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

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### 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, & 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 ( $\delta$ ) 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. In addition, MPR also revealed that, although affected by reinforcer type, a parameter interpreted as the rate of saturation of working memory ( $\lambda$ ), differed among the strains.

### 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 (Monteggia, Carlezon, DiLeone, 2008; Fernando & Robbins, 2010; 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; Bu an & Abel, 2002; Cryan & Holmes, 2005). Behavioral research with genetically engineered mice aims to identify phenotypes related to the psychopathology of a neuropsychiatric disorder (Tarantino & Bu an, 2000; Seong, Seasholtz, & Burmeister, 2002). 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

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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 and colleagues (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, however, researchers 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 increasingly 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 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, Rickard, Asgari, Body, Bradshaw, & Szabadi, 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 association 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 the every  $n$ th response is reinforced is

$$b = \frac{c}{\delta} - \frac{n}{\delta a} \quad (1)$$

where specific activation  $a$  is a measure of reinforcer value, response time,  $\delta$ , 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 will be 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 ( $c/\delta$ ). 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, with the event immediately preceding reinforcement, and therefore  $\lambda$  can be termed a saturation rate.

The rate parameter,  $\lambda$ , 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  $\lambda$  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  $\lambda$  is the rate at which saturation is approached (see Killeen, 2001; 2012).

Figure 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  $\lambda$  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  $\delta$ ; 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, Body, Zhang, Bradshaw, & Szabadi, 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 procedures reputed to assess executive function were due to differences in inherent value and/or the differential expression of motoric and mnemonic processes.

## 2. Methods

### 2.1. Subjects

Adult male BALB/c, C57BL/6n, and DBA/2 mice were purchased from Harlan Laboratories (Indianapolis, IN) at 6–8 weeks of age. Mice were housed (2 per cage) in clear polycarbonate cages with wire tops and woodchip bedding located in an AAALAC-accredited facility. A diagonal Plexiglas® barrier separated cage mates, who were always of the same strain, effectively creating single housing. The vivarium was temperature- and humidity-controlled and maintained on a 12-h light-dark cycle (lights on at 6:00 a.m.). Experimental sessions were conducted during the mice's light period. Mice had free access to water when in their home cages. Mice were maintaining at a target weight of 24g by feeding a measured quantity of food following each experimental session (usually 2.5g). Groups consisted of 4–8 mice of a given strain for a total of 41 mice (8:7 (pellet: milk) BALB/c, 7:8 C57BL/6n, and 7:4 DBA/2). All mice had previous experience lever pressing for flavored reinforcers when the present experiment commenced. Experimental sessions were conducted daily, at approximately the same time with few exceptions.

### 2.2 Apparatus

Experimental sessions were conducted in 12 operant conditioning chambers (12.0" L × 9.5" W × 11.5" H) manufactured by Med Associates (Med Associates Inc. St. Albans, VT, Model ENV-007) enclosed in sound-attenuating cabinets and modified to accommodate mice. The rear wall in each chamber was equipped with a non-retractable response lever (ENV-310W-X) and two Sonalert® tone generators located at the top of the chamber equidistant (L and R) from the centrally located houselight. The front wall of each chamber was equipped with two retractable response levers (ENV-312-2R). Only the left lever was used in the present experiment. The reinforcer delivery system was either a 20mg pellet dispenser (ENV-203M) or a liquid dipper system for mice (ENV-302W-SX). Reinforcers were single 20mg banana, chocolate, grain or sucrose/grain pellets (Purina) comprising a heterogeneous mix of flavors. Liquid reinforcers consisted of a 0.01 cc presentation of a 3:1 solution of water and sweetened condensed milk. In an adjacent room, a computer with Med

Associates® IV programming and interface system controlled experimental events and collected data with a temporal resolution of 0.01 s.

## 2.2. Procedure

Because all mice had prior experience lever pressing, no preliminary training was required. Mice from each strain were divided into two groups defined by reinforcer type. In the first 3–4 sessions all mice earned pellet or milk deliveries according to a fixed ratio (FR) 1 schedule of reinforcement during 30-minute sessions. Next, mice lever pressed for milk or pellets under fixed-ratio requirements that increased across consecutive, daily sessions (Raslear, Bauman, Hursh, Shurtleff, & Simmons, 1988). Following FR 1 training, the fixed-ratio was increased each day in ascending order: FR 15, 45, 90, 180, 360 and 590. Following completion of the highest ratio, each mouse returned to FR 1 for two sessions, and then experienced the same progression again with the FR value increasing each session. Thus, the mice experienced all ratio values greater than FR 1 two times, on different days. Data presented are from the second determination.

## 2.3. Data Analysis

Analyses presented in figures and subjected to statistical analyses were taken from the second series of ratio requirements experienced by each subject. All statistical analyses were conducted using SYStat 11® software (Systat Software, Inc., Chicago, IL). All dependent measures were analyzed by two- (strain × reinforcer type) or 3-way (strain × reinforcer type × fixed-ratio value) analysis of variance (ANOVA), with fixed-ratio value treated as a repeated measure. The threshold for statistical significance for all tests was  $P < 0.05$ . When appropriate, follow up comparisons between strains or reinforcer type with strains were conducted using Tukey's HSD for post hoc analyses.

### 2.3.1. Raw Data

**2.3.1.1. Overall response rate and maximum response rate:** Overall response rates were calculated as total lever presses divided by total session time (less reinforcer delivery time for milk). The peak of the response-rate function (see Fig. 5) for individual mice and taken as the maximum response rate. Maximum response rate was subjected to a square root transformation prior to statistical analyses because of unequal variances among groups.

**2.3.1.2. Reinforcers earned and proportion FR1 reinforcers earned:** The number of reinforcers earned at an FR1 schedule requirement is often considered a measure of unconstrained consumption (Hursh, Raslear, Bauman, Black, & Grunert, 1989). To assess the effects of increasing ratio requirements on reinforcers earned, we calculated the number of reinforcers earned at each ratio requirement relative to the number earned at FR1. We chose the proportion of FR1 reinforcers earned at FR15 for further analyses because, 1) response rate typically peaked at FR15, 2) the number of reinforcers earned generally decreased as a function of the increasing fixed ratio schedule, and 3) most published studies with inbred strains seldom employ greater schedule requirements,.

