Behavioural Brain Research 314 (2016) 143–151

Contents lists available at ScienceDirect

Behavioural Brain Research

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

Research report

Anticonvulsant medications attenuate amphetamine-induced deficits in behavioral inhibition but not decision making under risk on a rat gambling task☆

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HIGHLIGHTS

- Effect of valproate, lamotrigine and carbamazepine on a rat gambling task (rGT).
- Anticonvulsant drugs did not alter choice of various options on the rGT.
- Carbamazepine reduced motor impulsivity and increased choice latency on the rGT.
- Carbamazepine and valproate attenuated amphetamine-induced increase in impulsivity.
- Support for the use of carbamazepine and valproate in the control of impulsivity.

ARTICLE INFO

Article history:
Received 4 June 2016
Received in revised form 5 August 2016
Accepted 7 August 2016
Available online 8 August 2016

Keywords:
Antiepileptic drugs
Valproate
Lamotrigine
Carbamazepine
Impulsivity
Gambling disorder
Bipolar disorder
Amphetamine

ABSTRACT

Impulsivity is a major component of mania in bipolar disorder (BD), and patients also show impairments in decision-making involving risk on the Iowa Gambling Task (IGT). Similar deficits are observed in some patients with temporal lobe epilepsy (TLE), and incidence of problem gambling is higher in both these populations. Anticonvulsant drugs are widely used in the treatment of epilepsy, but also as mood stabilizers and prophylaxis for the management of BD. Unfortunately, little is still known about the precise mechanisms of action underlying their efficacy, and the specific behavioral aspect targeted by these drugs. This project explored the effect of the three anticonvulsant drugs currently also used as mood stabilizers- carbamazepine, valproate and lamotrigine on aspects of decision-making using a rat analogue of the IGT, the rat Gambling Task (rGT). In this task, rats choose between four distinct, probabilistic reinforcement schedules. Sugar pellet profits are maximized by adopting a conservative strategy, avoiding tempting high-risk, high-reward options. Effects of the anticonvulsant agents were assessed on baseline performance and also in conjunction with amphetamine administration, in order to approximate a "mania-like" state. Carbamazepine appeared to slow processing speed, decreasing premature responses and increasing choice latency, whereas valproate and lamotrigine had no effect. When administered prior to amphetamine, lamotrigine was the only drug that failed to attenuate the pro-impulsive effect of the psychostimulant. Further studies looking at chronic administration of anticonvulsants may help us understand the impact of this medication class on decision-making and impulsivity in healthy rats and disease models.

Abbreviations: 5CSRT, 5 Choice Serial Reaction Time Task; 5-HT, 5-hydroxytryptamine; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; Amph, amphetamine; ANOVA, analysis of variance; BD, bipolar disorder; CBZ, carbamazepine; D, dopamine receptor; DA, dopamine neurotransmitter; DOI, (+/−)-1-(2,5-dimethoxy-4-iodophenyl)-2-aminopropane; g, gram; GABA, gamma-aminobutyric acid; HDAC, histone deacetylase; IGT, Iowa Gambling Task; IP, intraperitoneal route; ITI, intertrial interval; LMG, lamotrigine; mg, milligram; mg/kg, milligram per kilogram; min, minute; ms, millisecond; Na^+, sodium; NAc, nucleus accumbens; NMDA, *N*-methyl-D-aspartate; P(1–4), pellet option 1 to 4; rGT, rat Gambling Task; Sal, saline solution; sec, second; SEM, standard error of the mean; TLE, temporal lobe epilepsy; VPA, valproate.

☆ MT designed research, performed research, administered the drugs, analyzed data, and wrote the paper; CAW designed research and wrote the paper.

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http://dx.doi.org/10.1016/j.bbr.2016.08.016
0166-4328/

1. Introduction

Although bipolar disorder (BD) and epilepsy appear to share little surface similarity, second-generation anticonvulsant drugs such as carbamazepine and valproate, considered first line treatments for complex partial and secondary generalized epilepsy, are also widely used for the management of BD. A range of cognitive deficits is broadly documented in both bipolar and epileptic patients [1–3], but one emerging area of overlap pertains to impulse control. Impulsivity is well-documented as a core symptom of the manic episodes characteristic of BD. However, it is increasingly recognised that psychiatric conditions associated with high impulsivity, particularly attention deficit hyperactivity disorder (AD/HD) [4–7] but potentially also gambling disorder (GD) [8], are also more prevalent in epileptic patients. However, whether this apparent overlap in vulnerability to elevated impulsivity reflects commonalities in the neurobiological basis of BD and temporal lobe epilepsy (TLE), which then contributes to the similarities in effective pharmacotherapies, is unknown.

