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Review article

Theoretical insights into the mechanism of action of atypical antipsychotics

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Abstract

The present work discusses some theoretical mathematical results that can be derived from the theory of receptor binding linked with PET experimental data and presents insights to the understanding of the differences between typical and atypical profile of antipsychotics regarding the generation of extrapyramidal syndrome. The first part of the paper discusses the importance of the drug affinity to dopamine D2 receptors (D2R) and of the therapeutic window of drug concentration for antipsychotic action without EPS, whereas the second part discusses the contribution of the plasma half-life in the time-course of D2R occupancy. Together with current experimental data, we concluded that the key factors leading to an atypical profile would be adequate posology, low affinity of the drug to D2R and/or short plasma half-life.

Keywords: D2R; Half-life; Law of mass action; Mathematical model; Schizophrenia; Therapeutic window

Contents

Abbreviations: $[A]$, concentration of antipsychotic; $[A_{0.65}]$, concentration of antipsychotic to block D2R in 65%; $[A_{0.78}]$, concentration of antipsychotic to block D2R in 78%; $[AD_2]$, concentration of blocked dopamine D2 receptor; ΔA, size of the therapeutic window of drug concentration without EPS; $C(t)$, plasma antipsychotic concentration; $[D]$, dopamine concentration; D2R, dopamine D2 receptor; $[D_2]$, concentration of free dopamine D2 receptor; $D_{2\text{Occup}}$, dopamine D2 receptors occupancy; ED50, effective dose 50 value; EPS, extrapyramidal motor side-effects; F, initial fraction of blocked receptors; K_{on}, association rate constant; K_{off}, dissociation rate constant; K_d, equilibrium dissociation constant; PET, positron emission tomography; SPECT, single photon emission computed tomography; $t_{1/2}$, antipsychotic plasma half-life; $T_{1/2}$, time necessary to reach half of receptor occupancy.

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1. Introduction

Antipsychotic therapy was first introduced in the early 1950s, and since then much effort has been employed to understand their mechanism of action, as well as the pathophysiology of psychotic disorders, such as schizophrenia. They are known to be effective in reducing positive schizophrenic symptoms, and some can to a lesser extent also reduce negative symptoms. Clinical doses of typical antipsychotics such as haloperidol are known to produce severe extrapyramidal motor side-effects (EPS), while atypical antipsychotics like clozapine and quetiapine do not.

Since the initial works of Farde et al. (1988, 1990, 1992), the use of positron emission tomography (PET) and of single photon emission computed tomography (SPECT) in psychiatry have provided insights into the understanding of antipsychotic mechanism of action. In the last decade, a body of evidence has been built by several reports indicating that the blockade of dopamine D2 receptors (D2R) is necessary and probably sufficient to achieve antipsychotic effect (Kapur and Remington, 2001; Kapur and Mamo, 2003), corroborating to the hyperactivation of the dopaminergic mesolimbic pathway theory of schizophrenia. However, it has also been consistently observed that excessive D2R blockade in the striatum is related to the generation of EPS (Kapur et al., 2000a). Therefore, the occupancy of striatal D2R receptors became an important objective measure for the development of EPS.

The present work aims to show and discuss some theoretical results that can be derived from the theory of receptor binding linked with PET experimental data and presents insights to the understanding of the differences between typical and atypical profile of antipsychotics regarding generation of EPS. The first part of the paper will discuss the importance of D2R affinity and of the therapeutic window of drug concentration for antipsychotic action without EPS, whereas the second part will discuss the contribution of plasma half-life of an antipsychotic in the time-course of D2R occupancy. Even though they are all straightforward theoretical results, we believe that such an exposition may clarify and review some key aspects related to antipsychotic action.

2. On the therapeutic window of drug concentration: the chief role of affinity

As cited above, it is currently accepted that antipsychotics block D2R in limbic regions, leading to antipsychotic action, whereas excessive D2R blockade in the striatum generates EPS. Using striatum D2R occupation as a marker, a level of 65% blockade is related in most cases to effective antipsychotic action, while EPS typically appear when more than 78% of D2R are blocked (Kapur et al., 2000a). Kapur and Seeman (2000, 2001) and Seeman (2002) have elegantly shown that typical antipsychotics, which commonly induce EPS, bind more tightly to D2R, in contrast to atypical antipsychotics, which present low or moderate affinity for this receptor, mainly because of a higher dissociation rate constant.

