American Journal of Pharmaceutical Education **2013; 77 (1) Article 11.**

INSTRUCTIONAL DESIGN AND ASSESSMENT

Use of a Three-Dimensional Virtual Environment to Teach Drug-Receptor Interactions

Alan Richardson, PhD, Luke Bracegirdle, BSc, Sarah I.H. McLachlan, PhD, and Stephen R. Chapman, PhD, MPharm

School of Pharmacy, Keele University, Keele, United Kingdom

Submitted May 24, 2012; accepted August 14, 2012; published February 12, 2013.

Objective. To determine whether using 3-dimensional (3D) technology to teach pharmacy students about the molecular basis of the interactions between drugs and their targets is more effective than traditional lecture using 2-dimensional (2D) graphics.

Design. Second-year students enrolled in a 4-year masters of pharmacy program in the United Kingdom were randomly assigned to attend either a 3D or 2D presentation on 3 drug targets, the β-adrenoceptor, the Na^+-K^+ ATPase, and the nicotinic acetylcholine receptor.

Assessment. A test was administered to assess the ability of both groups of students to solve problems that required analysis of molecular interactions in 3D space. The group that participated in the 3D teaching presentation performed significantly better on the test than the group who attended the traditional lecture with 2D graphics. A questionnaire was also administered to solicit students' perceptions about the 3D experience. The majority of students enjoyed the 3D session and agreed that the experience increased their enthusiasm for the course.

Conclusions. Viewing a 3D presentation of drug-receptor interactions improved student learning compared to learning from a traditional lecture and 2D graphics.

Keywords: 3-dimensional, virtual reality, drug-receptor interactions, pharmacology

INTRODUCTION

Students learning pharmacology and medicinal chemistry are usually required to understand the molecular basis of the interactions between drugs and their target(s) (eg, a receptor). This presents a teaching challenge because drugs and their targets usually adopt a specific 3-dimensional (3D) structure, which can be difficult to illustrate and explain in lecture sessions.

Computer software can be used to simulate chemical and pharmacological processes in 3D. The use of computer simulation to teach pharmacology has a long history.[1] Computer-aided simulations are at least as effective in teaching concepts in quantitative pharmacological as laboratory-based experimentation,[2] suggesting that molecular modelling may also be useful for teaching drug-receptor interactions.

Although individual researchers may have access to software and hardware that allows individuals to visualize drugs and proteins in 3 dimensions, in our experience, this technology is not widely used in undergraduate teaching with a large cohort of students. Instead, 2-dimensional (2D) representations of drug-protein interactions are more commonly used for teaching as these can easily be viewed by large groups of students. One exception to this is the use of 3D images embedded in portable document files (PDFs).[3] Although elegant, this approach has only been used so far to illustrate small organic molecules rather than large proteins. There are also several software solutions (eg, Jmol[4]) that allow the visualization and manipulation of 3D molecules, but the images are usually 3D representations presented on a 2D computer screen.

The Keele Active Virtual Environment (KAVE) created at Keele University in the United Kingdom provides hardware and software that allow students to view molecular structure in an interactive 3D rather than a 2D environment. While visually impressive, whether this 3D technology could actually improve students' understanding of drug-receptor interactions was not known. A review of the literature found no robust data supporting the pedagogical effectiveness of using 3D technology,[5] making an assessment of this technology desirable. This study evaluated students at Keele University School

Corresponding Author: Alan Richardson, PhD, School of Pharmacy, Keele University, Keele, Staffordshire, ST5 5BG, United Kingdom. Tel: 44-1782-733571. E-mail: a.richardson1@keele.ac.uk

of Pharmacy to determine whether viewing the drug targets in 3D rather than 2D improved their understanding and provided them with skills that could be applied when studying other molecules.