**2.3.1.3. Quantitative Analysis:** Eq. (1) was fitted to the overall response rate-function obtained for each mouse using least-squares regression. We used two approaches to fitting MPR to the present data. The first approach was a model-comparison approach (Burnham & Anderson, 2002) that uses Akaike weights to compare fits of MPR with different numbers of parameters allowed to vary across groups (e.g., Avila et al., 2009). The second, two-stage, approach was to fit MPR to the data of individual subjects and analyze the resulting parameter estimates at the group level with ANOVA. These two approaches to modeling the



data yielded nearly identical results, however, the ANOVA identified one additional effect of reinforcer type on  $\lambda$ . We report only the two-stage analyses below.

### 3. Results

#### 3.1. Raw Data

**3.1.1. Cumulative Records**—The major advantage of a cumulative record is the ability to detect visually changes in the moment-to-moment rate of a behavior and to identify similarities, or differences, across individuals in these patterns. Fig. 2 shows cumulative records of lever pressing from a single session for all mice in the study. The data were taken from a session in which mice responded for either milk or sucrose under an FR 15 schedule. This ratio was chosen because it was near the peak response rate for most mice and it was the ratio at which nearly all mice earned the greatest number of reinforcer deliveries, excluding reinforcers earned at FR 1. As can be seen in Fig. 1, milk supported more responding than pellets for all three strains, but the effect of reinforcer type was most evident for the BALB/c, intermediate for the C57BL/6, and less so for the DBA/2 mice. In addition, a strain-related difference in response rates occurred with milk but not pellet reinforcers. Also note from the cumulative records that responding occurred at a steady, consistent rate throughout the session; there was no evidence of satiation or fatigue, which would be evident as a negatively accelerated curve.

**3.1.2. Maximum response rate**—Fig. 3 shows the square-root transformed maximum rate of lever pressing across all ratios for each mouse strain and reinforcer type. There was a significant strain  $\times$  reinforcer type interaction ( $F(2,34) = 4.00, p = 0.027$ ) and a main effect of reinforcer type ( $F(1,34) = 28.48, p < 0.001$ ) but no significant effect of strain on maximum response rate ( $F(2,34) = 2.51, p = 0.09$ ).

The main effect of reinforcer type and the interaction between reinforcer type and strain were clarified by post hoc tests. BALB/c mice responded significantly more for milk than pellets ( $p < 0.01$ ), but no significant effect of reinforcer type was seen for the other two strains. Maximum response rate was the same for all three strains for the pellet reinforcer but for the milk reinforcer. BALB/c mice responded at higher rates than the other two strains. Maximum response rate did not differ between the C57BL/6 and DBA/2 strains and the rate of responding for DBA/2 mice did not differ from that of the BALB/c mice (all  $p$ 's  $> 0.1$ ).

**3.1.3. Percent FR1 reinforcers earned**—We compared the number of reinforcers delivered under the FR 1 schedule ('unconstrained' consumption) with the maximum number of reinforcers earned at ratios exceeding FR 1. The greatest number of reinforcers earned in a session when consumption was constrained by increasing costs (FR requirement) was under the FR 15 schedule for all but one mouse in the study. To examine constrained consumption relative to consumption under the FR1 we calculated the percent of reinforcers earned at FR 15 as a function of the number earned at FR 1. Table 1 shows the mean number of milk and pellet reinforcers earned under FR 1 for each strain.

Reinforcer type ( $F(1,34) = 10.35, p = 0.003$ ) and the interaction between reinforcer type and strain ( $F(2,34) = 6.13, p = 0.005$ ) significantly affected the number of reinforcers earned when consumption was unconstrained (Table 1). Fig. 4 shows the percentage of FR 1 reinforcers earned at FR 15. The decrease in consumption due to increased cost (FR 15) was greater for sucrose pellets ( $F(1,34) = 18.35, p < 0.001$ ). The main effect of strain and the strain by reinforcer type interaction on percent consumption were not significant. Note that a 15-fold increase in response cost reduced pellet consumption only 4–5 fold for pellets for all three strains, and 2–3 fold for milk. Thus, as cost increased so did response output, even as

total reinforcers delivered decreased. The mice increased response output more, and maintained consumption levels closer to unconstrained consumption more for milk than for pellets.

**3.1.3. Overall response rate**—Fig. 5 shows overall response rate as a function of fixed ratio schedule; the curves are the functions defined by Equation 1. Response rates tended to be lower for pellet-maintained responding than for milk-maintained responding. Repeated measures analysis of variance revealed a significant fixed ratio  $\times$  strain  $\times$  reinforcer type ( $F(12,204) = 2.714, p = 0.002$ ) interaction. There were main effects of strain ( $F(2,34) = 3.626, p = 0.036$ ), reinforcer type ( $F(1,34) = 23.98, p < 0.001$ ), and fixed ratio ( $F(6,204) = 43.964, p = 0.001$ ). There was a significant 2-way interactions between strain and reinforcer type ( $F(2,34) = 4.65, p = 0.016$ ), fixed ratio and strain ( $F(12,204) = 2.994, p = 0.001$ ) and fixed ratio  $\times$  reinforcer type ( $F(6,204) = 11.237, p < 0.001$ ).

### 3.2. Quantitative analysis: parameters of Eq. (1)

The MPR equation was fit to the response rate function of individual mice. Eq. (1) provided a good fit to the individual data accounting for on average 85% of the variance (MSE = 0.012). The values of the parameters derived from the fits to the data of individual mice are shown graphically for each group in Fig. 6.