The kinetics of the antipsychotic–D2R interaction is said to obey the law of mass action, which can be represented as

$$[A] + [D_2] \overset{K_{on}}{\rightarrow} [AD_2] \overset{K_{off}}{\rightarrow} [A] + [D_2]$$

where $[A]$ stands for the concentration of antipsychotics, $[D_2]$ for free D2R, $[AD_2]$ for blocked D2R by antipsychotics, and K_{on} and K_{off} denote the association and dissociation rate constants, respectively. The affinity of the antipsychotic for the D2R is inversely proportional to its equilibrium dissociation constant (K_d), defined by K_{off}/K_{on}. A straightforward derivation from the law of mass action predicts that the fraction of D2R occupancy (D_{2Occup}) is given by (Appendix):

$$D_{2Occup} = \frac{[A]}{[A] + K_d}. \tag{1.1}$$

This equation shows that larger K_d values are associated with more gradual increases in the fraction of bound D2R with increasing antipsychotic dosage. This is shown in Fig. 1 as plots of D_{2Occup} as a function of $[A]$ for representative antipsychotics. Moreover, by defining the size of the therapeutic window of drug concentration without EPS, denoted by ΔA, as being the magnitude of the dose range between $[A_{0.65}]$ and $[A_{0.78}]$ (the effective antipsychotic concentration that maintains the fraction of blocked D2R between 65% and 78%), we have that ΔA is given by (Appendix):

$$\Delta A = 1.69 K_d. \tag{1.2}$$

Eq. (1.2) shows that ΔA presents a linear relation with K_d, i.e. a K_d ten times higher will produce a therapeutic window ten times wider. Kapur and Seeman (2000, 2001) and Seeman (2002) have reported differences on K_{off}, and therefore on K_d, as much as 1000 times between atypical and typical antipsychotics. Therefore antipsychotics with low affinity for D2R (e.g. clozapine and quetiapine) do not cause EPS clinically, i.e., their extremely wide therapeutic window for drug concentration without EPS makes it difficult to exceed 78% of striatal D2R blockade.

However, by noting that the therapeutic index is the same for all antipsychotics ($[A_{0.78}]/[A_{0.65}] = 1.9$, Appendix), one could argue that it is only a matter of providing a better dosage partition, with more gradual increases of the dose when necessary, and that the therapeutic window of drug concentration without EPS has minimal influence in differing the

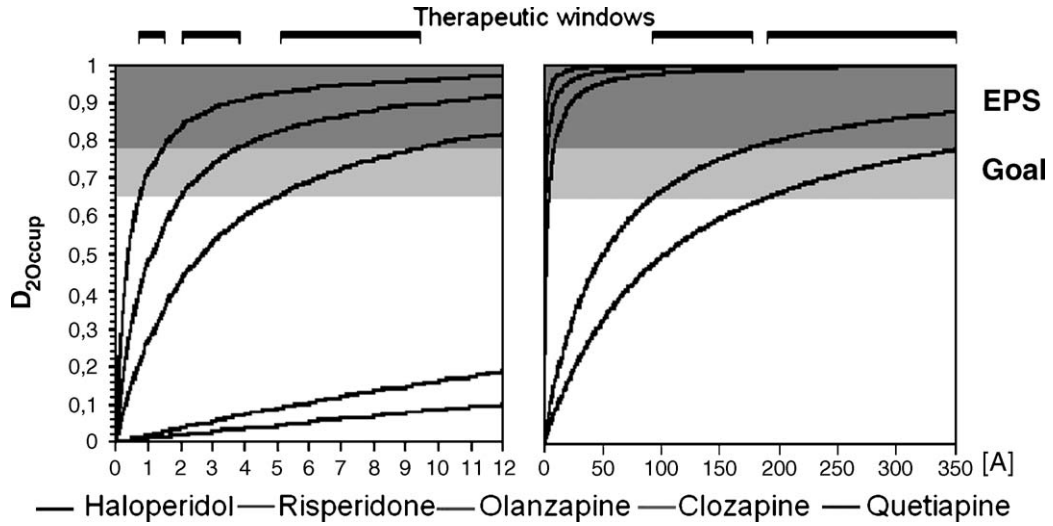

Fig. 1. Plots of D2R occupation (D_{2Occup}) vs. antipsychotic concentration ([A] (nM)) for some commonly used antipsychotics. The size of the therapeutic window without EPS of each antipsychotic is shown on top. Note that the left and right figures are the same, except for the horizontal axis scale. These simulations were performed considering haloperidol, risperidone, olanzapine, clozapine and quetiapine as having K_d values of 0.4, 1.1, 2.7, 51 and 104 nM, respectively (Seeman, 2002). It can be seen the higher the K_d, the wider the therapeutic window without EPS. Note that the [A] within therapeutic windows roughly correspond to the minimal effective dose of antipsychotic in mg/day.

