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FULL PAPER

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Interaction of graphene with antipsychotic drugs: Is there any charge transfer process?

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Abstract

Antipsychotics represent an effective therapy for schizophrenia (a chronic mental disorder). Their benefits are related to the interaction of the drugs with dopamine D2 receptor (D2R). Antipsychotics are classified as agonists or antagonists. One of the working hypotheses is that there is a charge transfer process between the drugs and the receptors, which is different for agonists and antagonists. To have more insight into the nature of the interaction of these molecules and the differences between agonists and antagonists, we analyze the interaction of graphene with three molecules: dopamine, pramipexole (an agonist of dopamine), and risperidone (an antagonist of dopamine). The idea is to use graphene as a simple model to analyze the charge transfer process of these three drugs. Optimized structures, atomic charges, and Density of States results indicate that global charges of dopamine and pramipexole are similar, while for risperidone, it is more than double. Pramipexole is an agonist, and the charge transfer process is similar to that of dopamine. Risperidone is an antagonist, and the charge transfer process is different from dopamine. The charge transfer is more significant with risperidone than with dopamine, and this could be related to the mechanism of action. This is in agreement with the working hypotheses that establish that it is possible to distinguish between agonists and antagonists since they have different capacity to transfer charge.

KEYWORDS

agonists, antagonists, dopamine, psychosis, schizophrenia

1 | INTRODUCTION

Schizophrenia is a chronic mental disorder affecting 1 % of the global population.[1,2] Individuals with schizophrenia may have positive symptoms such as hallucinations, delusions, and conceptual disorganization. These positive symptoms are associated with an excess of dopamine in the mesolimbic dopamine pathway. Other symptoms, named negative symptoms, are associated with cognitive deficits and they are maybe caused by hypo- dopaminergic activity in the mesocortical pathway.[3–8] Antipsychotics represent an effective therapy for schizophrenia. Their benefits are related to the interaction of the drugs with dopamine D2 receptor (D2R). These drugs are classified as agonists or antagonists. Agonists are indicated to reduce the negative symptoms while antagonists have been demonstrated clinical efficacy in the reduction of positive symptoms.[9]

Graphene is a watershed in material science that is also important in other areas of knowledge. It has unique electrical responses that make this material perfect to design electrodes, electronic devices, and sensors.[10–13] For biological applications, graphene is used as a biosensor for the detection of several biomolecules, such as DNA, ascorbic acid, uric acid, and dopamine (including its agonists and antagonists).[14–20] Voltammetry sensor for the detection of clonazepam,[17] dendritic nanostructures supported by graphene to distinguish diazepam[18] and graphene-Au for detection of dopamine and serotonin[19] are some examples of graphene-biosensors. All these applications are possible due to low reactivity and high conductivity

of graphene.[21–23] From previous studies done with graphene and transition metals, it is known that graphene transfers charge, making it the ideal candidate to analyze the behavior of organic molecules. Besides, these studies provide a robust methodology to use graphene to analyze the load transfer efficiently.[24,25]

Agonists and antagonists of dopamine D2 and D3 receptors (D2R and D3R) are used to treat Parkinson, depression, and schizophrenia.[26–31] These drugs have different behavior and are used for different purposes. Briefly, it can be said that antagonists of dopamine are molecules that interact but do not activate the receptor while agonists are those that bind and activate the receptor, as dopamine does. One of the working hypotheses is that there is a charge transfer process between the drugs and the receptors, which is different for agonists and antagonists.[32–34] There is also a physical model wherein a membrane is used to detect modifications on the electrical potential due to the presence of these drugs. The membrane noise produced by a polarizing drug is interpreted as a change in the electrical potential of the system.[35–37]

Despite all these investigations, little is known about the charge transfer mechanism on antipsychotics and its relation to the action mechanism. In order to have more insight into the nature of the interaction of these molecules and possible differences between agonists and antagonists, in this study, we analyze the interaction of graphene with three molecules: dopamine, pramipexole (an agonist of dopamine), and risperidone (an antagonist of dopamine). The idea is to use graphene as a simple model that can be used to analyze the charge transfer process of these three drugs.

