Less Is More: Antipsychotic Drug Effects Are Greater with Transient Rather Than Continuous Delivery

Anne-Noël Samaha, Greg E. Reckless, Philip Seeman, Mustansir Diwan, José N. Nobrega, and Shitij Kapur

Background: Most studies on the effects of antipsychotics focus on achieving threshold levels of the drug. The speed and frequency with which drug concentrations reach threshold levels and rise and fall within the day are generally ignored. Based on prior data, we predicted that variations in the within-day kinetics of antipsychotic drug delivery would produce different outcomes, even if we held achieved dose, route, and total duration of treatment constant.

Methods: We compared the effects of within-day continuous (via minipump) versus transient (via subcutaneous injection) haloperidol treatment ($n = 4–9$/condition/experiment) at doses that yield equivalent peak levels of striatal D2 receptor occupancy (~74%).

Results: Over time, transient haloperidol gained efficacy, while continuous haloperidol lost efficacy in two animal models of antipsychotic-like effects (the suppression of amphetamine-induced locomotion and conditioned avoidance responding). This was related to the fact that continuous treatment led to a greater increase in striatal D2 receptor numbers—particularly D2 receptors in a high-affinity state for dopamine—relative to transient treatment and produced behavioral dopamine supersensitivity (as indicated by an enhanced locomotor response to amphetamine following antipsychotic treatment cessation). Treatment kinetics also influenced the postsynaptic response to haloperidol. Transient treatment increased striatal c-fos messenger RNA (mRNA) expression, while continuous treatment did not.

Conclusions: Relative to continuous antipsychotic exposure, within-day transient exposure is more efficacious behaviorally and is associated with a distinct molecular and gene expression profile. Thus, differences in the within-day kinetics of antipsychotic treatment can have different efficacy, and the potential clinical implications of this should be explored further.

Key Words: Antipsychotics, conditioned avoidance, D2 receptors, dopamine, kinetics, supersensitivity

In the study of drug action, considerable attention is given to drug dose and the crossing of certain "threshold" levels of receptor occupancy (1). The kinetics of drug delivery are often regarded as secondary, simply a means to provide target levels of drug and receptor occupancy. This assumption is likely wrong. Independent of current drug levels, drug kinetics (i.e., the speed with which drug levels rise and the number of times they rise and fall in the day) are just as important in determining outcome. For example, withdrawal from continuous (via osmotic minipump) rather than transient (via daily subcutaneous injection) raclopride treatment more readily induces tolerance to the motor suppressant effects of raclopride and locomotor supersensitivity to amphetamine, even when transient treatment leads to markedly higher peak levels of striatal D2 receptor blockade (2). Similarly, continuous haloperidol or olanzapine treatment (via minipump) increases the likelihood of vacuous chewing movements (an animal model of tardive dyskinesia) relative to transient treatment (via subcutaneous injection), even when the latter leads to higher peak levels of D2 blockade (3,4,5).

From the Schizophrenia Program (A-NS, GER, SK), Centre for Addiction and Mental Health; Department of Psychiatry (PS, JNN, SK) and Department of Pharmacology (PS, JNN), University of Toronto; and Neuroimaging Research Section (MD, JNN), Centre for Addiction and Mental Health, Toronto, Ontario, Canada; and Division of Psychological Medicine and Psychiatry (SK), Institute of Psychiatry, London, England.

Address reprint requests to Shitij Kapur, M.D., Ph.D., Institute of Psychiatry, Box P054, De Crespigny Park, London SE5 8AF, United Kingdom; E-mail: Shitij.Kapur@iop.kcl.ac.uk.

Received October 18, 2007; revised December 13, 2007; accepted January 18, 2008.