antipsychotics. Indeed, every antipsychotic would have a perfect regime in which major symptoms are controlled without inducing EPS, and the therapeutic window upon rescaling can be as great as wished (i.e. a size of 1 mg/mL is a size of 1.000.000 ng/mL). Commercial and cultural aspects certainly influence this issue at least for some commonly prescribed typical antipsychotics. Accordingly, we can see that commercially available tablets of 25 mg of clozapine would correspond to a lesser change in the level of D2R blockaded than 1 mg haloperidol (Table 1 for some of these relations). Of note, risperidone presents high affinity to D2R, and even so it is sometimes considered as atypical drug. This could be explained by the effort employed in the search of its perfect dosage, compared to the mishandled use of haloperidol. Perphenazine, another typical antipsychotic, had also its adequate dose regime (i.e. control of symptoms without EPS) recently characterized (Talvik et al., 2004), resembling an atypical profile when correctly dosed. In that line, one would conclude that typical and atypical profile differences are strongly related to strategies to finding a perfect dose regime in the clinical setting.

Of clinical relevance, since the fraction between the upper and lower bound of effective dosage ($[A_{0.78}]/[A_{0.65}]$) is 1.9, once EPS is present, the model predicts that antipsychotic dosage could be halved and the level of D2R blockade should remain above 65%, which is compatible with optimal therapeutic effect.

Table 1
Minimum tablet dose of some typical and atypical commonly prescribed antipsychotics and their corresponding dose/size of the therapeutic window of drug concentration without EPS

Antipsychotic	mg	ΔA^* (nM)	mg/ΔA (mg/nM)	% of haloperidol
Haloperidol	1	0.93	1.07	100
Risperidone	1	1.86	0.54	50
Olanzapine	2.5	8.62	0.29	27
Clozapine	25	106.47	0.23	21
Quetiapine	25	206.18	0.12	11

* Calculated through Eq. (1.2). Constants values were obtained from Seeman (2002).

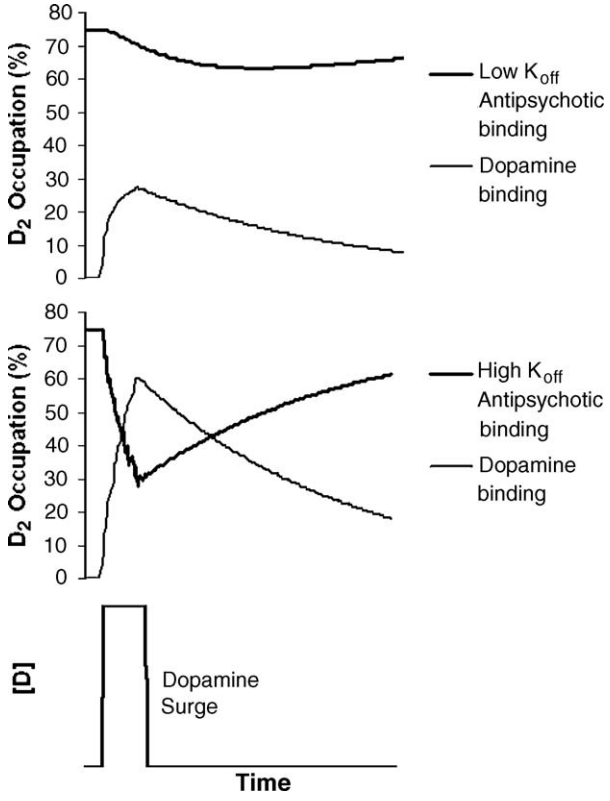

Fig. 2. Simulations of the levels of D2R blockade and dopamine binding during a surge of dopamine after the same level of blockade was obtained with a low and high K_{off} antipsychotic. The symbol [D] stands for the concentration of dopamine. It can be seen that the higher the K_{off}, the higher will be the permissiveness for dopamine binding.