2 | METHODS

Figure 1 reports a schematic representation of the molecules under study. These molecules are placed at 2.5 Å approximately on the pristine graphene supercell of 10 × 10. Three initial geometries with the molecules located at different positions and orientations are used. The initial structures are top-site (interacting with C atom), bridge-site (interacting with the C—C bond), and hollow-site (in the middle of one hexagonal ring). Quantum Espresso computational package[38] is used for all calculations with the Perdew-Burke-Ernzerhof exchange-correlation approximation.[39] Empirical dispersion correction with Grimme's method (D3-BJ) is incorporated.[40,41] From previous work, it is known that PBE-BJ is the appropriate methodology in terms of having more accurate results and less computation time.[25,42] The total energy is calculated as:

$$E_{\mathrm{PBE-D}} = E_{\mathrm{PBE}} + E_{\mathrm{disp}}, \quad (1)$$

in which $E_{\mathrm{PBE\text{-}D}}$ is the total energy calculated with the PBE functional and the dispersion correction, E_{PBE} is the total energy with the PBE functional only, and E_{disp} is the energy of the considering the dispersion correction.

The kinetic energy cut-off is equal to 40 Ry (around 544 eV). The pseudopotentials are PAW type. The details of the computational calculations are described in the Supporting Information. The adsorption energies E_{ads} are calculated as follows:

$$E_{\mathrm{ads}} = \left[E_{\mathrm{graphene-molecule}}\right] - \left[E_{\mathrm{graphene}} + E_{\mathrm{molecule}}\right] \quad (2)$$

$E_{\mathrm{graphene\text{-}molecule}}$ is the energy of the organic molecule adsorbed in the graphene surface; E_{graphene} is the energy of the pristine graphene, and E_{molecule} is the energy of the isolated molecule. Charge analysis is obtained with the Lödwin charge model.[43] The Density of States (DOS) and the Partial Density of States (PDOS) are also reported. PDOS indicates the orbital contribution of each atom to the total DOS.

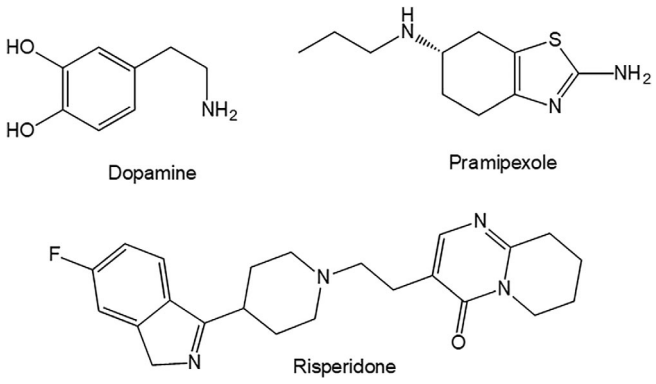

FIGURE 1 Schematic representation of molecules under study: dopamine, pramipexole (agonist), and risperidone (antagonist)

3 | RESULTS

Optimized structures of the systems under study are reported in Figure 2. These are the most stable structures. The shortest bond distances for each system are also included. The bond length between graphene and pramipexole is shorter than with the other molecules, being the largest for the graphene dopamine system. The optimized structure with dopamine locates the molecule parallel to graphene. Pramipexole is situated perpendicular to graphene, and some atoms of risperidone are parallel to graphene, but there are others in a perpendicular position.

It is important to note that dopamine is interacting with graphene through all the atoms of the ring, while the interaction of pramipexole is with the sulfur atom and with hydrogen atoms. Risperidone is a larger molecule and presents both interactions: with the atoms of the ring that is parallel to graphene and with hydrogen atoms. In this molecule, nitrogen atoms are also participating. This may influence the adsorption energies.