These and other findings (6-8) suggest that some of the antidopaminergic effects of antipsychotics are determined as much by the kinetics of receptor occupancy as by the peak levels of drug or receptor occupancy achieved. However, several issues confound the interpretation of these studies. First, the kinetics of drug delivery are confounded with dose in some studies (8) and duration of treatment in others (6). Second, most studies have investigated the effects of drug delivery kinetics on the period following withdrawal from antipsychotics (2,7,8). The more relevant clinical question concerns the effects of drug delivery kinetics while the drug is being taken, not after. To our knowledge, only Carey and DeVeaugh-Geiss (6) and Turrone *et al.* (3,4) measured antipsychotic effects without an overt withdrawal period. However, both measured indices of motor side effects rather than antipsychotic efficacy (spontaneous locomotion and extrapyramidal side effects, respectively). Thus, it remains to be determined whether the kinetics of antipsychotic treatment can influence antipsychotic efficacy.

In the current studies, therefore, we asked a simple question: If one holds the achieved dose, route, and total duration of antipsychotic drug treatment constant but varies the within-day kinetics of treatment, can one get differential drug effects? We found this to be the case. Remarkably, within-day transient antipsychotic treatment was much more effective than continuous treatment, even when we tested a 10 fold lower dose. We then investigated potential mechanisms and found that the kinetics of antipsychotic treatment influence 1) the number and sensitivity of striatal D2 receptors, and 2) the postsynaptic response to antipsychotic, as measured by induction of messenger RNA (mRNA) for the immediate early gene c-fos.

Methods and Materials

Male Sprague Dawley rats (Charles River Laboratories, Montreal, PQ, Canada) weighing 225 g to 250 g were housed two per cage in a climate-controlled colony room with a 12-hour reverse

0006-3223/08/$34.00
doi:10.1016/j.biopsych.2008.01.010

light/dark cycle (lights off at 8:00 AM). Food and water were available ad libitum. All testing was conducted during the dark phase of the animals' circadian cycle and was in compliance with the institute's animal care committee.

Drugs

Haloperidol (HAL; .05 or .5 mg/kg/day via minipump or .05 mg/kg/day via subcutaneous [SC] injection) (Sabex Inc., Boucherville, PQ, Canada) was dissolved in a .5% glacial acetic acid/water (H_2O) solution (pH adjusted to ~5 with sodium hydroxide [NaOH]) for treatment via minipump (Alzet model 2ML2, 19-day drug delivery according to the manufacturer, Durect Corporation, Cupertino, California) and was dissolved in 20 mmol/L phosphate buffered saline (PBS) for treatment via subcutaneous injection. D-amphetamine sulfate (AMPH; 1.5 mg/kg) (US Pharmacopoeia, Rockville, Maryland) was dissolved in .9% saline and given SC (1 mL/kg).

Rationale for Doses and Modes of Haloperidol Administration

The goal of the present set of experiments was to examine the contributions of the kinetics of antipsychotic drug delivery (i.e., maintaining continuous versus transiently high levels of drug within the day) to the neurobehavioural response to antipsychotic using equivalent and clinically representative doses. Positron-emission tomography (PET) studies in humans suggest that therapeutically efficacious doses of antipsychotic that do not also significantly increase the risk of motor side effects yield between 65% and 80% striatal D2 receptor occupancy (9-11). Similarly, doses of antipsychotic that disrupt conditioned avoidance responding (a widely used index of antipsychotic-like efficacy in animals) in animals without inducing catalepsy (a model of extrapyramidal side effects [EPS]) also occupy between 70% and 80% striatal D2 receptors (12,13).

In rats, HAL treatment via minipump leads to continuously high levels of D2 receptor occupancy (14,15), whereas HAL given via SC injection leads to only transiently high occupancy, which is greatly reduced 24 hours after injection (14). Therefore, we varied the kinetics of antipsychotic treatment by administering HAL via osmotic minipump or SC injection. To hold achieved dose/peak levels of D2 receptor occupancy constant, we selected doses that would achieve equivalent and therapeutically meaningful peak levels of striatal D2 receptor blockade under the two treatment conditions. Thus, we administered .5 mg/kg/day HAL via minipump (73% ± 14 SD striatal D2 receptor occupancy) (A-N. Samaha, PhD; G.E. Reckless, B.Sc; S. Kapur, MD, PhD; unpublished observations; February 16, 2006) and .05 mg/kg/day via SC injection (74% ± 7 SD striatal D2 receptor occupancy 2 hours postinjection and 19% ± 31 SD striatal D2 receptor occupancy 24 hours postinjection) (14). We also included a group of rats treated with .05 mg/kg/day HAL via minipump (41% ± 16 SD striatal D2 receptor occupancy) (14) to examine the effects of drug delivery kinetics while holding dose constant. Thus, four groups were generated: two groups receiving .05 mg/kg HAL either via daily SC injection (HAL-TRANS) or minipump (HAL-.05 CONT), a group receiving .5 mg/kg via minipump (HAL-.5 CONT), and a vehicle control group (VEH).