Lastly, we point to another important factor previously observed by Kapur and Seeman (2000, 2001) that could also explain the differences among typical and atypical profile. They have shown that the observed difference in affinity between atypical and typical antipsychotics is mainly due to larger dissociation rate constants (K_{off}) present in atypical drugs, with little variation on the association rate constant (K_{on}) (Kapur and Seeman, 2000, 2001; Seeman, 2002). As can be seen in Fig. 2, drugs with large K_{off} lose when competing against dopamine, allowing an effect of surges of dopamine transmission, whereas drugs with low K_{off} do not allow this transmission. Based on this property, Kapur and Seeman (2001) concluded that atypical antipsychotics would produce less EPS because they would permit at least some degree of phasic striatal physiological dopamine transmission. Of note, losing in competition against surges of dopamine is a property of high K_d rather then high K_{off} per se, once low K_{on} also leads to this same feature.

Until now, we have considered that a striatal blockade between 65% and 78% of D2R is observed when effective antipsychotic action without EPS takes place. Interestingly, it was recently demonstrated that the intermittent blockade of these levels could be as effective as continuous blockade to antipsychotic effect (Kapur et al., 2000b). This will be the subject of discussion of the next section.

3. On the time-course of D2R occupancy: the chief role of plasma half-life

The time-course of the D2R occupancy associated with antipsychotic therapy became an important issue in the treatment of schizophrenia. The presumed notion of the necessity of continuous D2R blockade to achieve control of symptoms was questioned by recent findings showing that transiently high D2R occupancy is sufficient for obtaining and maintaining antipsychotic effect, even in neuroleptic-naïve schizophrenic patients (Kapur et al., 2000b; Tauscher-Wisniewski et al., 2002). Next, we will show that the plasma half-life of an antipsychotic presents a leading role in the time-course of D2R occupancy.

As a first approximation, we can think that plasma levels of an antipsychotic are related to the levels of the available drug concentration at the synaptic cleft. There is also an equation to describe D2R occupancy very related to Eq. (1.1) based on peripheral parameters, which is given by:

$$D_{2Occup}(t) = \frac{100 \times C(t)}{ED50 + C(t)} \tag{2.1}$$

Note the similarity between Eqs. (2.1) and (1.1). With Eq. (2.1), we have only transferred our attention to plasma pharmacokinetics, instead of local synaptic events. In that line, the plasma concentration ($C(t)$) is equivalent to the concentration of the drug [A] at the synaptic cleft, whereas ED50, the drug plasma concentration able to block 50% of D2R, is equivalent to K_d. Moreover, note that from the Eq. (2.1), once we know at a given time the plasma concentration of the drug and the level of receptor occupancy achieved, we can determine the values of ED50, given by:

$$ED50 = \frac{(100 - D_{2Occup})C(t)}{D_{2Occup}} \tag{2.2}$$

And, in most studies, $C(t)$ is fitted as (Tauscher et al., 2002; Takano et al., 2004):

$$C(t) = me^{-bt} \tag{2.3}$$

where m is the plasma maximal concentration at 0 h, b is a constant dependent on the plasma half-life ($t_{1/2}$) of the drug (in fact, $b = \ln 2 / t_{1/2}$), and t is the time after the drug administration.

An important point that is often misleading in PET studies regards the time-course of D2R occupancy, namely the half-life concept. Classically, a function like Eq. (2.3) does have a property of presenting a half-life, which is defined as the time necessary for the plasma concentration to be reduced by 50%. In these cases, $t_{1/2}$ will be always given by $\ln 2 / b$, and this result is independent of the initial concentration being handled (Appendix), i.e. the time necessary for risperidone to drop from 6 to 3 ng/mL is the same as to drop from 3 to 1.5 ng/mL and so on (see Table 2). Inadequately, the same definition is also commonly employed to D2R occupancy (Gefvert et al., 1998; Tauscher et al., 2002; Takano et al., 2004). The point is that an equation like Eq. (2.1) does not present the same property, once the time required for the occupancy levels to be halved are dependent on the initial level being handled (Table 2), and the same is valid even if Eq. (2.1) is approximated by a linear polynomial, as is often the case (Gefvert et al., 1998; Tauscher et al., 2002; Takano et al., 2004). Moreover, starting from a D2R occupancy obtained from a given concentration $C(t_0)$, the time necessary to reach half of receptor occupancy ($T_{1/2}$) is given by (Appendix):

$$T_{1/2} = \frac{t_{1/2}}{\ln 2} \ln\left(\frac{C(t_0)}{ED50} + 2\right) \tag{2.4}$$

