Neurobiology of Learning and Memory 101 (2013) 85–93

Contents lists available at SciVerse ScienceDirect

Neurobiology of Learning and Memory

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

A quantitative analysis of the effects of qualitatively different reinforcers on fixed ratio responding in inbred strains of mice

Blake A. Hutsell *, M. Christopher Newland

Department of Psychology, Auburn University, Auburn, AL 36849-5212, United States

ARTICLE INFO

Article history:
Received 28 November 2012
Revised 21 December 2012
Accepted 14 January 2013
Available online 26 January 2013

Keywords:
Fixed-ratio schedule
Mathematical Principles of Reinforcement
Reinforcer quality
Lever press
Mouse
Strain comparison

ABSTRACT

Previous studies of inbred mouse strains have shown reinforcer–strain interactions that may potentially mask differences among strains in memory performance. The present research examined the effects of two qualitatively different reinforcers (heterogeneous mix of flavored pellets and sweetened-condensed milk) on responding maintained by fixed-ratio schedules of reinforcement in three inbred strains of mice (BALB/c, C57BL/6, and DBA/2). Responses rates for all strains were a bitonic (inverted U) function of the size of the fixed-ratio schedule and were generally higher when responding was maintained by milk. For the DBA/2 and C57BL/6 and to a lesser extent the BALB/c, milk primarily increased response rates at moderate fixed ratios, but not at the largest fixed ratios tested. A formal model of ratio-schedule performance, Mathematical Principles of Reinforcement (MPR), was applied to the response rate functions of individual mice. According to MPR, the differences in response rates maintained by pellets and milk were mostly due to changes in motoric processes as indicated by changes in the minimum response time (δ) produced by each reinforcer type and not specific activation (a), a model term that represents value and is correlated with reinforcer magnitude and the break point obtained under progressive ratio schedules. MPR also revealed that, although affected by reinforcer type, a parameter interpreted as the rate of saturation of working memory (λ), differed among the strains.

Published by Elsevier Inc.

1. Introduction

The goal of much research in the behavioral neurosciences is to develop and validate preclinical models of restricted features of neuropsychiatric disorders (Chadman, Yang, & Crawley, 2009; Nestler & Hyman, 2010). A number of techniques are available to researchers that allow for the production of animal models expressing neurobiological markers of these illnesses (Fernando & Robbins, 2011; Monteggia, Carlezon, & DiLeone, 2008; Markou, Chiamulera, Geyer, Tricklebank, & Steckler, 2009). Advances in molecular genetics have made it possible to produce mutant mice that model symptoms of human affective and psychiatric disorders (Grubb, Churchill, & Bogue, 2004; Bućan & Abel, 2002; Cryan & Homes, 2005). Behavioral research with genetically engineered mice aims to identify phenotypes related to the psychopathology of a neuropsychiatric disorder (Seong, Seasholtz, & Burmeister, 2002; Tarantino & Bućan, 2000). Mouse models of several prevalent disorders are now in existence and many reviews of the efforts of a number of laboratories to identify behavior phenotypes in these animals have appeared (Crawley, 1999, 2008; Sousa, Almeida, & Wotjak, 2006). Because the behavior phenotype of mutant mice is the product of both the targeted and background genes, a careful experimental analysis of the behavior of the background strain is critical to the interpretation of functional consequences of any mutation.

Crawley et al. (1997) provided a comprehensive overview and comparison of phenotyping studies conducted with several inbred mouse strains. Many reviews of behavior phenotypes of inbred mice have directed attention to issues of general health. Researchers, however, are also interested in making comparisons among inbred strains on more complex functions of the nervous system (i.e., learning and memory) to inform their choice of background (Hunsaker, 2012; Wehner & Silva, 1996). The prevailing tendency in this literature has been to make ordinal comparisons of performance of commonly used strains in learning and memory tasks. It is becoming increasing clear, however, that effects of strain on commonly employed measures of learning and memory may sometimes result from differential sensitivity to procedural variables (Cabib, Orsini, Le Moal, & Piazza, 2000; Crabbe, Wahlsten, & Dudek, 1999; Haluk & Wickman, 2010; Orsini, Buchini, Conversi, & Cabib, 2004). Common features of experimental protocols such as housing conditions, length of experimental sessions, and food restriction regimen have been shown to moderate strain differences.