**Specific activation ( $a$ )**—There were no effects of strain or reinforcer type on specific activation. The interaction between strain and reinforcer type on specific activation was also not statistically significant (all  $p$ 's  $> 0.15$ )

**Response time ( $\delta$ )**—Prior to statistical analyses the reciprocal of the  $\delta$  estimate for each mouse was square root transformed. Note that  $1/\delta$  is the estimate of maximum response rate possible according to Eq. (1). A regression was conducted on obtained maximum response rate versus that predicted according to Eq. (1). The regression results indicated that the estimated value of  $1/\delta$  explained 97.4% of the variance in obtained maximum response rate ( $\beta = 0.94, p < 0.001$ ;  $R^2 = 0.974, F(1,36) = 1355.85, p < 0.001$ ). Thus, in addition to providing a good description of the entire response rate function for each mouse, MPR also provided a good prediction of the ratio at which maximal responding occurred. The effects of strain ( $F(2,32) = 5.77, p = 0.007$ ) and reinforcer type ( $F(1,32) = 43.18, p < 0.001$ ) on response time were significant. The interaction between strain and reinforcer type was also significant ( $F(2,32) = 8.69, p = 0.001$ ). The nature of the significant interaction was clarified by post hoc tests. The effect of reinforcer type on response time appeared only for the BALB/c mice ( $p < 0.05$ ). In addition, the response times of the BALB/c mice were shorter (i.e., response rate was higher) than that of the C57BL/6 and DBA/2 strains ( $p$ 's  $< 0.05$ ).

**Saturation rate ( $\lambda$ )**—The effects of strain ( $F(2,34) = 6.87, p = 0.003$ ) and reinforcer type ( $F(1,34) = 4.78, p = 0.035$ ) on the rate at which the impact of reinforcement saturates were significant. The interaction between strain and reinforcer type was not significant. The larger  $\lambda$  indicates that milk delivery has a shorter temporal influence than sucrose delivery for all strains. The rate of saturation was also greater for BALB/c mice compared to the C57BL/6 and DBA/2 mice ( $p$ 's  $< 0.05$ ). There was no difference in rate of saturation between the C57BL/6 and DBA/2 mice ( $p > 0.4$ ).

## 4. Discussion

The present study was designed to evaluate the effectiveness of two qualitatively different reinforcers in maintaining fixed-ratio responding with genetically divergent mouse strains. The present study provided a direct and detailed assessment of each reinforcer by measuring

the rate of lever pressing as a function of the increasing cost (fixed-ratio) of each reinforcer delivery. Parametric manipulation of the ratio-schedule requirement afforded the opportunity to draw precise conclusions regarding milk and sucrose pellet reinforcers. Specifically, we asked whether the greater effectiveness of milk as a reinforcer is the result of a more efficient response topography or a greater inherent value as compared to sucrose pellets.

A distinction between reinforcer efficacy and value may be useful in interpreting the present results (see Rowlett, 2000). The efficacy of a reinforcer refers to the maximum response rate produced by a reinforcer under a particular fixed-ratio schedule (Rowlett, 2000; Bizo, Kettle, & Killeen, 2001). The value of a reinforcer is reflected in the maximum number of responses a subject will make to gain access to a single presentation of that reinforcer. Inspection of response-rate functions over a range of fixed ratios (see Fig. 5) confirms that milk is a more efficacious reinforcer than sucrose pellets, in the sense that milk produced substantially higher peaks in the response rate functions. The two reinforcers did not differ, however, in the response rates maintained at the higher fixed ratios. MPR, therefore, predicts that the reinforcers would not produce consistently different break points (i.e., the extrapolated x intercept) under a progressive ratio schedule because the specific activation parameter for each reinforcer was approximately equal. It is for this reason that existing economic-based models that attempt to quantify the elasticity or essential value of each reinforcer type (e.g., Hursh & Silberberg, 2008) provide limited insight regarding potential mechanisms that contribute to the differences observed. MPR, a mechanistic approach (Killeen, 1995), implies a difference in efficacy between milk and sucrose pellets and this difference in efficacy is produced by the differential expression of motoric and mnemonic processes, but not in the inherent value of each consumable as a reinforcer of lever pressing.

The MPR parameter  $\delta$  accounted for the difference in the maximum response rates ( $1/\delta$ ) supported by response-contingent delivery of milk and sucrose pellets. This parameter has frequently been taken as an index of the biomechanical limitations on responding imposed by the specific response device under study. For example, Bizo and Killeen (1997) found that  $\delta$  varied in a predictable manner when, in different conditions, pigeons were required to peck keys or press treadles for milo. The finding, here, that  $\delta$  is affected by reinforcer quality even though the response device is the same is not strictly predicted by MPR (Killeen & Sitomer, 2003). It should be noted that in the version of MPR used here,  $\delta$  is a composite of the minimum time taken to make a single response and longer pauses in responding that occur, for example, following food delivery or if the animal frequently checks the dispenser for a pellet (see Bradshaw & Killeen, 2012). If there was more pausing with pellets than with milk then this might explain why the  $\delta$  values obtained for pellets was longer.

A recent modification of MPR that separates post-reinforcement pausing from the minimum response time may have provided a better account of the relationship between  $\delta$  and reinforcer type (see Bradshaw & Killeen, 2012), but we did not have the pauses available that would permit such an analysis. It is possible that our estimates of  $\delta$  would have been shorter and constant across reinforcement types if pauses could have been isolated, thereby making a purer measure of response duration possible. The interpretation of the composite  $\delta$  used here is that it provides an index of the minimum interresponse time obtained under the particular contingencies of reinforcement examined.