DESIGN

The intended learning outcome of the teaching session was to increase students' ability to explain the molecular basis of the interaction between drugs and their targets, as well as mechanisms by which proteins carry out their biological function. The specific learning outcomes were for students to be able: (1) to explain the molecular basis of agonism, partial agonism, and antagonism at the beta adrenoceptor; (2) to describe the architecture and function of the nicotinic acetylcholine receptor, including how agonists binding leads to opening of the channel and the basis of cation selectivity; (3) to describe the structure of Na^+-K^+ ATPase, how it binds K^+ and ouabain (an analogue of digoxin), and how these interactions explain the need to consider a digoxin dose adjustment in hypokalaemic patients. These were chosen because they represent 3 distinct classes of protein molecule that are pharmacologically important. Teaching presentations were prepared using structures 2Y03, 2Y04, 2VT4 (β adrenoceptor), 2ZXE, 2A3Y, 3N23 (Na^+-K^+ ATPase), and 2BG9 (nicotinic acetylcholine receptor), downloaded from the Protein Data Bank.[6]

Participants were students enrolled in the second year of a 4-year nationally accredited master of pharmacy program in the United Kingdom. The students were randomly assigned to 1 of 2 groups and shown similar presentations to ensure learning outcomes were met. In both cases, the structures were presented using the molecular visualization software PyMol. The presentation was given to approximately half of the students (49) in a lecture theatre using 2D projection. The 3D group (40 students) watched the same presentation but in 3 dimensions in the KAVE (5 groups of 8 students because the number of students who could view the presentation at 1 time was limited by the size of the KAVE). To ensure consistency in the information delivered to each group, the same teaching plan, which described the key features of each molecule presented, was used to guide both presentations.

Keele Active Virtual Environment

The KAVE creates a totally immersive experience comprising images projected on visual walls and a floor. Four Mirage S+3K projectors (Christie, Wokingham, UK) project from behind separate stereoscopic 3D images onto the left, center, and right walls. A projector in the ceiling projects onto a mirror, which in turn casts an image onto the floor. Each image is synchronized with the others to create 1 larger image spread across all 4 screens of the KAVE, and the user's shadow is cast behind and away from the image on the floor to avoid occluding the projected image. For the purposes of this study, only 2 walls were used to allow an adequate number of students in the KAVE.

A cluster of 5 personal computers running a Microsoft Windows operating system, controlled the KAVE with a "master" computer communicating with a video matrix switch. A tracking system monitored the instructor's head and hand within the KAVE, continually updating the computer-generated visual displays relative to the user's assumed line of sight. The tracking system (Intersense IS900[7]) used a wireless ultrasonic motion detection system to report the location coordinates of the user to the computer. Additional "middleware" converted this data into coordinates that the active KAVE simulation used to create the illusion of a larger space, allowing the user to manipulate 3D virtual objects in the KAVE or to "walk around" in the projected environment. The perceived 3D image and feeling of depth were achieved by wearing liquid crystal display shutter glasses stimulated by an infrared emitter associated with each screen. Stereo synchronization was orchestrated by the computers and a controller head graphics unit. The instructor carried a handheld "wand" to interact with (zoom, rotate, or translate) the virtual objects. The students also wore glasses to visualize the 3D image, but their motion was not tracked. Protein structures were visualized using the molecular visualization system PyMOL.[8] This was implemented based on previous work by Virtalis and Hinton to accelerate the teaching of structural biology.[9]

EVALUATION AND ASSESSMENT

To evaluate the success of the teaching presentations, a 10-question analytical test was prepared that required students to solve a molecular docking problem. The structures in the test were prepared from the Protein Database based on the structures 2ZW3, 2VUK, 3N7R, 2GZ7 205D, 2HT7, 2P7U, 3LC5, 3BWK and 2HVX. Each of these structures shows a protein with a bound drug. In each question, the students were asked to predict which of 2 close analogues of the bound drug would bind to the protein. To generate these 2 compounds, a point was identified on the drug molecule where a short alkyl (methyl or ethyl) group could be attached without clashing with the protein structure, assuming the drug's mode of binding remained unaltered. A second point was identified where the alkyl group would clash with the protein structure. Addition of alkyl groups to these points

provided the drugs representing the correct and incorrect answers to the question.

During the test, students were given 2D illustrations showing the bound drug and the protein surface, as well as the structure of the bound drug and the 2 test drugs using standard chemical notation (test available from the corresponding author). The students were informed that the similar structure of the 2 additional compounds suggested that these were highly likely to bind to the protein in the same orientation and asked to identify which drug would bind and which would not. Prior to administering the test to students, the test was given to 2 experienced medicinal chemists, who correctly identified the anticipated answer in each case within the allotted time (30 minutes). Prior to taking the test, the students were provided with an example of a test question and the correct answer.