The adsorption energies of the three compounds are reported in Table 1. Dopamine and risperidone present similar adsorption energies, while pramipexole presents the smallest values. The explanation may be that, as explained previously, pramipexole is interacting through sulfur and hydrogen atoms while dopamine, and risperidone interacts with the atoms of the ring and other atoms. With these

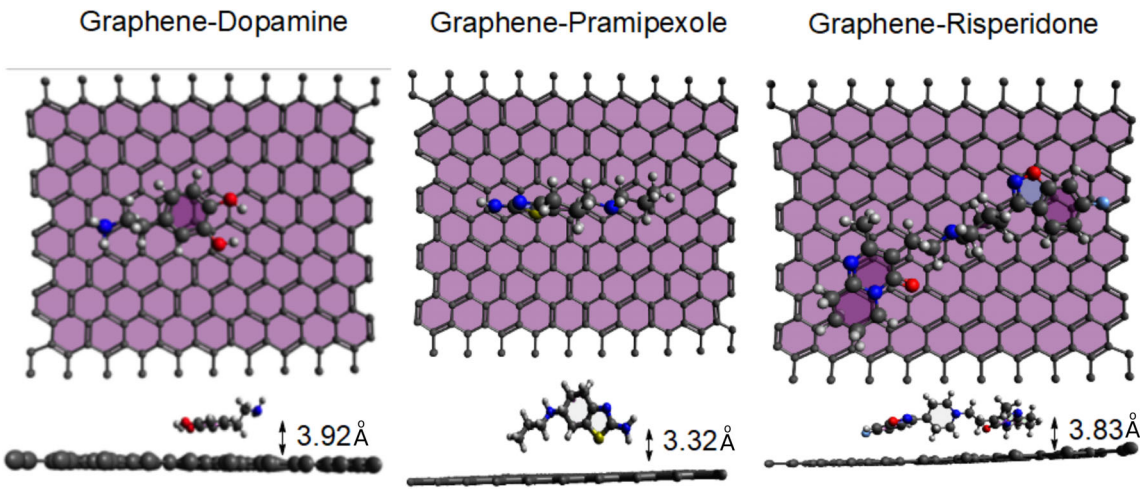

FIGURE 2 Optimized structures of dopamine, pramipexole, and risperidone with graphene. The shortest bond distance is included [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Adsorption energies of the ground-state configurations and global charges (Q) are reported

Adsorbed molecule	Adsorption energy (eV)	Q (C)
Dopamine	−1.84	0.5
Pramipexole	−0.64	0.3
Risperidone	−1.84	1.2

results, it is possible to say that dopamine and risperidone are equally adsorbed on graphene, but the adsorption of pramipexole is weaker than the others.

Figure 3 reports atomic charges (Lödwin) for the three systems. The atomic charge of graphene's carbon atoms that are close to the molecules is negative, indicating that, at a local level, graphene is accepting electrons from the molecules. For dopamine, the shortest bond distance is with one O atom of dopamine that presents an atomic charge equal to −0.35. The interaction of pramipexole with graphene is through the sulfur atom that presents an atomic charge equal to 0.39. The shortest distance between risperidone and graphene corresponds to the interaction with one nitrogen atom of risperidone that has an atomic charge of −0.11. In summary, dopamine and risperidone are linked to graphene through negative atoms, while pramipexole is interacting with a positive atom.

The global charge of the molecules is reported in Table 1. Graphene presents excellent charge transfer properties, and it can be expected a charge transfer process with the molecules that are adsorbed. The electron affinity of graphene is 3.22 eV (calculated at the same level of theory). Analyzing the atomic charges of the graphene's atoms that are close to the molecules, as we have already said, there is a charge transfer process from the molecules to the graphene. This is also consistent with the global charge of the adsorbed molecules, which is positive. The global charges of