Applied here, that interpretation might suggest that the termination of lever-pressing is more tightly controlled by milk than by pellet delivery. One important difference between liquid and pellet delivery systems is the extent to which delivery of each consumable competes with lever pressing (or other behavior). Delivery of liquid reinforcers is typically arranged



according to a limited hold, that is, the opportunity to consume lasts only a few seconds (3 s here). When a ratio-schedule requirement is met, lever pressing is interrupted by milk delivery and mice must stop pressing (and do so rather quickly) in order to consume the solution. In contrast, a pellet remains in the food tray until the mouse consumes it, so the functional contingences on lever-release and disengagement from the response bout are less restrictive for pellets than for milk. Therefore, it is possible that milk differentially reinforces releasing the lever compared to sucrose pellets, producing shorter response durations and, hence, shorter response times. Perhaps the parameter,  $1/\delta$ , reflects the biomechanics of the response device as well as other implicit contingencies of reinforcement produced by the device. Thus,  $\delta$  for milk is, in part, shorter because milk delivery is available for a limited period of time and is better discriminated.

Previous studies have found some effect of reinforcer quality or magnitude on response time,  $\delta$  (as a composite), and saturation rate ( $\lambda$ ). Killeen and Sitomer found a positive relationship between  $\delta$  and  $\lambda$  among rats (Killeen & Sitomer, 2003) and revised MPR by putting  $\delta$  in the expression for coupling. With this change,  $\delta$  and  $\lambda$  became orthogonal to one another. This is the version used in Equation (1). Rickard et al., (2009) found an inverse relationship between  $\delta$  and  $\lambda$  when the volume of a sucrose solution that reinforced rats' lever pressing was manipulated across conditions under a progressive-ratio schedule. This is consistent with what is seen across groups in the present study. The present finding of an effect of reinforcer type on the maximum response rate possible is difficult to reconcile with the simpler interpretation of  $\delta$  as a strict biomechanical limit within the MPR framework, but it should be noted that Herrnstein's quantitative statement of response strength (Herrnstein, 1970; de Villiers & Herrnstein, 1976), the most prominent quantitative treatment of schedule-controlled behavior, has had the very same difficulties (Dallery & Soto, 2004; McDowell, 2005; 2012). Clearly, the mechanisms contributing to the obtained minimum response time require further investigation (Killeen & Sitomer, 2003, Bizo & Killeen, 1998).

Our finding and that of Rickard et al., (2009), of a tradeoff between the model parameters  $\delta$  and  $\lambda$  (Fig. 6) suggest a probable dynamic interaction between two processes. Cumulative records of lever-pressing by mice in the current study (Fig. 2 & others not shown) consistently showed that responding was more 'ragged' (i.e., more pausing) when reinforced with pellets, particularly for the C57BL/6 and DBA/2 strains. The physical nature of the reinforcers (liquid vs. solid) likely played a role in this difference. In addition, delivery systems for liquid and pellet reinforcers may give rise to differences in the topography of lever pressing and the latency to consume each reinforcer. To the extent that mice consumed sucrose pellets moments after the lever press that produced them, these conditions are analogous to those arranged in studies of unsignaled, non-resetting delayed reinforcement (see Lattal, 2010). Therefore, the lower estimates of response time under sucrose pellets likely resulted from the effects of intermittent delayed reinforcement of lever pressing (or releasing), and greater coupling of non-target responses (Shahan & Lattal, 2005; Schaal, Shahan, Kovera, & Reilly, 1998).

The present findings are in keeping with those of Youn et al., (2012); that the observed phenotype of inbred mice is a result of genotype and specific motivational operations and/or qualitative properties of the reinforcer used in the particular study. Quantitative analyses with MPR showed that both motor and delay-of-reinforcement processes might be affected by reinforcer type (but see Calvert, Green, & Myerson, 2010). On a practical level, genotype-reinforcer interactions serve to guide researchers' choice of protocol – milk is a particularly efficacious reinforcer for mice, especially when only a few responses are required to earn a single presentation. In discrete-trial procedures used to assess attentional (Steckler, 2001; Humby, Wilkinson, & Dawson, 2005) and memorial (Estapé & Steckler,

2001; 2002) function in inbred mouse strains, milk reinforcement may therefore optimize training protocols. Theoretically, the present findings suggest researchers take great care when interpreting effects of strain in phenotyping studies. For example, the efficacy of milk as a reinforcer is not due to its intrinsic value, which apparently does not differ among these strains, but to its engagement of motoric and memorial processes, which appears to differ among strains. Hence, the complexity of environment-genotype interactions that impede researchers' attempts to determine the functional consequences of genetic differences among inbred mouse strains may be mitigated somewhat by identification of behavioral mechanisms and engaging formal theoretical models.

Finally, MPR suggests persistent differences in the coupling of reinforcers to target responses among the inbred strains studied here. If  $\lambda$  is large, then the influence of the reinforcer dissipates quickly, so it is coupled with fewer prior responses. Saturation rate was more rapid for BALB/c mice regardless of reinforcer type. Therefore, according to MPR, the delay of reinforcement gradient for BALB/c mice is steeper than that of C57BL/6 and DBA/2 mice (e.g. Killeen, 2011). Further support for this conclusion might be seen in species differences in temporal discounting. Previous studies have found differences between pigeons and rats in estimates of the rate of saturation: it is much larger for pigeons (cf., Killeen, Posadas-Sánchez, Borgå, & Thrailkill, 2009; Rickard, Body, Zhang, Bradshaw, & Szabadi, 2009). These findings are consistent with the steeper rates of discounting by pigeons compared to rats (Green, Myerson, Holt, Slevin, & Estle, 2004; Mazur & Biondi, 2009), suggesting that discount rate and  $\lambda$  may index similar behavioral mechanisms. The present findings, larger  $\lambda$  for BALB/c mice and comparable rates for C57BL/6 and DBA/2 mice, predict differences in the delay of reinforcement gradients for these strains. Remarkably, based on the few strain-comparison studies of delay discounting with mice, this prediction appears to be in accord with the available data (Helms, Reeves, & Mitchell, 2006; Otoabe & Makino, 2004). That is, BALB/c mice appear to discount the value of delayed reinforcers at a higher rate than C57BL/6 and DBA/2 mice, who discount at comparable rates.