It is also difficult to parse the contribution made by the diseases themselves from any treatment effects, particularly as medication history is typically complex in these patient populations. For example, both valproate and carbamazepine are consistently reported to lead to cognitive impairment [9,10]. On the contrary, newer generation antiepileptic drugs like lamotrigine are reported to have fewer side-effects and a better tolerability profile in both children and adults. Evidence indicates that cognitive function in BD patients with a depressive episode improves following treatment with lamotrigine [11]. Further complicating understanding of the contribution of these drugs on cognition, lithium, valproate and carbamazepine have also been suggested as potential treatment for GD, decreasing clinical scores in GD patients, or improving impulsive behaviour [12–14].

Animal models that capture both the cognitive processes impaired in BD and TLE, and the deficits observed in GD, could make a useful contribution in resolving some of these issues. Both BD [15,16] and TLE [17–20] patients perform poorly on the Iowa Gambling Task (IGT), a well-established neuropsychological test used to assess risky decision-making in a naturalistic way that nevertheless takes place in a laboratory setting [21]. In this paradigm, subjects must determine which of four decks of cards, each associated with different net gains and losses, will maximise returns. The optimal strategy is to pick from the decks associated with small gains and smaller penalties, whereas cards from the disadvantageous decks generate larger wins per trial but also heavy long-term losses. Rodent analogues of this task have been successfully developed, such as the rat gambling task (rGT) in which animals attempt to maximise their sugar pellet profits by choosing between four different options, each associated with distinct probabilities and magnitudes of reward and punishing time-out periods [22]. The IGT and rGT appear to be regulated by similar neural circuitries and neurochemical systems across species [22–25] increasing the validity of using the rodent task to explore the neurobiology underlying maladaptive decision making in health and disease.

In order to elucidate the potential contribution of anticonvulsant drugs to the decision-making deficits observed in patients with TLE or BD, we therefore determined the effects of the anticonvulsants valproate, lamotrigine and carbamazepine on performance of the rGT. We hypothesized that the effects of valproate and carbamazepine in healthy rats would be greater than lamotrigine, paralleling the effects observed in human patients. Administration of the psychostimulant amphetamine is often used as a proxy for a model of mania in animals, as the drug reliably elicits marked hyperactivity and motor impulsivity [e.g. 22,23,25–28]. In addition to producing a behavioural phenotype in rodents that closely resembles the manifestation of these symptoms in BD, amphetamine also appears to exert these effects through potentiating the actions of the dopamine system, in keeping with the suggested role of periodic elevations in dopamine triggering the transition from euthymia to mania [29]. Given that amphetamine has been found to increase premature (impulsive) responding and impair decision making on the rGT [22,25], we therefore also investigated whether anticonvulsant drugs would likewise attenuate these deleterious effects of amphetamine administration.

2. Material and methods

2.1. Subjects

Subjects were 16 male Long Evans rats (Charles River Laboratories, St. Constant, QC, Canada) weighing 250–275 g at the start of the experiment. Rats were food restricted to 85% of their free-feeding weight and maintained on 14 g of standard rat chow per day plus the sugar pellets earned in the task (~5 g per day). Rats were pair-housed in a climate-controlled colony room on a reversed 12 h light-dark cycle (lights off 08.00; temperature ~21 °C). Water was available ad libitum. Behavioral testing began one week following the start of food restriction. All housing conditions and testing procedures were in accordance with the guidelines of the Canadian Council on Animal Care, and all protocols were approved by the Animal Care Committee of the University of British Columbia.

2.2. Behavioral apparatus

Behavioral testing took place in 16 standard five-hole operant chambers, each enclosed within a ventilated sound-attenuating cabinet (Med Associates Inc., St. Albans, VT, USA). The chambers were configured similarly to those previously described [22,30] and were controlled by software written in Med PC by CAW running on an IBM-compatible computer.

2.3. Habituation and training

Training on the rat Gambling Task (rGT) has been described in detail previously (Zeeb et al. [22]). All subjects were initially habituated to the testing chambers by baiting each response hole and the food magazine with sugar pellets. Following two such 30 min sessions, animals were also trained to nose-poke into an illuminated response hole within 10 s to earn sugar rewards using a revised version of the five-choice serial reaction time task (5CSRT) adapted for training of the rGT and described in previous reports [31]. The spatial location of the stimulus light varied between trials across response holes 1, 2, 4, and 5. Each session consisted of 100 trials and lasted approximately 30 min. After five sessions, animals were consistently completing 100 trials with ≥80% trials correct and ≤20% trials omitted. Animals were then trained on a forced-choice version of the rGT for seven sessions before moving on to the full free-choice task. This ensured all animals had equal experience with all of the four reinforcement contingencies, and aimed to prevent sampling biases toward a particular hole from developing.

2.4. The rat gambling task (rGT)

A schematic illustrating the trial structure of the rGT is provided (Fig. 1). Subjects initiated each trial by making a nose-poke response in the illuminated food magazine. This response extinguished the tray light and triggered the start of a 5 s inter-trial interval (ITI). At the end of the ITI, holes 1, 2, 4, and 5 were illuminated for 10 s (in the forced-choice version of the task used in training, only one hole was illuminated). The trial was scored as an omission if animals failed to respond within 10 s, at which point the tray light was re-illuminated and animals could start a new