Subjective experience and dopamine D2 receptor occupancy in patients treated with antipsychotics: clinical implications

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Publication date
2004

Published in
Canadian Journal of Psychiatry

Subjective Experience and Dopamine D_2 Receptor Occupancy in Patients Treated With Antipsychotics: Clinical Implications

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Objectives: This paper gives an overview of studies on the association between dopaminergic neurotransmission and the subjective experience of patients with schizophrenia.

Methods: We undertook a review of the literature.

Results: Dopaminergic neurotransmission may be relevant for subjective experience. Higher striatal D_2 receptor occupancy by typical and atypical antipsychotics is related to worse subjective experience, more severe negative symptoms, and depression. Individuals with lower baseline dopamine function are at an increased risk for dysphoric responses during antipsychotic therapy with dopaminergic-blocking drugs. There is preliminary evidence that a window of striatal D_2 receptor occupancy between 60% and 70% is optimal for the subjective experience of patients. These occupancies are often reached even with low dosages of antipsychotic drugs.

Conclusions: Reaching an optimal dopamine D_2 receptor occupancy is clinically relevant, since subjective experience associated with antipsychotic medication is related to medication compliance. Antipsychotic drug dosages often need to be lower than levels in common use.

(Can J Psychiatry 2004;49:290–296)

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Clinical Implications

- Some patients are susceptible to dysphoric responses during treatment with antipsychotic medication.
- Imaging findings suggest that dopamine D_2 receptor occupancy associated with negative subjective experience is often reached with high dosages of antipsychotic medication.
- Optimal dopamine D_2 receptor occupancy associated with optimal subjective experience is relevant for medication compliance.

Limitations

- Longitudinal controlled research should investigate whether there is a causal relation between increased D_2 receptor occupancy and negative subjective experience.
- Research into the relation between extrastriatal D_2 receptor occupancy and subjective experience is lacking.
- Studies are needed comparing D_2 receptor occupancy during treatment with the dopamine system in a drug-free state in the same patient.

Key Words: *subjective experience, schizophrenia, dopamine D_2 receptor occupancy, antipsychotic medication, imaging*

Antipsychotic medication is an essential step in the treatment of psychoses. To suppress psychotic symptoms successfully, antipsychotic medication has to inhibit central dopamine neurotransmission by blocking dopamine D_2 receptors (1). Occupancy of dopamine D_2 receptors by antipsychotic medication, however, also influences the subjective experience of patients. A relation has repeatedly been found between subjective experiences of patients in response to treatment with antipsychotic medication and compliance with antipsychotic medication (2–5). Therefore, the subjective experiences of patients treated with antipsychotic medication may be clinically relevant and deserve further research. Since there is no generally accepted definition, we propose to define subjective experiences of patients in response to treatment with antipsychotic medication as "all experiences related to treatment with antipsychotic medication that patients report, whether positive or negative, at physical, emotional, and cognitive levels."

In this article, we discuss the relation between central dopaminergic neurotransmission, subjective experience, and antipsychotic medication. We review the results of neuroimaging studies on the relation between dopamine D_2 receptor occupancy and the subjective experience of patients treated with typical and second-generation antipsychotic drugs. We especially want to address the following 2 questions: Is antagonism of dopaminergic neurotransmission relevant for subjective experience? What are the implications of findings from imaging studies for clinical care of patients with psychotic disorders?

Dopaminergic Neurotransmission in Relation to Subjective Experience, Clinical Symptoms, and Cognitive Functioning