In conclusion, we have shown that common inbred mouse strains used as backgrounds for genetic mutations are sensitive to the specific reinforcer maintaining their behavior. The differences in reinforcer efficacy between milk and sucrose pellets may play an important role in the level of memorial performance observed with inbred strains. Thus, the presence or absence of strain differences in behavior phenotyping studies are likely to depend on the reinforcer and motivational operations employed to engage the animal in the procedure. In addition, the use of a formal quantitative model (MPR) provided a context to interpret the behavioral effects of differences in reinforcer efficacy. Use of a formal model aided the identification of behavioral mechanisms impacted by each reinforcer type and potential differences in these processes among inbred strains.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

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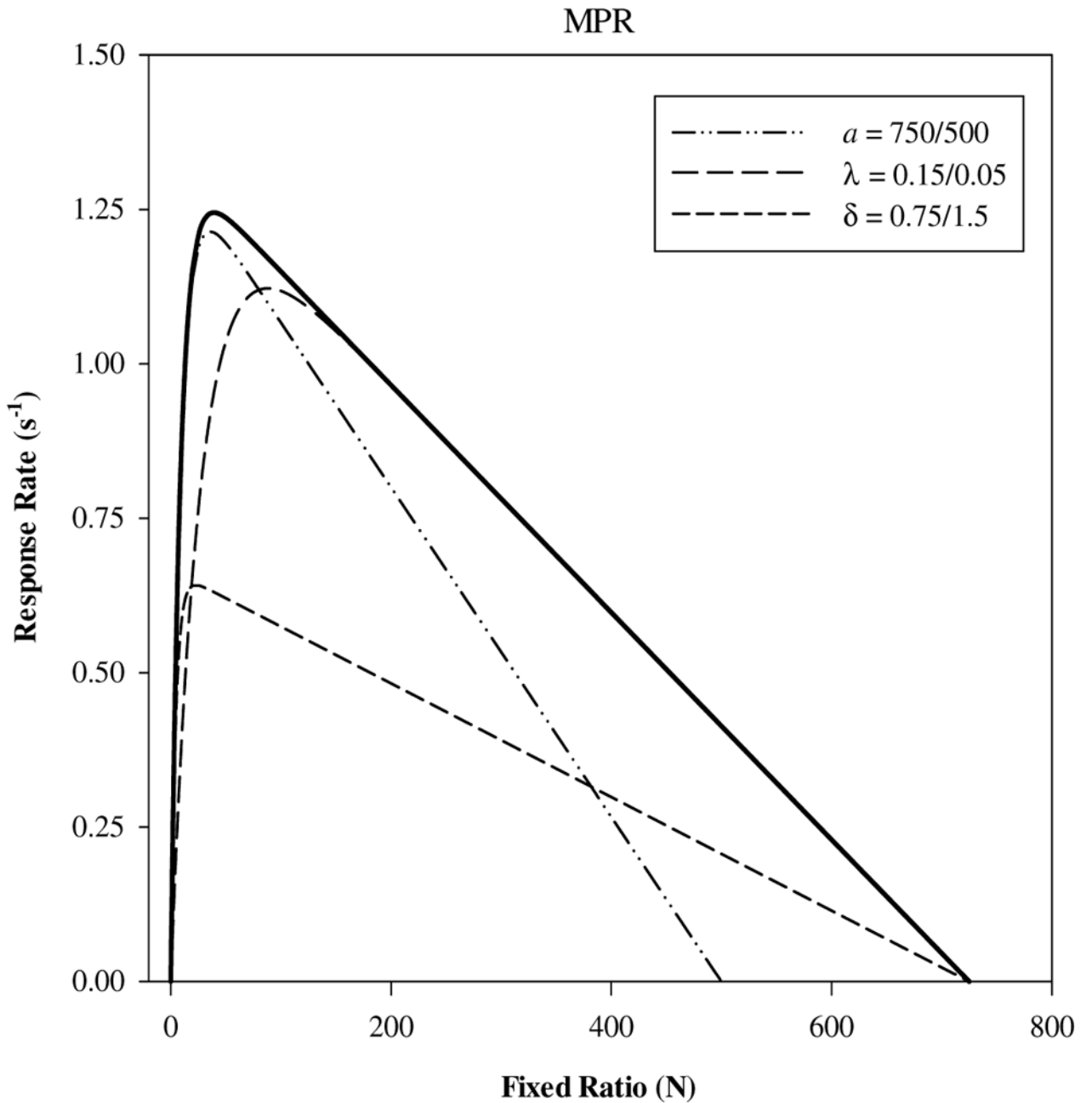
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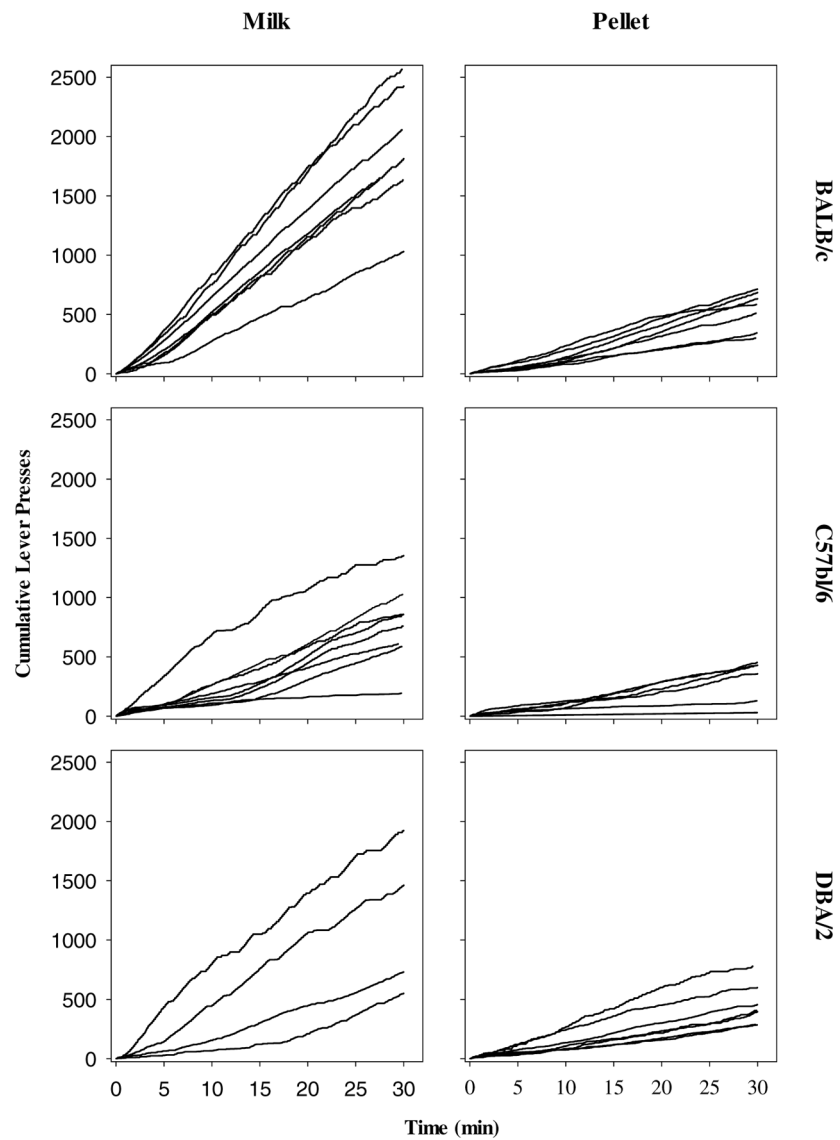
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### Highlights

