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Chairs, bells and students - a novel method to simulate and teach molecular interactions in pharmacology

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Abstract

Background: Pharmacy education requires an understanding of the fundamental principles of molecular pharmacology. Among these, abstract concepts such as affinity, association and dissociation rates and partial agonism may be difficult to demonstrate to students.

Aims: We wished to devise a method to simulate drug-receptor interactions that could readily be used in teaching sessions and that would promote student engagement.

Methods: A role play was carried out in which drugs (represented by students) associate with receptors (represented by chairs) and cause signal transduction (represented by a bell ringing). By varying the parameters associated with the role play (e.g. time taken to sit in the chair and how often the bell is rung) fundamental principles of drug-receptor interactions could be modelled.

Results: The simulation was considered by the students to improve their understanding of the intended learning outcomes.

Conclusion: This simulation offers a method to introduce students to drug-receptor interactions in a manner that promotes their engagement.

Keywords: *agonist, antagonist, kinetics, receptor, simulation*

Introduction

An understanding of the distinction between agonists, antagonists, partial agonists and inverse agonists is fundamental to the study of pharmacology. The ways in which drug kinetics and drug concentration influence receptor occupancy are also often introduced at an early stage in the study of pharmacology. Although some concepts may be considered straightforward, others are more challenging. For example: understanding why a receptor may not be fully occupied by a drug, even if the number of drug molecules far exceeds the number of receptors; understanding why a partial agonist can activate a receptor yet it may antagonise the effects of a full agonist. We wished to identify a method to facilitate the introduction of this material to students studying pharmacology within the context of a United Kingdom (UK) pharmacy degree.

It is not uncommon in medical and pharmacy education to introduce students to clinical practice by using patient simulators. Mannequins may be used to teach physiology (Harris *et al*., 2011) or be programmed to respond to pharmacological intervention (for example, Hassan *et al*., 2010). Alternatively, actors who appear to have the symptoms of a particular disease may be used. We considered whether simulations could be applied to teaching molecular pharmacology. This concept has already been used by others to introduce dose-response curves. The anti-pyretic effects of acetaminophen (paracetamol) were simulated in a population of students (Skau, 2004). In this approach, students simulated responding to different doses of the anti-pyretic, and the resulting population data was used to generate a dose-response curve. Although an elegant method to introduce a dose-response curve, this approach does not to provide a molecular model of receptor occupancy. We wished to introduce concepts such as association and dissociation rates, affinity, receptor agonism and antagonism. We have developed a role play to facilitate students' understanding of drug-receptor interactions. The simulation requires minimal equipment (chairs, bicycle bells and student volunteers) and preparation time yet provides a representation of the molecular mechanisms underlying fundamental pharmacological principles.

Methods

The relationship between drug association rates, dissociation rates, affinity and receptor occupancy

Students were asked to volunteer to participate in the simulation in front of the remaining student cohort. The student volunteers took on the role of a drug, and 5 chairs placed at the front of the class were used to simulate receptors. To simulate drug molecules binding to the receptor, students were asked to sit down in a chair and then "dissociate" by standing up again. Association rates were modelled as the time taken for the student to sit down (T_{down}),

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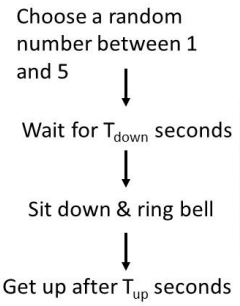
and dissociation rates were modelled as the time taken for the student to stand up (T_{up}). We considered it advisable to inform the volunteers that the simulation involved mild physical activity and that they should only participate if they were fit to do so.

To make the simulation more dynamic, and avoid all the students sitting down in unison, 5 student volunteers were asked to choose a random number between 1 and 5. At the start of the simulation, each volunteer was instructed to count silently to their chosen random number plus a further T_{down} seconds before sitting in their chair. Once seated, the volunteers silently counted T_{up} seconds before standing and then immediately restarted the cycle by counting T_{down} seconds (the random number was not used again) and sitting down once more. This was repeated until the instructor brought the simulation to a halt. To vary the simulation the instructor may select different values for T_{up} and T_{down} (see Figure 1 for examples) to alter the rates of association and dissociation. A long T_{down} represented slow association while a long T_{up} represented slow dissociation; shorter T_{up} or T_{down} periods model faster rates. It quickly became apparent that the students remained seated for a longer period of time - the "receptors" were occupied for a greater proportion of the time – if the association was rapid or the dissociation was slow. This demonstrated that receptor occupancy can be controlled by the rates of association and dissociation of the drug.