Therefore, as previously commented, $T_{1/2}$, differently from $t_{1/2}$, is dependent on the concentration of the drug (non-linearly) and will be higher if the concentration is higher and vice versa. Moreover, note also that $T_{1/2}$ is always greater

Table 2
Central and peripheral half-lives of risperidone

Time (h)	$C(t)$ (ng/mL)	D_{2Occup} (%)	$t_{1/2}$ (h)	$T_{1/2}$ (h)
0	45.0	87.6	19	60
19	22.5	77.8	19	47
38	11.2	63.7	19	36
57	5.6	46.8	19	29
60	5.0	43.8	19	28
66	4.0	38.9	19	27
74	3.0	31.8	19	25
76	2.8	30.5	19	24
86	2.0	23.4	19	23

Simulations performed using Eqs. (2.3) and (2.1) for calculations of $C(t)$ and D_{2Occup} respectively. We used $b = 0.036$, $m = 45.0$, ED50 = 6.4 ng/ml (Takano et al., 2004).

than $t_{1/2}$, and, curiously, $T_{1/2}$ approaches $t_{1/2}$ when the initial drug concentration becomes small (i.e., $T_{1/2} \rightarrow t_{1/2}$ if $C(t_0) \rightarrow 0$). Eq. (2.4) nevertheless gives a false impression that $T_{1/2}$ is dependent on the affinity of the drug, once the factor ED50 appears. This is certainly not the case, since antipsychotics with less affinity (high ED50) will also be required at higher concentrations to achieve the same level of D2R blockade. If we define $T_{1/2}$ as being the time necessary for a given fixed fraction (F) of D2R occupancy to drop to half ($F/2$), then we can find $T_{1/2}$ as a function of F (Appendix):

$$T_{1/2}(F) = \frac{t_{1/2}}{\ln 2} \ln\left(\frac{F}{100 - F} + 2\right) \quad (2.5)$$

In the particular case of defining $T_{1/2}$ as being the time for D2R occupancy to drop from 80% to 40% (i.e., $F = 80$), we have that $T_{1/2} = (t_{1/2}/\ln 2) \times \ln 6 = 2.6 t_{1/2}$. Eq. (2.5) shows that the higher the initial fraction of blocked receptors ($F = D_{2\text{Occup}}(t_0)$) considered, the higher the $T_{1/2}$ obtained (Fig. 3). As an illustrative example, in the work of Gefvert et al. (1998) they concluded that quetiapine presented lower $T_{1/2}$ for D2R then for 5HT2, but it should be remembered that quetiapine has higher affinity to 5HT2 receptors than to D2R, presenting therefore higher occupancy levels of this receptor than of D2R at the same plasma concentration, which was a confounding factor (Figs. 3 and 4). Moreover, Eq. (2.5) shows that once the initial occupancy fraction F is fixed, the half-life of the receptor occupancy is solely determined by the half-life of the drug plasma concentration, and in particular it is not dependent on its affinity. Which means, once the same

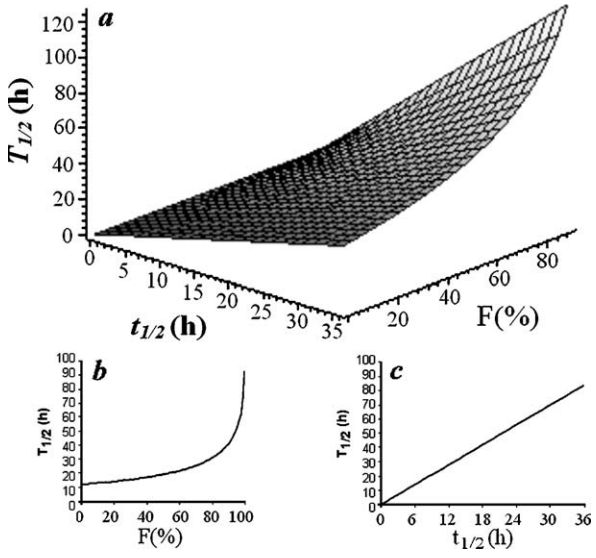

Fig. 3. (a) Plot of the "half-life" of D2R occupancy ($T_{1/2}$) as a function of the initial fraction of D2R receptors blocked (F) and of the plasma half-life of the antipsychotic ($t_{1/2}$); we have plotted $T_{1/2}$ for values of F up to 80% in order to keep clarity (above this, $T_{1/2}$ grows very fast, reaching very high values, as shown in (b)). Note that the higher $t_{1/2}$ or F, the higher is $T_{1/2}$, and this dependence is non-linear on F and linear on $t_{1/2}$, as shown in (b) and (c) respectively. These plots were performed using Eq. (2.5); in (b) we fixed $t_{1/2} = 12$ h and in (c) we fixed $F = 75\%$.

