Journal of Neuroscience Methods 238 (2014) 105–111

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

journal homepage: www.elsevier.com/locate/jneumeth

A novel open-source drug-delivery system that allows for first-of-kind simulation of nonadherence to pharmacological interventions in animal disease models

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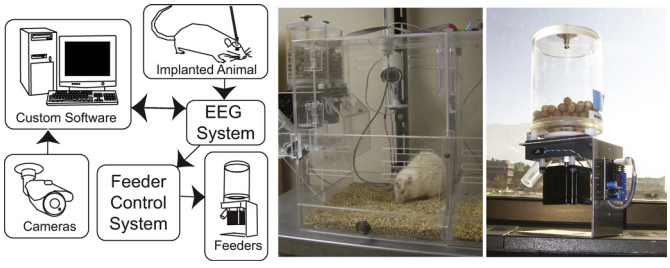
HIGHLIGHTS

- Novel model of nonadherence which uses drug-in-food to treat animals chronically.
- Future studies will examine the consequences of nonadherence in epileptic rats.
- Utility extends to nonadherence in any etiologically-relevant animal disease model.
- Open-source method allows for implementation of a system for modeling nonadherence.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 6 August 2014
Received in revised form 4 September 2014
Accepted 16 September 2014
Available online 26 September 2014

Keywords:
Nonadherence
Epilepsy
Drug discovery
Noncompliance
Anti-seizure drug
Chronic drug delivery

ABSTRACT

Background: Nonadherence to a physician-prescribed therapeutic intervention is a costly, dangerous, and sometimes fatal concern in healthcare. To date, the study of nonadherence has been constrained to clinical studies. The novel approach described herein allows for the preclinical study of nonadherence in etiologically relevant disease animal model systems.
New method: The method herein describes a novel computer-automated pellet delivery system which allows for the study of nonadherence in animals. This system described herein allows for tight experimenter control of treatment using a drug-in-food protocol. Food-restricted animals receive either medicated or unmedicated pellets, designed to mimic either "taking" or "missing" a drug.
Results: The system described permits the distribution of medicated or unmedicated food pellets on an experimenter-defined feeding schedule. The flexibility of this system permits the delivery of drug according to the known pharmacokinetics of investigational drugs.
Comparison with other methods: Current clinical adherence research relies on medication-event monitoring system (MEMS) tracking caps, which allows clinicians to directly monitor patient adherence. However, correlating the effects of nonadherence to efficacy still relies on the accuracy of patient journals.
Conclusion: This system allows for the design of studies to address the impact of nonadherence in an etiologically relevant animal model. Given methodological and ethical concerns of designing clinical studies of nonadherence, animal studies are critical to better understand medication adherence. While the system described was designed to measure the impact of nonadherence on seizure control, it is clear that the utility of this system extends beyond epilepsy to include other disease states.

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http://dx.doi.org/10.1016/j.jneumeth.2014.09.019
0165-0270/

1. Introduction

Patient nonadherence to a doctor-prescribed therapeutic regimen is a widespread problem across all prescribed pharmaceutical treatments and is often associated with expensive and sometimes fatal consequences. It is estimated that one-half to one-third of patients practice imperfect adherence across almost all disease categories (Osterberg and Blaschke, 2005). In the United States alone, it is estimated that nonadherence is responsible for as many as 125,000 preventable deaths per year (McCarthy, 1998) and $290 billion in preventable health care spending per year (Cutler and Everett, 2010). This makes nonadherence a major disease category on its own.

In the field of neurological diseases, patients practicing proper adherence has been linked to more positive outcomes. Improved adherence to cholinesterase inhibitors has demonstrated a marked improvement in quality-of-life for Alzheimer's patients (Brady and Weinman, 2013). Patients with Parkinson's disease have a reduction in motor deficits when practicing proper adherence to levodopa treatments (Grosset et al., 2009). Post-mortem toxicology has suggested that better anti-depressant adherence could reduce suicide rates (Isacsson et al., 1994). For the treatment of epilepsy, near-perfect adherence may result in nearly two-thirds fewer pharmacoresistant patients (Modi et al., 2014). However, the study of nonadherence has previously been limited to clinical research.