Figure 1: A schematic representation of the "chairs simulation"



Association rate	Dissociation rate	Affinity	T_{down} (sec)	T_{up} (sec)
slow	moderate	low	5	1
moderate	moderate	moderate	1	1
moderate	slow	high	1	5

T_{up} and T_{down} are used to reflect the association and dissociation rates of drugs binding to a receptor

This demonstration was adapted to explain the concept of equilibrium dissociation constant (K_D, the concentration at which half the receptor is occupied). The simulation was repeated, but this time the instructor started the simulation by introducing one student at a time. This allowed the instructor to gradually increase the "drug concentration" and demonstrate the "concentration of drug" (number of students) required to occupy half the chairs. If T_{up} and T_{down} are chosen to model a high affinity interaction, very few students enter the simulation before half the chairs are occupied. However, if T_{up} and T_{down} were chosen to model low affinity, far more students were required to occupy half the chairs. It was even possible to measure the number of occupied chairs as the number of students was gradually increased to create a crude dose-response curve during the teaching session. When T_{up} = 1 second and T_{down} = 10 seconds to mimic very low affinity, the number of students required to occupy half the chairs exceeded the number of chairs. This provided a demonstration that even if the drug is in excess of the number of receptors, the receptors may not be fully occupied and that the key determinants of receptor occupancy are drug concentration and affinity.

Agonists and antagonists

The distinction between agonists and competitive antagonists was made by equipping each student with a bicycle bell. To mimic receptor signal transduction by the receptor, students who were representing agonists rang their bell every time they sat down in the "receptor". Students who modelled antagonists did not ring a bell. The students were informed that they could only sit down if the chair was vacant. If someone else was occupying the chair they had to start counting again. The students playing the role of antagonists were advised that they may not interact with the agonists in any way other than occupying the chair.

To demonstrate competitive antagonism, the simulation was started with 2 chairs and 2 students playing the role of agonists (e.g. T_{down} = 2 seconds, T_{up}= 1 second). In the absence of the antagonists, the agonists were free to sit on a chair and ring their bell, simulating receptor signalling. The instructor gradually added students playing the role of antagonists one at a time (e.g. three students with T_{down}= 2 seconds, T_{up} = 1 second). As the number of student antagonists was gradually increased, simulating an increased concentration of the antagonist, fewer of the student agonists could occupy the chair and the bell ringing decreased. This demonstrated the inhibition of receptor signalling by a competitive antagonist. However, when even more students playing the role of agonists were included in the simulation, they were able to compete with the antagonists for the chair and the bell ring increased again. This demonstrated that the effects of a competitive antagonist could be overcome by an increased "concentration" of agonist.

Irreversible antagonism was also be demonstrated. In this scenario, once the antagonists were seated, they did not get back up again. It soon became apparent that once all the chairs are occupied by the irreversible antagonist, adding in more student agonists could not overcome the effect of the irreversible agonists. In principle, non-competitive antagonism could also be modelled by asking students playing the role of non-competitive antagonists to turn their chair on its side intermittently, but we did not pursue this because of the potential for injury.

Partial agonists

The simulation was also used to demonstrate that partial agonists may produce a maximum effect that is less than that observed with full agonists. The simulation was first repeated with the students acting as full agonists, ringing the bell every time they sat down. The audience was asked to note mentally the frequency at which the bells rang. The simulation was then repeated, only this time students played the role of partial agonists, and were asked to only ring their bell every other time they sat down. Even when the number of students was sufficient to occupy all the chairs, the frequency of bell ringing was less when the students acted as partial agonists than that achieved by full agonists. In principle, it was possible to ask the students to ring the bell every 3 or 4 times they sat down in the chair, providing a demonstration that efficacy may differ between drugs.

This simulation was then adapted to show that if there is an adequate receptor reserve, a partial agonist can elicit a maximum response. The simulation was repeated first with 3 chairs and 6 students acting as full agonists to establish the maximum response. Then the simulation was conducted with 3 chairs and 6 students acting as partial agonists (ringing the bell every other time they sat down). Unsurprisingly, the frequency of signalling was diminished. Finally the simulation was run with 6 students still acting as partial agonists but now 6 chairs were used. The frequency of bell ringing was comparable to that with the full agonists. Thus, by increasing the "receptor reserve" partial agonists were able to approach the activity seen with the full agonists.

A further adaptation was to demonstrate that partial agonists can antagonise the effect of full agonists. Using 3 chairs, 3 students played the role of full agonists (e.g. T_{down} = 2 seconds, T_{up} = 1 second) and ringing their bell whenever they sat down. The instructor then gradually introduced 4 students playing the role of partial agonists (who rang their bell every other time they sat down). As the concentration of partial agonist was increased, the frequency of bell ring decreased, demonstrating reduced receptor signalling because the partial agonists occupied the receptor in place of the full agonist.