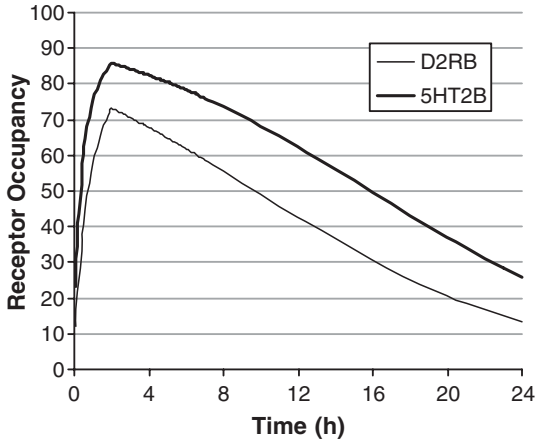

Fig. 4. Simulation of blockade of dopamine D2R and serotonine 5HT2 receptors obtained for quetiapine (continuous lines). We have used Eq. (2.3) for plasma concentrations after drug peak (and a linear polynomial until this) and Eq. (2.1) for receptor occupancy. We considered plasma half-life ($t_{1/2}$) of quetiapine as 5.3 h, ED50 for D2R of 550 ng/mL and for 5HT2 receptors of 247 (since quetiapine present a ratio of affinity between D2R/5HT2 of 1:2.22). Considering the time that the receptor occupancy takes between the peak and half of this value as the half-life of receptor occupancy ($T_{1/2}$), then quetiapine would present higher $T_{1/2}$ for 5HT2 than to D2R. However, if we define $T_{1/2}$ as being the time to decrease a fixed occupancy interval, e.g., the time to drop from 80% to 40%, than $T_{1/2}$ is the same for both receptors.

levels of receptors blockade are achieved with distinct antipsychotics, if they present the same plasma half-life, they will have the same time-course of decrease in occupancy, independently of their affinity (Fig. 4). Of note, as cited above, in a work questioning the need or not of continuous D2R blockade to achieve control of symptoms in schizophrenia, Kapur et al. (2000b) have recently shown only transiently high D2R occupation by quetiapine given once daily. In the same way, the transient blockade observed by Kapur et al. (2000b) was due to the short half-life of quetiapine (5.3 h), and not by its known low affinity to D2R (or large ED50).

4. Discussion

With all these ideas in mind, we can turn back to the discussion of what renders an atypical profile for an antipsychotic. If the transiently high D2R blockade is really proved to be sufficient to achieve control of symptoms, and based on the results presented above, we can thus postulate that an ideal antipsychotic would be the one presenting a short half-life. We can even question the results obtained in the first section of this paper attributing the atypical profile of quetiapine to its wide therapeutic window of drug concentration without EPS in favor of its short half-life. Analogously, the same question could apply for clozapine, which is known for its low D2R occupancy levels (at the time of scan), and presents a 12 h plasma half-life (compared to 24 h for haloperidol, 19 h for risperidone, 24 h for chlorpromazine and 30 h for olanzapine).

Moreover, generally speaking, one can also suppose that it does not matter if small levels above the threshold for EPS are reached after an administration of a short plasma half-life

antipsychotic, meaning that the half-life would be more important than the affinity. In fact, motor side effects would also be transient and bedtime administration would minimize the chance of experiencing EPS.

Based on the concepts above, what one can conclude as being really necessary to a D2R antagonist have an atypical profile? To present a lower affinity and therefore large therapeutic window of drug concentration without EPS? To possess an adequate dose regime? To present high K_{off} and therefore permit the effect of surges of dopamine? To present a short plasma half-life? Most probably, all these factors contribute, and they should be taken into account to the design of new atypical antipsychotics, not to mention other recent strategies, such as partial agonist activity in the case of aripiprazole.