Central dopamine neurons reside predominantly in the mesencephalon in 3 neuronal groups: the retrobulbar area, the substantia nigra, and the ventral tegmental area. Dopamine neurons from the retrobulbar area project to the hypothalamus, where they regulate hormone secretion from the pituitary. Dopamine neurons from the substantia nigra pars compacta project predominantly to the dorsal striatum and are mainly concerned with initiation and execution of movement. Those from the ventral tegmental area project predominantly to limbic and limbic-connected areas (for example, the ventral striatum, amygdala, and orbital and cingulated cortices) and are involved in reinforcement, motivation, mood, and the organization of thought. Experimental research in animals indicates that drug-induced dopaminergic blockade in mesolimbic circuits, especially in the nucleus accumbens (an area of the ventral striatum), leads to impaired pleasure response and dysphoria. Dopamine has an essential role in reward and reinforcement. According to Wise and others, dopamine is a neurochemical mediator of "life's pleasures" (6). Dopamine is also involved in aversive stimuli (7,8), and dopamine release is seen in the anticipatory phase of pleasure (9,10). These findings gave rise to the motivational salience hypothesis, according to which dopamine is thought to mediate the conversion of the neural representation of an external stimulus from a neutral bit of information into an attractive or aversive entity (11,12). In particular, the mesolimbic dopaminergic system is seen as a critical component in the "attribution of salience," a process whereby events and thoughts come to hold attention, drive action, and influence goal-directed behaviour, owing to to their association with reward or punishment (11,12). On the basis of these findings, Kapur recently described an elegant theory of dopamine's role in psychosis (13). A central role of dopamine is to mediate the salience of environmental events and internal representations. A dysregulated hyperdopaminergic state at brain level leads to an aberrant assignment of salience to the elements of experience at mind level (13).

Recently, the following findings have been published about characteristics of dopamine transmission and their relation to symptoms and subjective experience of healthy persons and patients.

Healthy Subjects

Significant decrease in subjective happiness scores were observed on acute dopamine depletion with alpha-methyl paratyrosine (AMPT) in 6 healthy subjects. The occupancy of striatal D_2 receptors by endogenous dopamine was evaluated in vivo with positron emission tomography (PET) and the radiotracer [^{11}C]raclopride; the D_2 receptor binding potential was compared before and after acute dopamine depletion (14). Another study showed that reduced availability of striatal D_2 receptors (both in the putamen and in the nucleus caudatus) was related to motoric as well as cognitive disturbances in healthy persons (15).

Patients With Schizophrenia

In 10 neuroleptic-naïve schizophrenia patients and 13 healthy control subjects, Hietala and others studied striatal dopamine synthesis capacity with [^{18}F]-6-L-fluorodopa PET (16). Depressive symptoms in neuroleptic-naïve, first-admission schizophrenia patients appear to be associated with low presynaptic dopamine function.

Lower striatal D_2 receptor density in 8 drug-naïve and 2 drug-free schizophrenia patients was related to more severe blunted affect and alogia (17). However, negative symptoms were found to be associated with increased availability of striatal D_2 receptors, perhaps because of decreased concentrations of endogenous dopamine in drug-free schizophrenia patients after neuroleptic withdrawal (18).

Patients With Depression, Anxiety, or Avoidant Personality Traits

A reduced presynaptic dopamine function was found in the left caudate of depression patients with flattened affect and psychomotoric retardation (19). The results of a single photon emission computerized tomography (SPECT) study suggested that the antidepressant benefits of sleep deprivation, used as a treatment in depression patients, are related to the endogenous release of dopamine (20). A link was found between avoidant personality traits and reduced dopamine D_2 receptor density (21,22), as well as reduced dopamine transporter density (23). A relation was also found between low D_2 receptor binding capacity and severity of social phobia (24).

Substance Abuse

Dopamine transporter reduction is related to slower motoric skills and memory defects in detoxified methampetamine abusers (25). D_2 receptor antagonists have been shown to decrease the subjective ratings of pleasant sensations induced by cocaine (26,27). Nicotine stimulates the release of dopamine and the energy metabolism in the basal ganglia, especially in the ventral tegmental areas and the nucleus accumbens (28), putamen, and nucleus caudatus (29); this is probably the central reinforcing mechanism of addictive substances (30). Cannabinoids also increase the activity of dopaminergic neurons in the ventral tegmentum and mesolimbic projections, accompanied by the desired subjective effects, which reinforce use (31). In this context, the frequent smoking of patients with schizophrenia can be understood as a form of self-medication to reduce negative symptoms (32). In addition, smoking reduces the blood level of antipsychotic medication (33) and could in this way also affect the inhibiting function of antipsychotic medication experienced as unpleasant by the patient. A smaller quantity of D_2 receptors predicts a pleasant subjective response to psychostimulants in healthy persons (34).