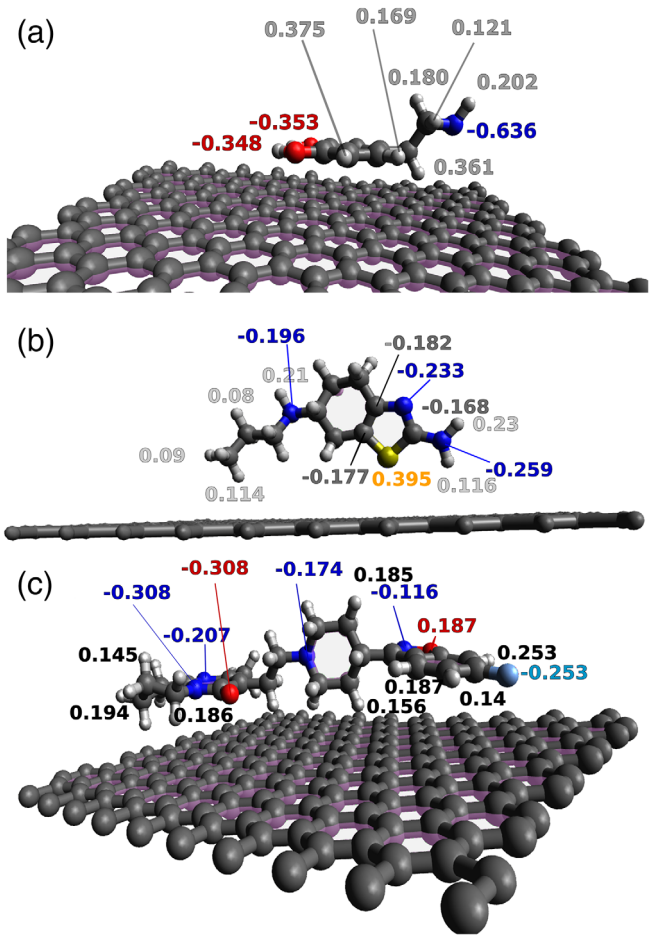

FIGURE 3 Selected atomic charges (Lödwin) of dopamine, pramipexole, and risperidone interacting with graphene are reported. Atomic charges of the hydrogen atoms are in gray. (a) Graphene-dopamine, (b) graphene-pramipexole, and (c) graphene-risperidone [Color figure can be viewed at wileyonlinelibrary.com]

dopamine and pramipexole are similar, while for risperidone, it is more than double. This is in accord with the working hypotheses that establish that it is possible to distinguish between agonists and antagonists since they have different capacity to transfer charge. Agonists are similar to dopamine while antagonists are different. The data of Table 1 corroborates this hypothesis. Pramipexole is an agonist, and the charge transfer process is similar to that of dopamine. Risperidone is an antagonist, and the charge transfer process is different from dopamine. The charge transfer is more significant with risperidone than with dopamine, and this could be related to the mechanism of action.

TABLE 2 EF values of absorbed molecules in graphene and the difference between Dirac point (DP) and EF

System	EF (eV)	DP-EF (eV)
Graphene	−1.72 (DP)	—
Graphene-Dopamine	−1.59	−0.13
Graphene-Pramipexole	−1.34	−0.38
Graphene-Risperidone	−0.99	−0.73

The electronic chemical potential is useful for the analysis of the charge transfer process. At zero temperature, it is possible to identify the chemical potential with the Fermi level (EF) of a solid. When two systems are interacting (graphene and molecule, in this case), there will be an electronic flow from the system with the highest electronic