Clinical studies of nonadherence are confounded by poor patient and/or guardian reporting of adherence (Modi et al., 2011a). Newer technologies, such as electronic medication event monitoring system (MEMS) caps (Cramer et al., 1989), have increased the fidelity of patient adherence data. It has is widely appreciated that patient adherence is highly irregular (Buelow and Smith, 2004; Grosset et al., 2009). However, only one clinical report thus far has demonstrated actual patient patterns of nonadherence following prescription (Modi et al., 2011b). Additionally, clinical results often group patients without regards to which pharmacotherapy they are prescribed, thus confounding the results. Finally, patient reporting may still be unreliable in these systems, as well as adequate descriptions of symptoms and adverse events (Buelow and Smith, 2004; Hoppe et al., 2007). This, in turn, increases the error when attempting to correlate nonadherence to specific disease state outcomes; e.g. efficacy and adverse events (Faught, 2012). A novel system that can directly measure the impact of nonadherence in an etiologically relevant animal disease model would begin to address these concerns.

Simulating daily patterns of nonadherence is possible without use of an automated system. However, it would require a substantial commitment of resources (i.e. 24 h a day, 7 days a week), in order to deliver drugs on a fixed schedule; thus, it is not feasible for a long-term chronic experiment. To make the study of nonadherence feasible requires an automated system that can reliably deliver a fixed dose of drug for a protracted period of time. One method to deliver drugs to animals is through the use of food pellets that are formulated with a specific quantity of a given drug (Grabenstatter et al., 2007). Thus, adherence can be simulated by administering medicated pellets for a single meal to simulate "taking" a dose, and administering unmedicated placebo control food pellets to simulate "missing" a dose.

Having the drug-in-food pellets available still requires a means to deliver them to the animal at a schedule that meets the needs of the individual investigator. This need led to the design and creation of the system described herein; i.e. an automated pellet delivery system capable of delivering medicated or unmedicated food pellets 24/7 according to an experimenter defined feeding schedule. The proof-of-principle experiments that were conducted to demonstrate the feasibility of the approach employed epileptic rats housed individually in a cage that was equipped with two feeders, thereby allowing each animal to have independent levels of experimenter-defined nonadherence. Section 2 describes the design and implementation of this system. While the system is integrated with video-EEG so that the delivery and consumption of anti-seizure drugs could be correlated with seizure control, the implementation of this system without video-EEG would certainly permit the study of nonadherence in a variety of animal disease models. Moreover, it would also allow for chronic delivery of drug for the purpose of conducting pharmacokinetic/pharmacodynamic studies.

2. Methods

2.1. System architecture overview

The system is able to administer medicated and non-medicated pellets to up to twelve individual epileptic rats in an effort to simulate clinically relevant patterns of nonadherence (Modi et al., 2011b). Additionally, the system coordinates the recording of EEG and video so that the resulting impact of nonadherence in an animal model of epilepsy can be assessed. The overall system design contains 24 automated feeders (Fig. 1A), a Feeder Control System, a BioPac MP150 EEG recording system, and a computer running custom videoEEG software (Fig. 1B). The feeder control system consists of 6 breakout boards and a main control board (Fig. 1C). The breakout board is a custom printed circuit board (PCB) that controls up to four feeders. The main control board consists of an open-source Arduino Uno microcontroller and a custom PCB that works as an Arduino shield, i.e. an expansion PCB which is designed to fit into the standardized Arduino pin-headers. Custom PCBs were designed using the freely available ExpressPCB software, and fabricated by ExpressPCB (www.expresspcb.com). PCB designs are included in the Supplementary materials.

The system works by generating commands in the custom software and using the feeder control system to distribute the commands to the individual feeders. The methods that follow describe how commands are executed, starting at the software, and ending with the confirmation that a pellet was delivered.

2.2. Simulating nonadherence via daily feedings

Because patient nonadherence is dynamic (Glass et al., 2010), the simulation of nonadherence requires the ability to simulate randomized patterns of either "missed" and "taken" doses. For the purpose of this study, nonadherence is simulated by giving each animal a randomized pattern of medicated and unmedicated feedings. To perform this randomization, the determination of whether the animal receives a medicated or unmedicated meal is based on a set integer percentage specified by the user. In the case of a fractional number of meals, the number of medicated meals is rounded up. At the beginning of a new week (Sunday night), or when the medication % value is entered in for a new animal, the software creates an array for all the remaining meals in the week. Then, values are sequentially removed from the array, until the medication % has been reached. This way, the percentage of meals that are medicated is fixed, while the actual patterns of nonadherence are randomized in an independent manner. This system also provides the ability to manually change the rate of adherence so that different levels of nonadherence can be administered to a single animal over the course of a treatment paradigm. Fig. 2 shows how all of the options are defined by the software. Up to six feedings can be delivered per day in our current configuration and any meal can be disabled by entering a time of 0:00:00. Thus, no meals can occur at midnight. Increasing the number of daily feedings beyond six would require only trivial changes to the C# code. Additionally, more complex