After completing the analytical test, students in the 2D group were given the 3D presentation in the KAVE to ensure their learning was not compromised. The study design received approval from Keele School of Pharmacy's ethical committee.

After the KAVE presentations students from both the 2D and 3D groups were asked to complete a questionnaire assessing their perceptions of the KAVE as a resource for teaching a pharmacology module. Students rated their perceptions of the extent to which the KAVE improved their understanding of 5 aspects of pharmacology: how drugs interact with their targets; and the functions of receptors, transporters, enzymes, and transcription factors. Students also rated the degree to which the KAVE had increased their enthusiasm for the subject and how much they enjoyed the session in the KAVE. Each of these self-report ratings was made on a 5-point Likert-type scale anchored by "not at all" (1) and "very much" (5). To assess the perceived transferability of knowledge gained through the KAVE, students were asked to rate how confident they felt in applying what they had learned in the KAVE to the study of other drugs and other drug targets. These ratings were made on a 5-point Likert-type scale anchored by "not at all confident" (1) and "very confident" (5). Finally, students responded to 2 open-ended questions that asked for comments on their experiences of the KAVE.

The group of students who had undergone the teaching session in the 3D virtual environment prior to taking the test performed significantly better overall on the test than the students who had seen the teaching material presented in 2D (2D group mean, 63%; 3D group mean 72%; $p < 0.05$). The percentage of students answering the questions correctly ranged from 49% to 80% in the 2D group and from 60% to 85% in the 3D group. Additionally, more students from the 3D group than from the 2D group gave the correct answer for 8 out of 10 questions on the test. To rule out whether this difference was attributable to a difference in academic ability between the 2 student groups, the average grades on students' end-of-year examinations from the previous year were compared and found to be similar (2D group, mean grade 57%, 3D group, mean grade 58%).

Sixty-eight (76%) of the 89 students who participated in the study completed the questionnaire. Seventy-four percent of students indicated that they enjoyed the sessions in the KAVE (Table 1). Fifty-seven percent agreed that the KAVE increased their enthusiasm for the course. Eighty-one percent of students also believed that participation in the 3D exercise improved their understanding of the interaction of drugs with their targets. Students perceived that their understanding of the function of receptors and enzymes had noticeably improved (63% and 69%, respectively). Forty-four and forty-three percent of the students were somewhat confident or very confident, respectively, that what they learned during the KAVE presentation could be applied to other drugs and other drug targets.

As part of the questionnaire, students were also invited to provide written comments. The majority of comments were positive; many referred to the value of the KAVE in supporting, building upon, and applying learning from associated lectures. Students felt that the KAVE was an excellent visualization tool and that it brought pharmacology to life through demonstrating what happens in the body when drugs are taken. The technology was described by 1 student as providing a "fully interactive and immersive learning environment." The value of 3D over 2D representations in consolidating understanding was emphasised by several students.

Further comments about the KAVE reflected students' enjoyment of the sessions and their renewed interest in pharmacology. Two students considered that the KAVE sessions were not useful, and 7 students felt that some subjects were covered in too much depth without providing sufficient background information on the relevant drugs.

DISCUSSION

This study represents the first analytical demonstration that 3D presentation of drug-receptor interactions improves student learning. The molecules presented to the students in the test were different from those used in the teaching session, suggesting that the students' learning was transferable to other protein molecules.

Students' responses on the questionnaire suggested that the students enjoyed the sessions in the KAVE and

Table 1. Pharmacy Students' Perceptions of Their Participation in an Interactive Three-Dimensional Learning Experience in Pharmacology

Item	Mean (SD)
How much has the KAVE improved your understanding of how drugs interact with their targets?	4.0 (0.8)
How much has the KAVE improved your understanding of the function of receptors?	3.8 (0.8)
How much has the KAVE improved your understanding of the function of transporters?	3.3 (1.0)
How much has the KAVE improved your understanding of the function of enzymes?	3.7 (0.8)
How much has the KAVE improved your understanding of transcription factors?	3.1 (1.1)
How much has the KAVE increased your enthusiasm for this course?	3.5 (1.1)
How much did you enjoy the sessions in the KAVE?	4.0 (0.9)
How confident are you about applying what you have learned in the KAVE to the study of other drugs?	3.4 (0.7)
How confident are you about applying what you have learned in the KAVE to the study of other drug targets?	3.3 (0.8)

Responses were rated using a 5-point Likert scale on which 1= not at all, 2= a little, 3= somewhat 4=quite a bit, 5= very much.

that the KAVE increased their enthusiasm for the course to a moderate extent. This increased enthusiasm may have led to enhanced engagement with the analytical test, and this may have contributed to the higher scores by students in the 3D group. There was some indication in the comments that the KAVE may be particularly suited to those with a "visual" learning style and less helpful for students who prefer to learn from text.