Effect of Antipsychotic Medication on Occupancy of Dopamine D_2 Receptors and Subjective Experience

In view of the above-mentioned findings, it can be expected that antipsychotic medications (which all inhibit central dopaminergic transmission) influence the subjective experiences of patients. Antipsychotics dampen the salience of abnormal experiences and, by doing so, permit the resolution of symptoms (13). Perceptions and ideas can become less meaningful for patients. The desired effect of antipsychotic medication is also to reduce the significance of false beliefs (delusions) and perceptions (hallucinations); however, treatment with antipsychotic medication can reduce a desirable sense of significance. This is a major problem, considering that reduced drive, motivation, spontaneity, and sense of significance already inhere in schizophrenia.

Some recent indications are that second-generation antipsychotic drugs may be associated with a better subjective experience than typical antipsychotic drugs. However, if the severity of negative subjective experience is related to D_2 receptor occupancy of second-generation drugs, these agents may not demonstrate more benefits for subjective experience than do typical antipsychotic drugs in dosages that lead to the same range of D_2 receptor occupancy. In other words, if subjective experience is related to D_2 receptor occupancy, there may be no essential difference in influence on subjective experience of some atypical and typical antipsychotics if they are compared at equal D_2 receptor binding levels (35). It is also possible that the fast-off characteristics of antipsychotic drugs, and not their absolute occupancy rates, have important effects on subjective experience. Kapur and Seeman proposed that fast dissociation from the D_2 receptor could make an antipsychotic medication more accommodating of physiological dopamine transmission, permitting antipsychotic effect without major side effects (36). This proposed mechanism may also account for superior subjective experience associated with atypical antipsychotic drugs.

Neuroleptic-Treated vs Drug-Free Patients

Heinz and others examined anhedonia and psychomotor slowing in 8 drug-free and 8 neuroleptic-treated schizophrenia patients (37). Reaction time and motor speed were measured using a computer-aided system, and striatal dopamine D_2 receptor availability was assessed using [^{123}I]iodobenzamide ([^{123}I]IBZM) SPECT. Psychomotoric reaction time, parkinsonism, affective flattening, and avolition were increased in treated patients, relative to the untreated cohort, and were negatively correlated with dopamine D_2 receptor availability. Their findings supported the hypothesis that neuroleptic-induced dopamine D_2 blockade in the striatum can mimic certain negative symptoms, such as affective flattening and avolition.

Subgroup With Different Vulnerability for Dysphoric Responses

Voruganti and others induced dysphoric responses by acute dopamine depletion with AMPT and simultaneously quantified baseline striatal dopamine D_2 function with [^{123}I]IBZM SPECT imaging in 12 drug-free schizophrenia patients (38). The authors concluded that striatal dopaminergic activity is not uniformly elevated in all schizophrenia patients and that the subgroup of individuals with lower baseline dopamine function are at increased risk for dysphoric responses during antipsychotic therapy with dopaminergic-blocking drugs.

Typical Antipsychotic Drugs

A study by Bressan and others suggested that high striatal dopamine D_2 blockade by typical antipsychotic drugs may contribute to the emergence of depressive symptoms (39). They found that, in 18 patients with schizophrenia, striatal D_2 receptor occupancy by typical antipsychotic drugs, measured with [^{123}I]IBZM SPECT, significantly positively correlated with the depressive subscale of the Brief Psychiatric Rating Scale.

Olanzapine and Risperidone

We evaluated the relation between subjective experience and striatal D_2 receptor occupancy in 22 schizophrenia patients clinically stable on either olanzapine or risperidone (35). Of the patients, 4 were women and 18 were men (mean age 22 years).

We measured patients' subjective experiences with the Subjective Well-Being Under Neuroleptic Treatment (SWN) scale. We also assessed patients' psychopathology and extrapyramidal symptoms (EPS). SPECT was performed after a stable dosage period of at least 6 weeks of olanzapine (mean dosage 14.7 mg daily) or risperidone (mean dosage 4.1 mg daily). We found that SWN scores correlated with the percentage of D_2 receptor occupancy. Negative symptoms ratings and depression scores also correlated with D_2 receptor occupancy. EPS were almost absent.

We concluded that, in the absence of EPS, higher striatal D_2 receptor occupancy by olanzapine and risperidone was related to worse subjective experience, more severe negative symptoms, and depression. This may have important implications for dosing strategies and compliance with antipsychotic medication. Moreover, this finding urges comparison of subjective experience between typical and atypical antipsychotics at dosages that lead to comparable D_2 receptor occupancy.

