threshold of striatal D_2 receptors occupancy (about 80%) above which extrapyramidal side effect (EPS) are likely to occur.[2,3] Moreover, occupancy levels of greater than approximatively 70% are associated with a high risk of elevated prolactin.[3] At last, clinical response in patients treated by typical antipsychotic can be predicted when 65% of receptor D_2 occupancy is achieved.[3] PET imaging will thus allow to choose and to narrow the dose range to be tested in phase IIb clinical trial, in order for example to minimize EPS (occupancy of less than 80%) or establish receptor occupancy at various doses below a maximal dose. This technique is also used to establish the likely dosing interval for a new compound.[4]

Prolactin elevation is a well-known feature of typical, haloperidol-like, antipsychotics. The blockade of dopamine D_2 receptors releases the lactotrophs from dopaminergic inhibition and

results in a heightened release of prolactin into the bloodstream.[5] In comparison, atypical, clozapine-like, antipsychotic that were first thought not to elevate prolactin levels[6–8] have demonstrated an increase but in a different degree and duration than with typical antipsychotics.[9] Indeed, to the exception of risperidone and amisulpride, atypical antipsychotics seems to increase the level of prolactin in a transitory, not in a sustained manner.[10]

Finally, a D_2 receptors blockade by neuroleptics will also tend to induce an extrapyramidal syndrome (EPS),[11] *i.e.* variety of iatrogenic movement disorders such as dystonia, akathisia and parkinsonism.[12] This effect is another signature of typical antipsychotics and is linked to the degree of D_2 receptor brain occupancy. Kapur *et al.*[3] showed that haloperidol-treated patients presented a D_2 occupancy ranging from 37% to 89%. Among them the 5 patients that experienced EPS presented a D_2 receptors occupancy above 78%. This result may explain why atypical antipsychotic induce lower rate of EPS since their D_2 receptor occupancy at therapeutical dose is lower: 55% for olanzapine, 69% for risperidone[13] and 32% for clozapine.[14] In addition, activity of a drug compound at other receptors than D_2 may balance the consequences of a D_2 blockade. In this line, it has been shown that D_3 receptors blockade in a fashion opposite to D_2 receptor blockade, favours motor function.[15] Thus, a proportionally high degree of D_3 *versus* D_2 receptor blockade would be predictive of a low EPS potential.

Consequences of D_2 receptor blockade can thus be directly assessed *in vivo* using PET imaging and indirectly using the measure of plasma prolactin level and the effect on motor function. In this paper, we will discuss the usefulness of this physiological markers in the clinical development of a potential antipsychotic compound, S 33138, a preferential D_3 *versus* D_2 receptor antagonist (~25-fold). S 33138 also depicts antagonist activity on serotoninergic 5-HT2A and α2C-adrenoreceptors.[16,17] At low concentrations, S 33138 behaves as a pure antagonist at cloned human D_3 sites but, at higher doses, D_2 receptor blockade occurs. We will present results obtained with S 33138 in cerebral imaging, its effect on prolactin secretion and on extra pyramidal symptoms in humans and animals and how these results were used in order to prepare subsequent clinical studies.

2. Marker of dopaminergic brain occupancy: PET studies with S 33138

In healthy volunteers, PET Scan studies allow, at an early stage of development, to establish the relationship between the dose administered and the occupancy of brain receptors for which the compound has an affinity; it also gives an estimation of the doses to be tested in phase II efficacy trials. In this line, Kapur *et al.*[3] found that 65% of receptor D_2 occupancy predicted clinical response in patients treated by typical antipsychotic. However, lower D_2 occupancies have been found with olanzapine, clozapine, ziprazidone, and amisulpride with respectively 55%, 32%, 56%, 60% and 56%.[14,18,19] In addition, PET Scan studies help to determine the level of doses corresponding to undesirable side effects: *e.g.* a D_2 receptor occupancy $\geqslant$70% predicted hyperprolactinemia and a D_2 receptor occupancy $\geqslant$80% predicted extrapyramidal side effects.

A first PET Scan study using [^{11}C]-raclopride in 9 healthy young male volunteers showed that S 33138 single dose bound D_2 receptor in a dose dependant manner with a mean striatal occupancy of respectively 41 ± 11% at 10 mg, 58 ± 8% at 40 mg and 79 ± 3% at 70 mg one hour post dose. After single oral administration of 40 mg, D_2 receptor occupancy remained roughly unchanged (≈60%) during 24 hours, with a slow subsequent decrease ($t_{1/2}$ ≈ 60 h) [figure 1]. In a second PET study using [^{11}C]-raclopride, 11 healthy young male volunteers, aimed to assess the degree of dopaminergic D_2 receptors occupancy after 14 days of repeated administrations of S 33138. Results showed a dose-dependant D_2 occupancy, with a low central occupation of about 35% at 5 mg/d, a moderate central occupation of about 50% at 10 mg/d and an significant central occupation of about 65% at 20 mg/d. At 20 mg/d, the central occupation was still about 60% 4 hours post dose and remains at about 50% 24 hours post dose (figure 2). Interestingly, this level of 65% of occupancy corresponds to D_2 occupancy reached with risperidone at 2 mg/d whereas therapeutical doses in schizophrenic patients are usually 4 to 6 mg/d. At these dosages, D_2 brain occupancy is of respectively 73 and 79%[10,20] suggesting that a possible higher dose of S 33138 would be requested to insure full effects on positive symptoms. When simulating what would be the occupancy at higher doses, it appears that 30 and 40 mg/d of S 33138 would mirror the occupancy that is observed with risperidone at 4 and 6 mg/d.

3. Peripheral marker of D_2 dopaminergic activity: plasma prolactin levels

S 33138, being an antagonist of D_2 receptors, was expected to induce a dose dependent increase in plasma prolactin levels. However, its D_3 and 5-HT2A antagonist activities would have lower the effect showing either no or transient prolactin elevation. Our data show that S 33138 single dose elicits a significant and dose-dependent (0.16 to 40 mg/kg, by subcutaneous injection [SC]) elevation in circulating levels of prolactin from the lower dose in rat. The magnitude of this effect was less pronounced than that of haloperidol (0.16 to 2.5 mg/kg SC). After repeated oral administration of S 33138 (0.8, 2.5, 7.5 mg/kg in rat and 5, 10, 15 mg/kg