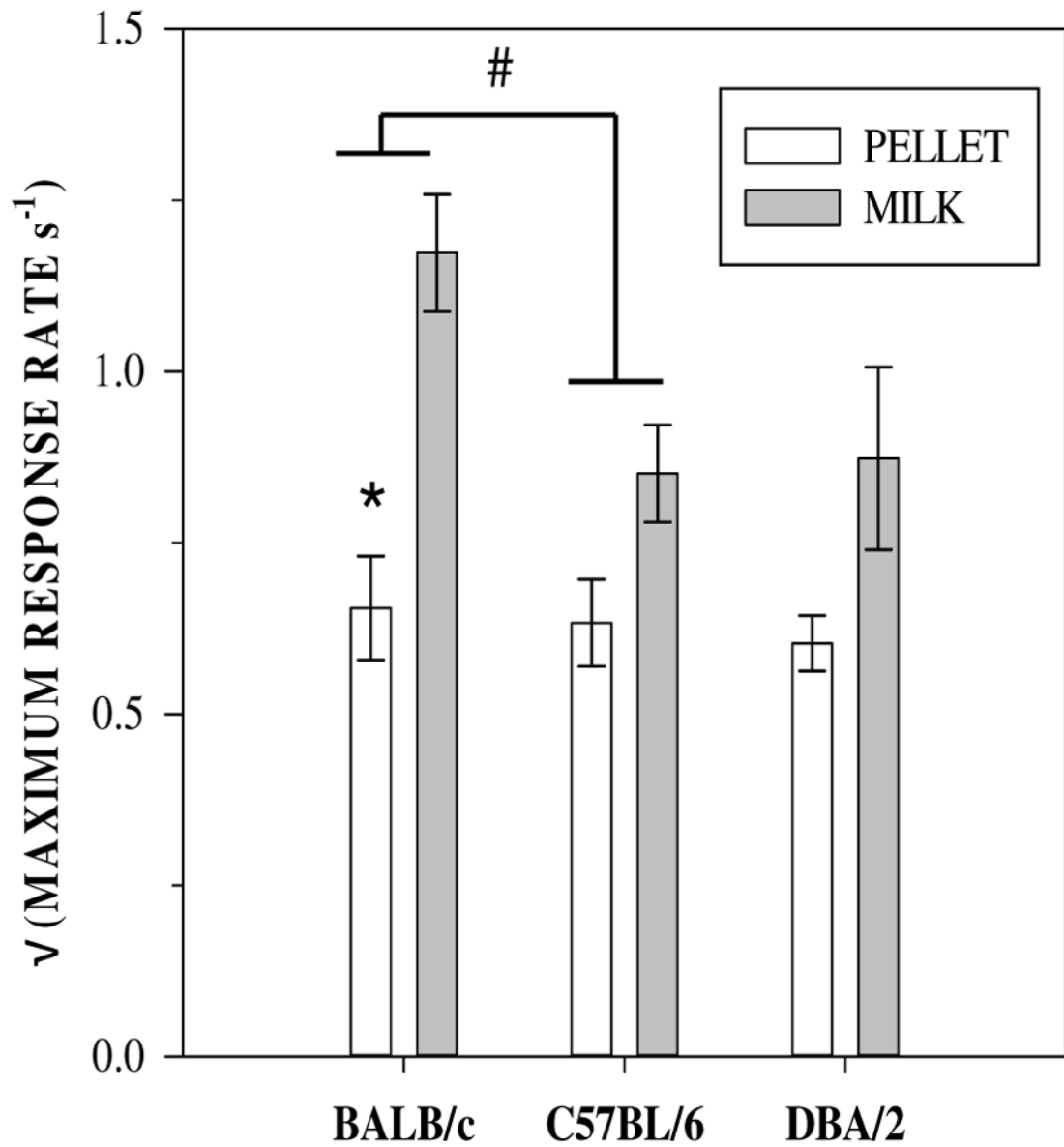
- Three inbred mouse strains (BALB/c, C57BL/6, DBA/2) responded on fixed-ratio schedules of reinforcement.
- The effects of two qualitatively different reinforcers on response rate were assessed.
- Response rates were higher for milk compared to sucrose pellets on moderate ratios.
- The responding of inbred mice is sensitive to reinforcer type.