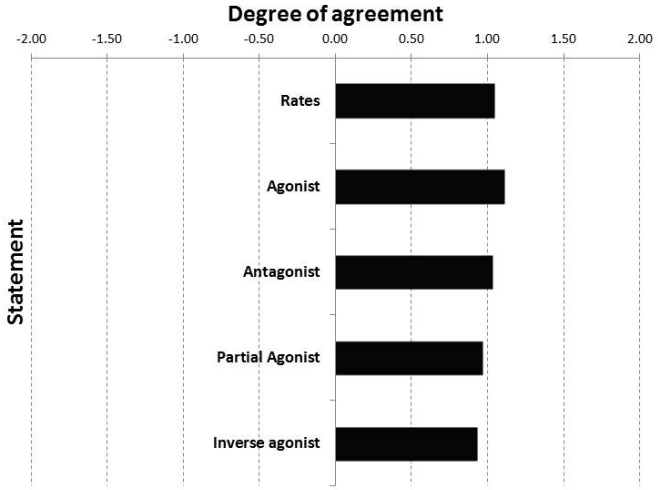
Inverse agonists

The simulation was next used to demonstrate the function of inverse agonists. Five chairs were used and 5 students equipped with a bell were asked to stand one behind each chair. If the chair was empty, these students were asked to ring their bell every 3 seconds. This mimicked the basal activity of the receptor that is observed in the absence of an agonist. Five further students played the role of inverse agonists; these were not given a bell. Whenever the inverse agonists occupied the chair, the students with the bell were instructed to not ring the bell but instead to restart counting 3 seconds once the student playing the role of an inverse agonist had "dissociated". The inverse agonists were gradually introduced into the simulation by the instructor (e.g. T_{down} = 2 seconds, T_{up} = 1 second) which led to a decrease in signalling. This was next contrasted with antagonists. When students simulating an antagonist occupied the chair, the students simulating the basal activity were told not to change the frequency at which they rang the bell. This allowed the distinction between inverse agonists and antagonists to be clarified. If necessary, students acting as full agonists (i.e. equipped with their own bell and ringing it every time they sat down) could also be introduced at this stage to contrast their behaviour to the inverse agonists.

Evaluation

We have used this simulation for 3 years at Keele University School of Pharmacy and in general the simulation has been well received. In 2011, students were asked to complete a survey assessing their attitude to the "chairs" simulation as a method of teaching and learning. 74% of the students responded (60 respondents) to the survey. This included the students who had volunteered to participate in the simulation, but since these students represented less than 10% of the total number of respondents, their comments are unlikely to bias the results significantly. Students were asked to rate their agreement with five statements evaluating whether the simulation improved their understanding of receptor theory, the mechanism of action of agonist, antagonists, partial agonists and inverse agonists (Figure 2). The degree of agreement was assessed using a 5-point Likert scale ranging from "strongly disagree" to "strongly agree". There was overall agreement that the simulation developed and reinforced helped their understanding of all these learning outcomes.

Figure 2: A questionnaire to assess student attitudes to the "chairs simulation".



Students were asked whether they agreed with the statement that (1) "the chairs simulation helped me to understand the contribution of association and dissociation rates to determining receptor affinity". Students were also asked whether they agreed with the statement that the simulation "helped me to understand the mechanism of action of action" of (2) "agonists", (3) "antagonists", (4) "partial agonists", and (5) "inverse agonists". A score of -2 represents strong disagreement with a statement and a score of +2 represents strong agreement.

Discussion

The receptor theory is a fundamental concept in pharmacology and is commonly, if not universally, studied by students of pharmacy. In our experience, students may initially confuse agonists, antagonists, partial agonists and inverse agonists and may struggle with the concept of affinity and how it affects receptor occupancy. The simulation we have described here brings this concept to life with a demonstration that can easily be incorporated into teaching sessions and which costs little to run. The continued association with and dissociation from the chairs by the volunteers emphasizes the dynamic nature of drug action rather than the static picture that may emerge from studying without the aid of simulation.

One drawback with this approach is that some students are reluctant to volunteer to participate in the simulation. We have usually encouraged students to participate and only on one occasion was it impossible to get sufficient volunteers to conduct a simulation. However, we have found that the demonstration is generally well received. In particular, the participation of students as agonists and antagonists competing for the same chair can inject humour into the teaching session, the frequent ringing of bells in the lecture

theatre and the unique nature of the teaching method further encourages engagement with the subject matter and thus deeper learning. We have used similar simulations to demonstrate pharmacokinetic principles such as half-life, clearance and the effect of absorption rates on drug elimination and have found it to be beneficial in teaching these concepts too. The simulation is easy to adapt and adopt by others to teach fundamental concepts within pharmacology.

References

Harris, J. R., Helyer, R. J. & Lloyd, E. (2011) Using high-fidelity human patient simulators to teach physiology. *Medical Education*, **45**, 1159-1160.

Hassan, Z., Dilorenzo, A. & Sloan, P. (2010) Teaching clinical opioid pharmacology with the Human Patient Simulator. *Journal of Opioid Management*, **6**, 125-32.

Skau, K. (2004) Teaching Pharmacodynamics: An Introductory Module On Learning Dose-Response Relationships. *American Journal of Pharmaceutical Education*, **68**.