5. Limitations

It is worth pointing that our work is focused on the central role of D2R, which we are assuming to be the key target for antipsychotic therapy. However, it is still a matter of debate to involve or not other neurotransmitters systems in the treatment of psychosis or schizophrenia. Also, different affinities for D2 long and short receptors can play an important role. Moreover, this theory does not address why clozapine can effectively treat refractory patients, which probably involves actions unrelated to D2R blockade. Of note, we have focused on D2R and antipsychotics, but clearly several results are valid for any receptor and ligand, as long as the steady state of occupancy is reached in a time scale shorter (i.e. seconds, minutes) than the time scale of the drug metabolism (i.e. hours, days).

Several factors may also account for the discrepancies between the theoretical results presented here and real data, such as the effects of the metabolites of a given antipsychotic. It is often the case that metabolites of an antipsychotic are also D2R antagonists and present different plasma half-lives. Therefore, when not taking into account the influence of these metabolites, the simulations will underestimate the real level of D2R occupancy.

Another important factor is the pharmacokinetics profile of an antipsychotic in the central nervous system, which in the present model was considered to be the same as in plasma. Other confounding factors are the variations associated to the plasma determinations of antipsychotics and to the measurement of D2R occupancy, since the latter could vary in about ±10% depending on the study (Takano et al., 2004), and also the influence of up-regulation of D2R presented in patients already medicated with antipsychotics (Silvestri et al., 2000). Moreover, it must be considered that the data defining the 65–78% D2R blockade as effective without EPS is based on few studies with a limited number of patients.

Lastly, it is worth pointing that these derivations are based on a mathematical model, which, as every model, is an approximation of the reality and presents limitations. Particularly, this mathematical model is based on derivations from the law of mass action and on the fitting of drug blood concentrations from an equation like Eq. (2.3). The law of mass action presents some assumptions (Appendix) that are known not to be valid in some cases, as well as the fitting of peripheral concentrations by an exponential function is also not always accurate (especially at low or high concentrations). Finally, given the variable levels of D2R blockade that can be achieved with similar doses of antipsychotic in distinct patients, the results presented in this work should be regarded as referring to the average behavior.

6. Conclusion

The present work linked known PET experimental data to the theory of receptor binding and drug pharmacokinetics and could provide some insights to the understanding of the atypical profile presented by some antipsychotics. Although many of the insights presented here are subject to several limitations, we believe that research on this theoretical field together with experimental work will help to improve the models and consequently provide deeper knowledge to the understanding of the mechanism of antipsychotic action.

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Appendix A

A.1. Proof of Eq. (1.1)

From the law of mass action applied to receptor binding, we have that the ratio of $[AD_2]$ formation per unit of time ($d[AD_2]/dt$) is given by

$$\frac{d[\mathrm{AD}_2]}{dt} = K_{on}[A][D_2] - K_{off}[\mathrm{AD}_2] \tag{1}$$

We now create a new variable, called D_{2Occup}, which represents the fraction of blocked D2R from all D2R (free and bound), so D_{2Occup} is given by

$$D_{2\mathrm{Occup}} = \frac{[\mathrm{AD}_2]}{[D_2] + [\mathrm{AD}_2]} \tag{2}$$

By the assumption that the number of D2R, even if up-regulated by antipsychotic treatment, reaches a constant level (i.e., $[D_2]+[AD_2]=C$), and by noting that $1-D_{2Occup}=[D_2]/([D_2]+[AD_2])$, we can use Eq. (2) in Eq. (1) to arrive at the following ordinary differential equation for D_{2Occup}

$$\frac{dD_{2\mathrm{Occup}}}{dt} = K_{on}[A]\left(1 - D_{2\mathrm{Occup}}\right) - K_{off}D_{2\mathrm{Occup}} \tag{3}$$

If we now consider the steady state, where the equilibrium between bound and free D2R is reached (i.e. equal association

and dissociation rates, meaning that $dD_{2Occup}/dt=0$), we have the following equation for D_{2Occup}

$$D_{2Occup} = \frac{K_{on}[A]}{K_{on}[A] + K_{off}} \tag{4}$$

which gives rise to Eq. (1.1).