Because 21 of the 89 students did not complete the questionnaire, we cannot rule out the possibility that we overestimated the students' enthusiasm for the course and enjoyment of the KAVE. Despite this caveat, 64% of all students (those who responded and those who did not) indicated that their enthusiasm for the course had increased "somewhat," "quite a bit," or "very much," and 72% of all students indicated they enjoyed the KAVE presentation.

To avoid disadvantaging those students who were randomly assigned to the 2D group, we had that group participate in the 3D presentation after completing the testing phase of the study; however, this limited the value of long-term follow-up testing of the 2 groups to determine differences in retention of understanding.

We only evaluated the effectiveness of the KAVE with 1 cohort of students. We intend to repeat this study with other students to confirm the observations we have made. The KAVE only accommodates approximately 8 students at a time, so conducting these teaching sessions requires a significant commitment of staff resources to teach a large cohort of students. Nevertheless, the improvement in student performance and their significant enthusiasm for the technology warranted the effort invested.

Finally, the acquisition of technology such as the KAVE can be costly, although "entry-level" systems are available for around $50,000, which may be within the reach of many universities. This technology is not limited to teaching pharmacology and could be used to teach several other disciplines (eg, anatomy). Also, the Virtalis system,[10] which has been installed at more than 65 institutions worldwide, could be used collaboratively with other colleges and schools on campus, thereby reducing the cost to individual colleges or schools. Alternatively, the enthusiasm for 3D technology in the entertainment/gaming industry raises the possibility that such technology will be adapted for teaching purposes, although it is not clear whether this technology would provide the fully immersive experience offered by the KAVE.

SUMMARY

We demonstrated that the use of a 3D virtual environment improves student understanding of drug receptor interactions.

ACKNOWLEDGEMENTS

Funding for the purchase of the KAVE was provided by a strategic development fund award from the Higher Education Funding Council of England. The authors would like to thank Professor L. Gifford for helpful discussions and Professor Peter Jones for providing advice on statistics.

REFERENCES

1. Kerecsen L, Pazdernik TL. From mainframe to Web-based: 30 years of experience in computer-aided instruction of pharmacology. *N-S Arch Pharmacol.* 2002;366(1):83-89.
2. Hughes IE. Do computer simulations of laboratory practicals meet learning needs? *Trends Pharmacol Sci.* 2001;22(2):71-74.
3. Cody JA, Craig PA, Loudermilk AD, Yacci PM, Frisco SL, Milillo JR. Design and implementation of a self-directed stereochemistry lesson using embedded virtual three-dimensional images in a portable document format. *J Chem Educ.* 2012;89(1): 29-33.
4. Jmol. Jmol: an open-source Java viewer for chemical structures in 3D. http://www.jmol.org/.Accessed July 10, 2012.

5. Oloruntegbe KO, Alam GM. Evaluation of 3d environments and virtual realities in science teaching and learning: the need to go beyond perception referents. *Sci Res Essays.* 2010;5(9):948-954.
6. Research Collaboratory for Structural Bioinformatics Protein Data Bank. Home page. http://www.rcsb.org/pdb/home/home.do. Accessed November 15, 2011.
7. Intersense. Intersense, sensing every move - IS-900 system. http://www.intersense.com/pages/20/14. Accesed July 9, 2012.
8. Pymol - a user sponsered molecular visualization system on an OPEN-SOURCE foundation. http://www.pymol.org/. Accesed July 9, 2012.
9. University of Arkansas Department of Chemistry and Biochemistry. Virtual reality gives insight on protein structures. http://chemistry.uark.edu/3579.php. Accesed July 9, 2012.
10. Virtalis. Virtalis - leaders in virtual reality. http://www.virtalis.com/. Accesed July 9, 2012.