Olanzapine and Haloperidol

It has been suggested that a threshold in the range of 60% to 70% D_2 receptor occupancy is needed to obtain satisfactory antipsychotic response. Kapur and others found that prolactin elevation became prominent beyond 72%, while EPS were evident beyond 78% (40). We found that D_2 receptor occupancy levels well below those that cause EPS are associated with negative subjective experience; therefore, to avoid excessive inhibition of dopamine neurotransmission that leads to a negative impact on subjective experience, we proposed that D_2 binding should not exceed 70%. Conversely, D_2 occupancy below 60% leaves patients in a psychotic state (with too high a functional level of the dopamine system) that is also accompanied by negative subjective well-being. We hypothesized that there is a window for the influence of antipsychotic medication on patients' subjective experience. Further, we hypothesized that optimal occupancy of D_2 receptors lies between 60% and 70%. In this context, the recent findings of Volkow and others are of interest, specifically, that an optimal range exists within which D_2 receptor stimulation by drugs of abuse can be perceived as reinforcing. Too low levels may not be sufficient to induce a subjective "high," but too high levels may have an aversive effect (34).

Our main objective was to test the hypothesis that, in patients with recent-onset schizophrenia, dopamine D_2 receptor occupancy between 60% and 70% results in optimal subjective experience. Our additional goal was to find preliminary evidence for the superior influence of olanzapine on subjective experience, compared with haloperidol.

We randomly assigned 24 subjects with schizophrenia to a double-blind trial in which they received either 7.5 mg daily olanzapine or 2.5 mg daily haloperidol for 6 weeks. We assessed subjective experience, psychopathology, and EPS at baseline and at endpoint. At week 6, striatal D_2 receptor occupancy was assessed with SPECT (41). Our main finding was that dopamine D_2 receptor occupancy between 60% and 70% was associated with optimal subjective experience. Olanzapine 7.5 mg daily did not show superior subjective response, compared with haloperidol 2.5 mg daily. In fact, subjective experience improved significantly only during treatment with haloperidol. This was an unexpected finding, given the advantages in subjective experience found during treatment with olanzapine in former studies. Too high levels of D_2 receptor occupancy in the typical comparison group have confounded these studies. However, our study may be biased by the relatively low D_2 receptor occupancy associated with olanzapine 7.5 mg daily. We could not therefore discard the possibility that an olanzapine dosage leading to D_2 receptor occupancy beyond 70% may still result in superior subjective well-being. The decline in subjective well-being occurring with striatal D_2 receptor occupancy above 70% may only be relevant for haloperidol. However, future studies are needed to test this hypothesis.

Discussion and Clinical Implications

We conclude that antagonism of dopaminergic neurotransmission is relevant for subjective experience. Findings from imaging studies have the following implications for clinical care of patients with psychotic disorders.

Neuroleptic-induced dopamine D_2 blockade in the striatum can mimic certain negative symptoms, such as affective flattening and avolition (37). Higher striatal D_2 receptor occupancy by typical and atypical antipsychotics is related to worse subjective experience, more severe negative symptoms, and depression, in the absence of EPS. Even small differences in D_2 receptor occupancy may have consequences for the subjective experience of patients (35,39,41). A

relation between high dopamine D_2 receptor occupancy and subjective experience has been found in chronically ill patients treated with various typical antipsychotic drugs in a wide dosing range (39). The relation has also been found in patients with first-episode schizophrenia stabilized on olanzapine, risperidone, or haloperidol in a low-to-moderate dosage (35,41). Comparable findings in such different groups of patients with schizophrenia support the notion that more (antipsychotic medication) could be less (that is, giving a favourable result) (42). However, not all patients are equally susceptible to these effects. Striatal dopaminergic activity is not uniformly elevated in all schizophrenia patients, and the subgroup of individuals with lower baseline dopamine function are at an increased risk for dysphoric responses during antipsychotic therapy with dopaminergic-blocking drugs (38). Preliminary evidence exists that a window of D_2 receptor occupancy between 60% and 70% is optimal for the subjective experience of patients. This occupancy level is already reached by using very low dosages of antipsychotic drugs (41).