Treatment

Under 1.5% isoflurane anesthesia, HAL-.5 CONT and HAL-.05 CONT rats were implanted with minipumps containing HAL as described previously (15). The HAL-TRANS and VEH animals received sham surgery, which consisted of an incision that was then closed with wound clips. Starting 1 day later, animals in the HAL-TRANS group were injected with HAL once a day. All remaining animals were injected with VEH once a day. Thus, all animals were subjected to equivalent surgical, handling, and injection procedures.

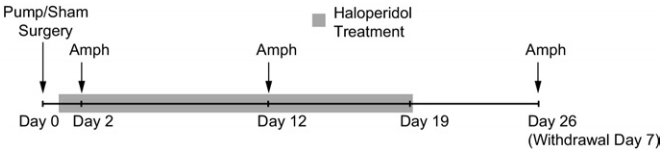

Figure 1. Graphical depiction of the sequence of treatment and testing for Experiment 1, where the effects of HAL on amphetamine-induced locomotion were assessed on the 2nd and 12th days of neuroleptic treatment as well as on the 7th day following neuroleptic cessation. HAL, haloperidol.

Experiment 1: Behavioral Sensitivity to AMPH as a Function of Mode of HAL Administration

In Experiment 1, we assessed the effects of the mode of HAL treatment on the locomotor response to AMPH over time.

Apparatus. The locomotor response to AMPH (1.5 mg/kg, SC) was assessed in clear Plexiglas cages (27 × 48 × 20 cm) as described previously (15).

Groups and Procedures. As illustrated in Figure 1, AMPH-induced locomotion was assessed on the 2nd and 12th days of treatment in independent groups of animals (n = 8/group/day). The animals that were tested on day 12 continued to receive neuroleptic or VEH treatment for an additional 7 days (until day 19, at which time the minipumps in the HAL-CONT groups were empty of drug solution) and their locomotor response to AMPH was again assessed on the seventh day following HAL treatment cessation (day 26). On test days, animals were brought to the locomotor activity room and animals in the HAL-TRANS group were injected (SC) with HAL and animals in the other groups received VEH injections. The animals were then placed in the locomotor activity cages and locomotor activity was monitored for 30 min. Animals were then injected with AMPH and locomotor activity was recorded for 60 min.

Experiment 2: Conditioned Avoidance Responding

In Experiment 2, we monitored the effects of the mode of HAL treatment on the avoidance response to a conditioned aversive stimulus over time.

Procedures. Rats were trained and tested in two-way active avoidance shuttle boxes as described previously (15). Each conditioned stimulus presentation was immediately followed by foot shock. Movement to the other compartment during the 10 sec conditioned stimulus presentation was recorded as "avoidance." Spontaneous movement to the other compartment was recorded as "crossover." Fifty-four naïve rats were trained once a day for a total of 9 days. Animals that reached a training criterion of ≥80% avoidance on days 8 and 9 (36 out of 54 rats) were randomly assigned to the HAL-TRANS, HAL-.05 CONT, HAL-.5 CONT, or VEH condition (n = 9 per group). Starting on day 3 of treatment, the same animals were tested for conditioned avoidance responding (CAR) once a day for 5 consecutive days (i.e., until day 7 of treatment) and then on days 10, 12, 14, and 16 of treatment using the same procedures as during training, including presentation of the foot shock. Testing was conducted 1 hour after VEH or HAL injections. On days when no testing occurred, animals were injected in their home cages.