MEDIA REVIEW

The Neuron Connection: Modeling Parkinson's Disease

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Stererotaxic surgery in rodents provides a valuable means to produce lesions of particular neuronal pathways, allowing scientists to examine the effects of these lesions on the subsequent behavior of animals post-surgery. A well-known application of this approach is the creation of unilateral dopamine-depleted rats using a stereotaxic injection of the neurotoxin 6-hydroxydopamine (6-OHDA) into the substantia nigra pars compacta (SNc). This rat model of Parkinson's disease was established several decades ago and can be used as a bioassay to screen for novel anti-Parkinson drugs or as an animal model to study the role of dopamine and other neurotransmitters in the basal ganglia. Several weeks post-lesion 6-OHDA rats exhibit some spontaneous ipsilateral rotational behavior due to release of dopamine on the unlesioned side, yet upon casual observation their motor behavior appears surprisingly normal. However, when unilateral 6-OHDA rats are treated with drugs that release dopamine such as amphetamine (AMPH) or that stimulate dopamine receptors such as apomorphine (APO), 6-OHDA rats exhibit moderate to intense rotational behavior, the direction of which, ipsilateral (AMPH) or contralateral (APO), is dependent on the mechanism of action of the drug administered.

While the necessity of stereotaxic surgery to create 6-OHDA rats is clear, many faculty, especially those at smaller institutions, may find it difficult or impossible to use this approach in an undergraduate teaching laboratory due to the prohibitive cost of stereotaxic frames (several thousands of dollars a piece) or the intense supervision required in order to monitor survival surgery in anesthetized rats. Another impediment is class size. For example, I have 16 students in each of two laboratory sections of my Neurobiology course at the University of Massachusetts-Boston. With such a large class, it would be difficult to teach 16 students how to do stereotaxic surgery even though I use this procedure in my own research and I have two stereotaxic frames in my laboratory. However, the applications of this rat model of Parkinson's disease can now be brought into every classroom using a novel web-based computer simulation (www.davidson.edu/neuroscience/neuronconnection/default.aspx), which was created through a unique interdisciplinary effort between students and faculty at Davidson College. The authors of this web site include undergraduate students from three departments: Mathematics (Rose Feor), Psychology (Nicole Mah), and Physics (Tuti Penev), who worked under the supervision of faculty from Psychology (Julio Ramirez), Mathematics (Donna Molinek), and Instructional Technology (Mur Muchane). This project is one component of a joint effort entitled The Neuron Connection, which was funded by a NSF grant to Julio Ramirez (Davidson College), Carol Ann Paul (Wellesley College), and Bruce Johnson (Cornell University) (DUE-0231019). Additional support was also provided to Dr. Ramirez from the NSF (DEB-0336919).

The 6-OHDA lesion simulation is based on a meta-analysis of behavioral data gathered from a set of papers from the primary scientific literature in which the extent of dopamine depletion was reported along with the amount of ipsilateral and contralateral rotational behavior measured in response to treatment with AMPH or APO. Using these data, mathematical models were devised that could simulate the direction (ipsilateral or contralateral) and magnitude of rotational behavior for a group of rats treated with AMPH or APO at a given percentage of dopamine-depletion. This is a fascinating concept and serves as an interesting means to try to predict the type of rotational behavior one might expect to see when 6-OHDA rats with a particular degree of dopamine depletion are challenged with drugs that have a certain mechanism of action.

To begin the simulation students choose the degree of unilateral dopamine depletion, from 0-100%, the number of rats in the group, and the drug to be administered, AMPH or APO. Within seconds the results unfold before their eyes with a dynamic graphical representation of each animal's magnitude and direction of rotation pre- and post-lesion. Pre-lesion rotational behavior is based on empirical data gathered by Dr. Ramirez's students, while the post-lesion behavioral data are calculated using mathematical models developed by the authors that are described in great detail in a PDF file contained in the web site references.

The main purpose of the simulation is to allow students to test the effects of varying degrees of dopamine-depletion on the direction and magnitude of rotational behavior elicited in response to administration of AMPH or APO, two dopamine agonists that have different mechanisms of action. While students can select which drug to test in a given group of 6-OHDA rats, unfortunately, they cannot vary the dose of drug in order to examine dose-dependent effects on the magnitude of the rotational response. However, one impressive aspect of the simulation is that the resulting behavioral data mirror the type of response variation often present in individual animals within a treatment group. In fact, testing the identical parameters in repeated simulations yields slightly different results each time – similar to what you would see if you were actually doing an experiment. To guide students' inquiry there are several questions located at the bottom of the simulated data page that provide a framework for further investigation. By contrast, the

questions in the discussion section of the web site seem too complex for students to be able to answer because they are based on details from articles in the references. However, if students were assigned these articles to read beforehand, the discussion questions should lead to a deeper understanding of the 6-OHDA rat model. A novel component of the web site is an interactive rat brain atlas, which can be shifted to convey three levels of section (coronal, horizontal, and sagittal) to allow students to see the location of the SNc (site of the 6-OHDA injection) along with several adjacent brain structures that can be identified/highlighted by placing the mouse over them.

While the introduction of the web site provides a brief background of Parkinson's disease and the 6-OHDA rat model, students will also require a good understanding of how the brain controls motor behavior, including the role of the basal ganglia, otherwise it will be difficult for them to understand the simulation. It can be conceptually confusing: why does a lesion placed on one side of the brain lead to enhanced activity of the ipsilateral limbs following AMPH, but enhanced activity of the contralateral limbs following APO? Along these lines, the differences between the mechanism of action of AMPH and APO need to be explained in more depth, along with the phenomenon of dopamine receptor supersensitivity. For example, when two of my undergraduate research students tested the web site simulation, they understood why APO produced contralateral rotations because they have done this in my laboratory, but they did not understand why AMPH produced ipsilateral rotations.

The web site has many compelling features, but it is uncertain how accurately the simulation models the behavioral response of partially lesioned 6-OHDA rats that are <90% dopamine-depleted. However, this is no fault of the authors, their methods or approach; but is due to the data available in the primary literature. In their description of the mathematical models, the authors acknowledge that the rotational data they gathered for partially lesioned 6-OHDA rats were less "reliable," had "…wide fluctuations in the number of rotations regardless of drug administered" and "…did not appear in the literature with the same frequency as those where damage was greater than 90%" (PDF file in web site references). This explanation probably accounts for a surprising result that occurs after setting unilateral dopamine-depletion to "0%," which produces low to moderate levels of ipsilateral rotational behavior (20-50 ipsilateral rotations during one simulation) following treatment with AMPH. It is doubtful whether this degree of ipsilateral bias really happens in sham-lesioned rats treated with AMPH.

In sum, this innovative web-based 6-OHDA rat simulation provides a powerful, accessible tool for undergraduate neuroscience students. It takes a clinically relevant animal model and allows students to test original hypotheses exploring the relationship between dopamine-depletion and drug action using a quantifiable behavior. A particularly helpful feature of the web site is a brief video showing a rat rotating in response to a drug, allowing students to visualize this unique behavior. For instructors that wish to go beyond a computer simulation, the authors have a CD available for purchase that includes beautifully detailed explanations, photos, and videos, which lead students through all of the procedures necessary to carry out these experiments on live animals. This web site should also serve as a valuable resource for any teaching laboratory that currently uses 6-OHDA rats. For example, as a pre-lab exercise students could run the simulation, read select articles from the references and answer the questions from the discussion before performing their 'wet-lab' experiment. However, for faculty without the means for such an intense hands-on experience, this web-based simulation allows all students to be active researchers and to discover the joys of neuropharmacology.