The complex performances that are generated in the laboratory to model behavior seen in neuropsychiatric disorders require

* Corresponding author. Fax: +1 334 844 4447.
E-mail address: blakehutsell@auburn.edu (B.A. Hutsell).

1074-7427/$ - see front matter Published by Elsevier Inc.
http://dx.doi.org/10.1016/j.nlm.2013.01.005

careful control over the quality and magnitude of the reinforcing consequences used to establish and maintain these performances. This is true of animal models of impulsive choice (Madden & Johnson, 2011), short-term memory (Brown & White, 2005, 2009), and behavioral flexibility or reversal learning (Chudasama & Robbins, 2006). Moreover, differences in reinforcer impact among strains may be mistaken for differences in the genetic contribution to a particular behavioral domain. For example, Youn et al. (2012) reported that the appearance of a difference in spatial memory among C57BL/6 and DBA/2 strains depended on the reinforcer for finding an escape cylinder in a modified Barnes maze. Specifically, when spatial search in the Barnes maze was maintained by negative reinforcement (i.e., escape from strong winds) the C57BL/6 mice located an escape cylinder faster than DBA/2 mice. When spatial search was maintained by positive reinforcement (opportunity to consume almond chips in the escape cylinder), however, the differences between the strains disappeared. Youn and colleagues also identified inconsistencies across prior reports of spatial memory among these strains that may have been confounded by similar procedural factors. Specifically, Youn and colleagues took note of variables that affect a strain's response to stressful or novel environments as one determinant of the apparent inconsistencies in the literature (Ohl, Roedel, Binder, & Holsboer, 2003). Thus, prior studies likely found important differences among inbred strains, but may have attributed the difference to the incorrect mechanism(s).

Ratio schedules of reinforcement are an oft-used tool in behavioral pharmacology (Katz, 1990; Richardson & Roberts, 1996; Roberts & Richardson, 1993). Properties of responding on ratio schedules (e.g., Baron, Mikorski, & Schlund, 1992) have been employed to compare the efficacy of qualitatively different reinforcers (e.g., drugs with demonstrated abuse potential versus novel compounds (Griffiths, Brady, & Bigelow, 1981)), to assess the effects of neurotoxic lesions (Bezzina et al., 2008; Kheramin et al., 2005) and in investigations of the motoric/motivational effects of acute drug treatments (Mobini, Chiang, Ho, Bradshaw, & Szabadi, 2000; Zhang et al., 2005) Because some measures of progressive ratio-schedule responding, such as the ratio at which responding ceases ('break point') and peak response rate, are sensitive to the nature of the progression employed and thus, are likely not an unambiguous index of reinforcer value (Killeen, Posadas-Sánchez, Borgå, & Thrailkill, 2009; Stafford & Branch, 1998), some research groups have applied formal models to ratio-schedule performance in an attempt to circumvent such interpretive difficulties (e.g., Bradshaw & Killeen, 2012).

Mathematical Principles of Reinforcement (MPR; Killeen, 1994; Killeen & Sitomer, 2003) is a general quantitative framework that predicts various measures of operant behavior on simple schedules of reinforcement. MPR posits three fundamental processes that underlie all schedule-controlled operant behavior: (1) presentation of an appetitive or reinforcing stimulus produces nonspecific activation of behavior; (2) the ceiling on the rate of a given behavior (e.g., lever pressing) is set by the minimum time required to emit an instance of that behavior; (3) arranging a contingency between behavior and a reinforcer causes certain responses to become coupled to the reinforcer. The strength of this coupling decreases as a function of events or time interposed between behavior and reinforcement. The equation for predicting response rate b on a fixed ratio schedule of reinforcement (Killeen & Sitomer, 2003) in which every nth response is reinforced is:

$$b = \frac{c}{\delta} - \frac{n}{\delta a} \tag{1}$$

where specific activation a is a measure of reinforcer value, response time, δ, is the minimum time to complete a target response, and coupling, c, the degree of association between a target response class and reinforcer arranged by a schedule of reinforcement (Killeen, 1994; Killeen & Sitomer, 2003). The coupling coefficient, c, has been interpreted as the proportion of all behavior activated by the reinforcer that is measured by the target response (Killeen & Bizo, 1998).

The expression for c depends on the nature of the contingencies arranged by a schedule of reinforcement (see Killeen, 1994). For fixed-ratio schedules, $c = 1 - e^{-\lambda\delta n}$. Because ratio schedules require a fixed number of target responses and these typically occur as an uninterrupted run, as the ratio requirement increases more target responses be will coupled with the reinforcer. At low ratios, events other than the target response will become coupled to the reinforcer, but as the ratio requirement increases the number of reinforceable responses approaches a ceiling (c/δ). This ceiling represents a response count beyond which the influence of a reinforcer on non-target behavior is insignificant (Killeen & Sitomer, 2003). Coupling reaches an asymptote of 1.0, or saturates, for events immediately preceding reinforcement, and therefore λ can be termed a saturation rate.

The rate parameter, λ, in the expression for coupling in ratio schedules captures the fact that a reinforcer has a diminishing impact on responses as they retreat into the past or, according to Killeen and colleagues, as quantifying "the rate of decay of response traces" (Killeen & Sitomer, 2003, p. 54). Thus as λ increases, the coupling to events more distal to reinforcement decreases. Coupling in the MPR framework serves the same role as eligibility traces in temporal difference (TD) learning algorithms (Sutton & Barto, 1998) to solve the temporal assignment of credit problem. In these models, responses or other events more distal from a reinforcer are eligible for less of its effect and other, competing, distal events may be strengthened. Eligibility traces in TD models may represent persistent neural activity observed in a number of cortical and subcortical areas in working memory and decision-making tasks (see Curtis & Lee, 2010). If it is assumed that a discrete number of events can be credited for reinforcement then, according to Killeen and colleagues, coupling is related to the construct of working memory capacity and λ is the rate at which saturation is approached (see Killeen, 2001, 2012).

Fig. 1 illustrates the theoretical function for fixed ratio schedules given by MPR, along with changes in the shape of the function produced by changes in different parameters. The figure demonstrates the contribution of each constituent process to the shape of the response rate function. The saturation parameter λ dictates the position along the x-axis (fixed ratio) where the peak rate of responding will occur. The peak occurs when a value of the ratio schedule (i.e., number of target responses) is reached that exhausts the influence of the reinforcer. The minimum response time reflecting the biomechanics of the response device and the animal's motor capabilities is δ; extrapolating to the y-axis gives the unconstrained maximum rate of target responding ($1/\delta$). The x-axis intercept of the function, the breaking point, is given by the activation parameter and may be gainfully employed to construct a scale of reinforcer value (Reilly, 2003; Rickard, Body, Zhang, Bradshaw, & Szabadi, 2009).

A number of studies have now confirmed the interpretive utility of MPR to consistently distinguish between manipulations that affect motivational (Reilly, 2003; Rickard et al., 2009) and motoric processes (Avila et al., 2009; Stafford & Branch, 1998). A recent review by Bradshaw and Killeen (2012) establishes the power of the formal approach offered by MPR to illuminate the specific behavioral mechanisms affected by neurobiological interventions. The present study was designed to examine the determinants of responding of three inbred mouse strains reinforced with either flavored pellets or milk under fixed-ratio schedules. Application of MPR to the resulting response rate functions would clarify if the relative effectiveness of milk and sucrose pellet reinforcers in