**Fig. 1.**

Predicted overall response rate ( $s^{-1}$ ) plotted as a function fixed ratio schedule by MPR (Eq. 1). The thick reference line represents predictions with  $a = 750$ ,  $\lambda = 0.15$ , and  $\delta = 0.75$ , respectively. Each dashed line indicates the changes in the shape of the predicted function given the change in one parameter as indicated at the right of the forward slash. The change in  $a = 750/500$  (dot-dot-dash) corresponds to a less valued reinforcer that produces a lower break point and intercepts the x-axis at a smaller fixed ratio. The change in  $\lambda = 0.15/0.05$  (long dash) corresponds to a decrease in the rate at which working memory saturates and a larger fixed ratio when the peak of the rate function is reached. The change in  $\delta = 0.75/1.5$  corresponds to an increase in the minimum response time and a decrease in the peak response rate from 1.3 to .66 responses  $s^{-1}$ .

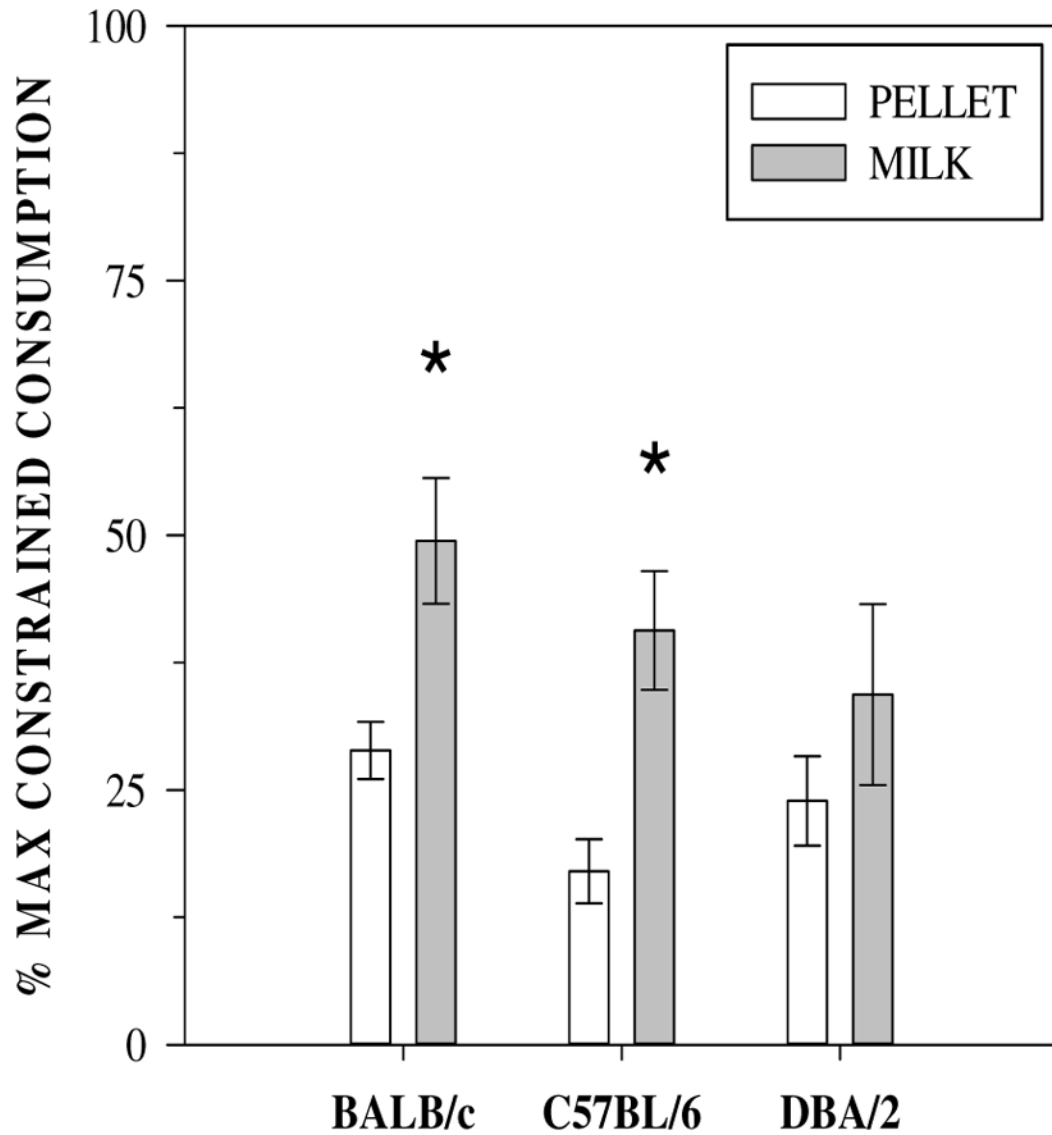


**Fig. 2.** Cumulative records of lever pressing for milk (right) and sucrose pellets (left) for an entire session. Lever pressing was reinforced according to a FR 15 schedule. Rows correspond to strain.

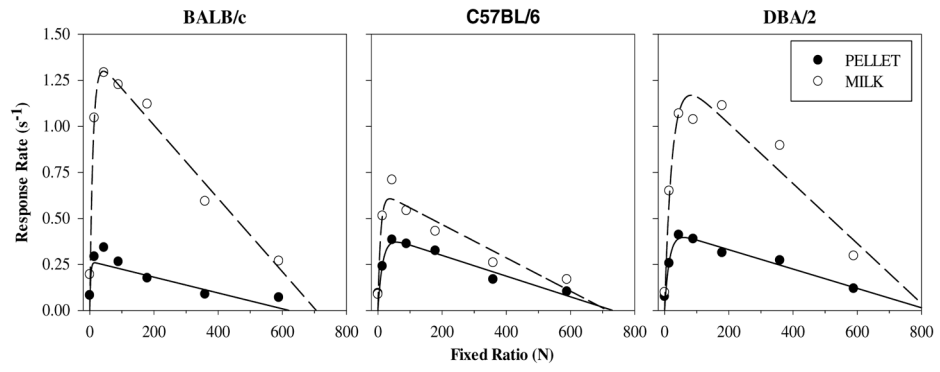


**Fig. 3.** The (square-root transformed) maximum response rate ( $s^{-1}$ ) obtained for each strain of mice responding for milk or sucrose pellets. # \*BALB/c mice responded at significantly higher maximum rates under milk compared to pellet reinforcers and at higher maximum rates than C57BL/6 mice.