A.2. Proof of Eq. (1.2)

If we isolate $[A]$ in the Eq. (4), and using the index D_{2Occup} to denote the dependence on D_{2Occup}, we get

$$\left[A_{D_{2Occup}}\right] = \frac{K_{off} D_{2Occup}}{K_{on}\left(1 - D_{2Occup}\right)} \tag{5}$$

We can now define the size of the therapeutic window without EPS, denoted by ΔA, as being the magnitude of the dose range between $[A_{0.65}]$ and $[A_{0.78}]$ (the effective amount of antipsychotic that maintains the fraction of blocked D2R between 65% and 78%), thus ΔA is given by

$$\Delta A = [A_{0.78}] - [A_{0.65}] \tag{6}$$

Upon simple calculation, using Eq. (5) in Eq. (6), we get ΔA as function of K_{off} and K_{on}

$$\Delta A = \frac{K_{off} 0.78}{K_{on}(1 - 0.78)} - \frac{K_{off} 0.65}{K_{on}(1 - 0.65)} = 1.69 \frac{K_{off}}{K_{on}} \tag{7}$$

which is Eq. (1.2).

A.3. Proof of the constant value of the therapeutic index among distinct antipsychotics

Using Eq. (5) and the definition of $[A_{0.65}]$ and $[A_{0.78}]$, we calculate the therapeutic index, which is the fraction between the upper and lower bound of effective dosage without EPS ($[A_{0.78}]/[A_{0.65}]$), getting

$$\frac{[A_{0.78}]}{[A_{0.65}]} = \frac{K_d 0.78}{1 - 0.78} \cdot \frac{1 - 0.65}{K_d 0.65} = 1.9 \tag{8}$$

as stated.

A.4. Proof of the existence of the half-life concept for an exponential function

Suppose that at a given time t_0 we have a certain concentration $C(t_0)$ of drug in the plasma. We are asking how long it takes for the concentration to reach half of this initial value. Mathematically speaking, we are searching a time $t_{1/2}$ such that at time $t_0+t_{1/2}$ we will have

$$C\left(t_0 + t_{1/2}\right) = \frac{C(t_0)}{2} \tag{9}$$

By using Eq. (2.3) in Eq. (9) we get to:

$$me^{-b\left(t_0 + t_{1/2}\right)} = \frac{me^{-bt_0}}{2} \tag{10}$$

After some algebra, Eq. (10) becomes:

$$t_{1/2} = \frac{\ln 2}{b} \tag{10}$$

Hence the plasma half-life of a given antipsychotic is a constant, and therefore independent of the initial level of drug concentration being handled, as stated.

A.5. Proof of Eq. (2.4)

Suppose that at a given time t_0 we have a certain level of D2R blockade given by $D_{2Occup}(t_0)$. We are asking how long it takes for the fraction of blocked receptors to reach half of this initial value. Mathematically speaking, we are searching a time $T_{1/2}$ such that at time $t_0+T_{1/2}$ we will have

$$D_{2Occup}\left(t_0 + T_{1/2}\right) = \frac{D_{2Occup}(t_0)}{2} \tag{12}$$

By using Eq. (2.1) in (12) we get to:

$$\frac{100 \times C\left(t_0 + T_{1/2}\right)}{ED50 + C\left(t_0 + T_{1/2}\right)} = \frac{50 \times C(t_0)}{ED50 + C(t_0)} \tag{13}$$

We now substitute Eq. (2.3) in Eq. (13), arriving at:

$$\frac{100 \times me^{-b\left(t_0 + T_{1/2}\right)}}{ED50 + me^{-b\left(t_0 + T_{1/2}\right)}} = \frac{50 \times me^{-b(t_0)}}{ED50 + me^{-b(t_0)}} \tag{14}$$

With a little algebra, Eq. (14) becomes:

$$T_{1/2} = \frac{1}{b} \ln\left(\frac{me^{-bt_0}}{ED50} + 2\right) \tag{15}$$

which is Eq. (2.4).

A.6. Proof of Eq. (2.5)

We are now fixing a given initial fraction of D2R blocked denoted as F. We ask for the time necessary to reach half of this value ($F/2$). We proceed exactly as the proof above to get Eq. (15). Now we note that Eq. (2.2), with a change of notation, can be rearranged as:

$$\frac{C(t_0)}{ED50} = \frac{F}{(100 - F)} \tag{16}$$

Substituting Eq. (16) into Eq. (2.4), we get the desired result. Hence the time required to reach half of values is dependent on the initial value being handled, and the concept of "half-life" is therefore incorrectly employed in this case.

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