Reaching an optimum dopamine D_2 receptor occupancy is clinically relevant, since subjective experience during treatment with antipsychotic medication is associated with medication compliance. Dosing of antipsychotic drugs often needs to be lower than is common in treatment.

Other Arguments for Treatment With Low Dosages of D_2 Antagonists

There are various other arguments for treatment of psychosis with low dosages of D_2 antagonists.

A metaanalysis involving 1638 patients who were treated with less than 2 to 3 mg haloperidol equivalents daily showed that positive symptoms were not adequately treated. Similarly, dosages above 7 mg daily were not associated with optimal clinical efficacy but were accompanied by more side effects (43). McEvoy and others also found that patients do not improve more if they receive a higher dosage than the one at which they develop minimal EPS (44), known as the neuroleptic threshold dose (45). With higher dosages, EPS and negative symptoms increase. Stone and others found no difference in clinical improvement between the group of patients receiving 4 mg haloperidol daily and the group receiving 10 mg haloperidol daily (46). Marder and others (47) and Hogarty and others (48) found that the percentage of psychotic relapse over 2 years in the group that received a very low dosage of fluphenazine decanoate (approximately 5 mg every 2 weeks) was little higher than the percentage in a group that received a standard dosage (25 mg every 2 weeks). The group with the low maintenance dosage had fewer negative and depressive symptoms and better social functioning. Research on binding has shown that 60% to 74% occupancy of D_2 receptors is optimal for therapeutic effect (49). This occupancy is already reached in first-episode patients with 2 mg haloperidol daily. Zhang-Wong and others found that 2 or 5 mg haloperidol daily was the optimal dosage for 72% of patients with a first episode of psychosis (50). Subjects with a dosage of 2 mg haloperidol daily showed the greatest improvement.

Thus, raising dosages above 7 mg haloperidol daily or an equivalent is not associated with greater improvement of psychotic symptoms; in most cases, it is associated with more side effects. Low dosages (between 2 and 4 mg daily) are particularly important for patients with a first psychotic episode. This advice appears similarly applicable to new antipsychotic medications with a strong D_2 antagonism.

Limitations of Available Imaging Studies

Most studies measured D_2 receptor occupancy in the neostriatum, an area not specific for psychosis and schizophrenia. Assessing D_2 receptor occupancy in the ventral striatum is thought to be more specifically important and has recently been made possible by high-resolution cameras and coregistration of structural magnetic resonance imaging.

In most studies, patients are compared with healthy individuals. However, because of the high interindividual variation, it is desirable to study patients in a drug-free and in a drug-treated state. In many publications, plasma concentrations of antipsychotic drugs are not assessed. Imaging of extrastriatal D_2 receptor occupancy with epidepride could tell us more about the impact of antipsychotic drugs on subjective experience.

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Manuscript received and accepted January 2004.
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Résumé : L'expérience subjective et l'occupation du récepteur de la dopamine D_2 chez les patients traités aux antipsychotiques : implications cliniques

Objectifs : Cet article donne un aperçu des études sur l'association entre la neurotransmission de la dopamine et l'expérience subjective chez les patients souffrant de schizophrénie.

Méthodes : Nous avons procédé à une analyse de la documentation.

Résultats : La neurotransmission de la dopamine peut avoir un lien avec l'expérience subjective. Une occupation striée plus élevée du récepteur D_2 par les antipsychotiques typiques et atypiques est reliée à une expérience subjective plus mauvaise, à des symptômes négatifs plus graves et à la dépression. Les personnes qui ont une fonction de base de la dopamine plus faible sont à risque accru de réactions dysphoriques durant le traitement aux antipsychotiques avec des médicaments bloquant la dopamine. Des preuves préliminaires indiquent qu'un intervalle d'occupation striée du récepteur D_2 entre 60 % et 70 % est optimal pour l'expérience subjective des patients. Ces taux d'occupation sont souvent atteints même avec de faibles doses d'antipsychotiques.

Conclusions : Atteindre une occupation optimale du récepteur de la dopamine D_2 est cliniquement utile, puisque l'expérience subjective associée aux antipsychotiques est reliée à l'observance du médicament. Les dosages des antipsychotiques doivent souvent être plus faibles que ceux couramment utilisés.