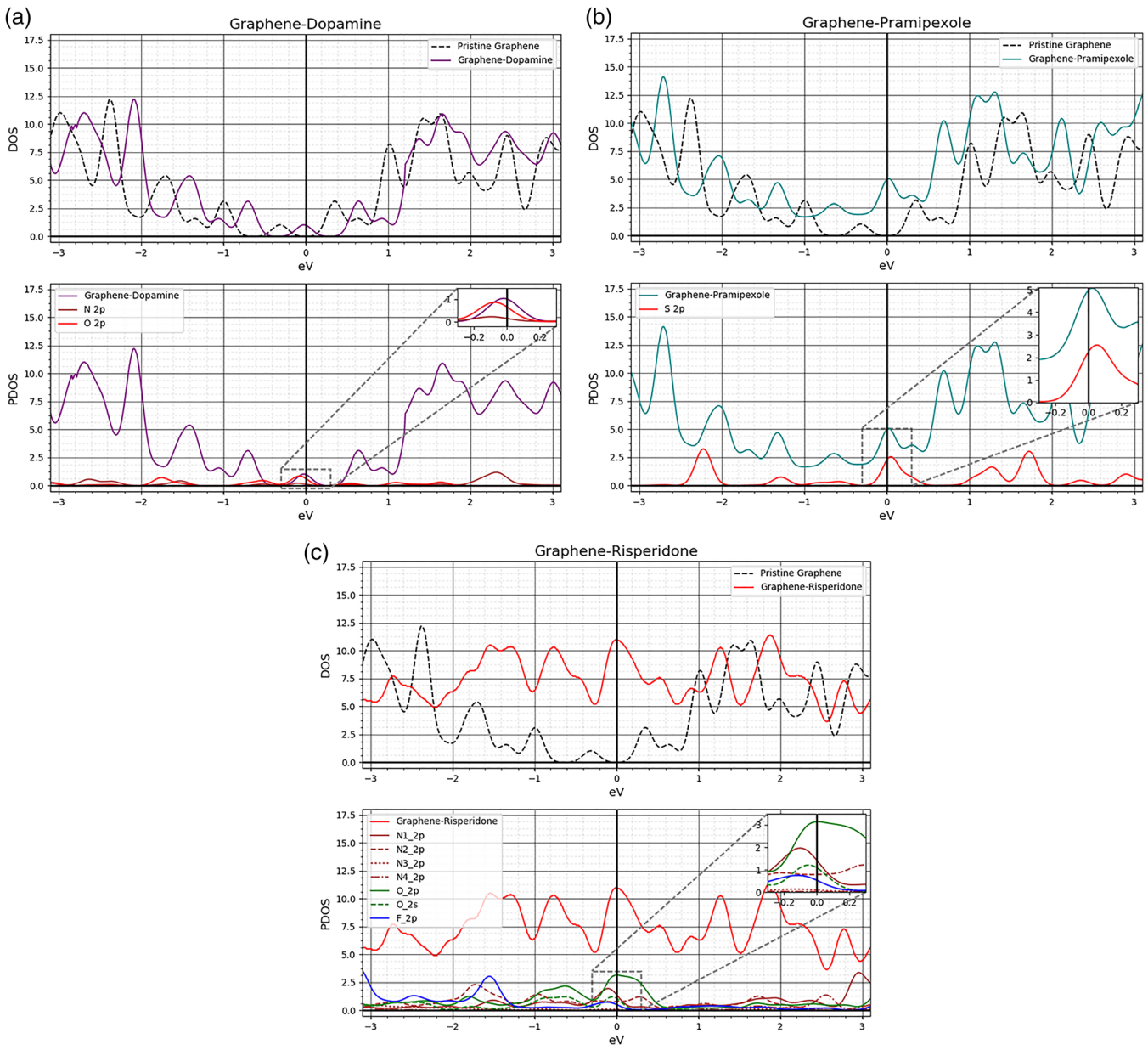

FIGURE 4 The total and partial density of states (a) Dopamine, (b) Pramipexole, and (c) Risperidone adsorbed on graphene on the most stable configuration. Units are states/eV [Color figure can be viewed at wileyonlinelibrary.com]

chemical potential to the system with the lowest. We used the EF to analyze this electron transfer, EF values for the systems under study are reported in Table 2. For pristine graphene, we identify EF as the Dirac Point (DP) since the conduction and the valence band coincide at a single point. The DP of pristine graphene (10 × 10 supercell) is located at 1.72 eV.