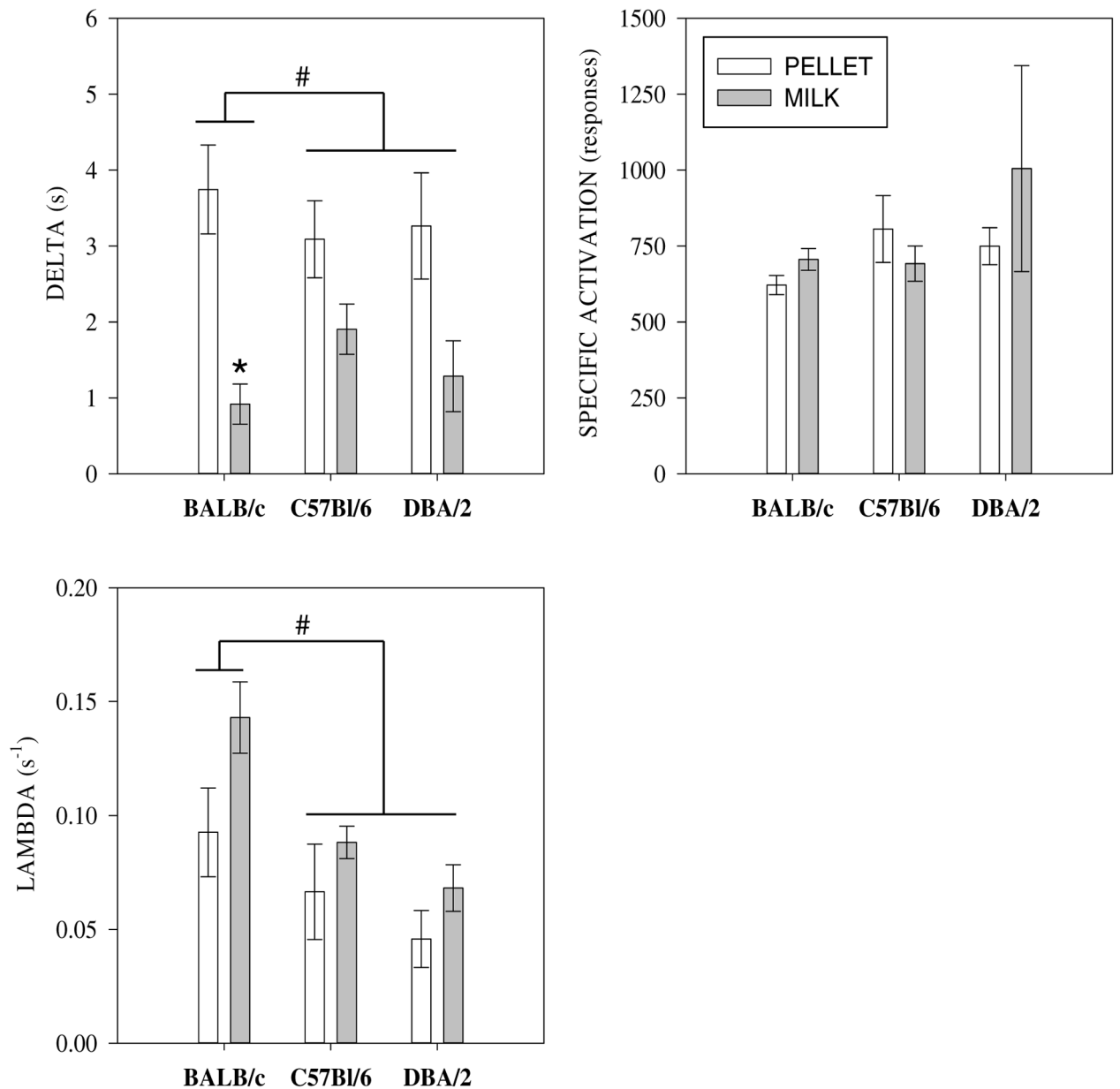




**Fig. 4.** Percentage of reinforcers earned under FR 15 relative to the number earned under FR 1 ( $100 \times (R_{FR15}/R_{FR1})$ , where R = reinforcers earned). # The reduction in reinforcers earned was significantly less for BALB/c and C57BL/6 mice earning milk relative to sucrose pellets.



**Fig. 5.** Response rate ( $s^{-1}$ ) plotted as a function of fixed ratio for each strain and reinforcer type. The dashed and solid curves are the predictions of MPR to the group data for milk and pellets, respectively.



**Fig. 6.** Parameters obtained from fits of Eq. (1) to response rate functions of individual mice. (A) Delta ( $\delta$ ): #\*BALB/c mice responded at significantly higher maximum rates under milk compared to pellet reinforcers and at higher maximum rates than C57BL/6 mice. (B) Specific Activation ( $a$ ): Effects of strain, reinforcer type, and their interaction were all non-significant. (C) Saturation rate ( $\lambda$ ): #\* Rate of saturation is significantly greater for BALB/c mice compared to C57BL/6 and DBA/2 mice.

**Table 1**

Mean (+/- SEM) number of pellet or milk reinforcers earned under a FR 1 schedule for each strain. This unconstrained consumption is also the number of responses during the thirty-minute session. Reinforcers earned was the mean number across the two FR 1 sessions of exposure for each subject. BALB/c mice earned significantly more milk than pellet reinforcers ( $*p < 0.02$ ) and more milk reinforcers than C57BL/6 mice ( $\#p < 0.04$ ).

	Strain		
	BALB/c	C57BL/6	DBA/2
Pellet	144.8 (13.4) *#	166.4 (11.9)	134.4 (17.1)
Milk	240.7 (9.2)	155.9 (9.0)	175.0 (27.9)