According to the EF, we can classify these materials as *n*-type or *p*-type doping semiconductors. The difference between DP of pristine graphene and EF of graphene with the adsorbed molecule allows this classification. When DP values are smaller than EF, there is *n*-type doping, and the adsorbed molecule donates electrons to graphene. Therefore, graphene is negatively doping. On the contrary, when the values are higher for the system with the molecule adsorbed (EF) than for pristine graphene (DP), then the system is *p*-type doping, and this indicates that graphene is positive doping. If this were the case, there is an electron transfer from graphene to the adsorbed molecule. Analyzing the results of Table 2, it is possible to say that EF is higher than DP for the three systems. This result indicates a charge transfer process from the molecules to carbon atoms of graphene, which agrees with the charge transfer analysis discussed previously. The charge transfer is larger for risperidone than for the other two molecules. This is in agreement with the working hypothesis.

Risperidone is an antagonist of dopamine, and its charge transfer process is different. Pramipexole is an agonist, and the charge transfer is similar to the charge transfer process of dopamine.

The DOS of the molecules for pristine graphene and graphene with adsorbed molecules are reported in Figure 4. EF is located at zero value for a better reference. For the graphene-dopamine system (Figure 4a), it is possible to observe that there are available states nearby the EF, but the main contribution is from dopamine. The occupied and unoccupied regions close to the EF are signals with high symmetry, indicating that there are π states of the carbon atoms. The difference between the DOS of pristine graphene and DOS of graphene-dopamine shows that the molecule is chemisorbed. With the PDOS, it is possible to determine the orbital contribution of each atom to the total DOS and to identify the atoms of the dopamine that contribute to the adsorption phenomenon. We noticed that the contribution of dopamine is due to the 2p electrons mainly associated with the oxygen atom (red curve) that is more intense at zero than those corresponding to nitrogen (brown curve).

The DOS of the graphene-pramipexole system is presented in Figure 4b. The adsorption energy is smaller than the corresponding values for dopamine and risperidone. The DOS of pramipexole adsorbed in graphene is similar to that for the pristine graphene, but the difference in the number of states is more significant nearby EF. There is also a contribution of π states of the carbon atoms. From the PDOS, it is possible to see that the main contribution at EF is from the sulfur 2p electrons.

The DOS of the graphene-risperidone system (Figure 4c) is different from the DOS of pristine graphene, specifically in the vicinity of EF. This is because different atoms of risperidone molecule interact with graphene. PDOS indicates that the atoms with more contribution to the adsorption phenomenon are oxygen and nitrogen located at the hexagonal ring. The oxygen contributes to more states (2p and 2s) at EF (see green lines).

From DOS, it is possible to say that both pramipexole and risperidone have a higher distribution of allowed states near EF than dopamine. Pramipexole has a stronger interaction between sulfur and graphene surface, and the distance is shorter than the one presented by the other two molecules (3.32 Å). This explains the more significant population of allowed states. Risperidone presents the highest distribution of states near EF. This might be due to the contribution of aromatic ring atoms of risperidone interacting with graphene. This also agrees with the charge transfer that is higher for risperidone than for the other two molecules. The different interactions are also reflected in EF shifts for pramipexole and risperidone, which are higher than the one showed for dopamine.

4 | CONCLUSIONS

Most stable optimized structures indicate that dopamine is interacting with graphene through all the atoms of the ring, while the interaction of pramipexole is with sulfur atom and with hydrogen atoms. Risperidone is a larger molecule and presents both interactions: with the atoms of the ring that is parallel to graphene and with hydrogen atoms. This affects the adsorption energies, which is smaller for pramipexole than for the other two molecules.

Atomic charges and Density of States indicate that global charges of dopamine and pramipexole are similar, while for risperidone, it is more than double. Pramipexole is an agonist, and the charge transfer process is similar to that of dopamine. Risperidone is an antagonist, and the charge transfer process is different from dopamine. The charge transfer is more significant with risperidone than with dopamine, and this could be related to the mechanism of action. The results of this research allow us to corroborate the working hypotheses, which establish that there is a process of charge transfer between drugs and receptors, which is different for agonists than for antagonists.

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