The Assessment of Motivation in Reln Deficient Mice Using a Progressive Ratio Schedule of Reinforcement

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**Introduction**

This project is specifically designed to answer the question: Does deficient Reln expression affect motivation? The performance of three strains of mice, each with a different level of Reln expression, will be assessed on a schedule of reinforcement to determine whether or not motivation to press a lever to gain food pellets as a reward differs among the strains. Data from an assay previously conducted in the same lab showed that mice deficient in Reln were poorer at a behavioral timing task than normal mice. However, the genotype differences revealed by the timing task could be due to poor motivation rather than a timing deficit. This study is designed to assess the possibility that differences in motivation exist among the three strains. The genotypes used in this study include the wild type normal (+/+; 100% Reln expression), heterozygous (+/rl; 50% Reln expression), and the reeler mouse (rl/rl; 0% Reln expression).

The genotypes of particular interest to this study are the Reln deficient strains. The rl/rl mice have two copies of the defective gene that causes problems in producing a specific protein. This protein, known as Reln, is responsible for proper brain development and is absent in these mice (Laviola, Ognibene, Eomano, Adriani & Keller, 2009). This causes a host of behavioral abnormalities in the mouse, such as poor motor coordination, ataxia, and a loss of interest in pleasurable activities (Alter, Liebo, Desnick & Strommer, 1968; Laviola et al., 2009). Reelin deficiencies arose as a spontaneous mutation and were first described by D.S. Falconer in 1951 in subjects he dubbed “trembler” mice. (Falconer, 1951; Fatemi, 2001). Now known as reeler mice, the strain has become a model for human lissencephaly, or “smooth-brain” disease (Fatemi, 2001). Further, the +/rl, has become a possible animal model for analyzing human
psychopathology (Teuting et al., 1999) However, the +/-rl mouse has generally not been consistently found to have behavioral abnormality (Salinger, Ladrow & Wheeler, 2003; Podhorna and Didriksen, 2004; Fatemi, 2001). The +/-rl mouse is well-worth further investigation as it has brain abnormalities that are similar to those found in brains of people with schizophrenia (Fatemi, 2001). Further, behavioral symptoms that suggest poor motivation have been found in people with schizophrenia, making motivation an important aspect of behavior to explore. Moreover, it is reasonable to expect that Reln deficient mice will show poorer motivation than +/-+ mice. This expectation is due to the fact that dopamine up-regulation, or over expression, is also found in reeler mice brains (Laviola et al., 2009), and dopamine over expression has been directly related to a reduction in operant motivation (Drew et al., 2007).

Previously, progressive ratio (PR) schedules have been used to assess motivation in genetically abnormal mice (Vaughan, Moore, Haskell-Luevano & Rowland, 2006). This schedule of reinforcement requires the subject to press a lever in order to receive a food pellet. After each pellet the lever press requirement increases systematically. A breakpoint is reached when the subject emits a final number of responses and then pauses for an amount of time specified by the experimenter. The breakpoint is the total number of responses the subject emits in a given session. This schedule is a strong measure of motivation because the subject is required to make a greater number of responses than during the last cycle to receive its next food pellet (Richardson & Roberts, 1996; Chaney & Rowland, 2008).

**Rationale**

This study is of particular importance because the reelin deficiency found in +/-rl mice is directly analogous to the same protein deficiency found in the brains of people suffering from autism, schizophrenia, and bipolar disorder (Salinger et al., 2003; Persico et al, 2001; Ballmaier,
Analyzing performance moderated by a progressive ratio schedule may lead to the development of behavioral strategies to increase operant motivation in subjects suffering from the deficiency and related psychiatric disorders.

I am interested in pursuing a career in behavioral therapy for special needs children, especially children with autism. This research will help me learn more about the research behind identifying possible genetic causal variables and the development of treatment for these children. Analyzing the behavior of mice on these behavioral assays now in a controlled laboratory setting will help me implement real-life techniques later in my career.

**Methods**

The cohort of mice used in this experiment is housed in the Psychopharmacology Lab in a colony room maintained at a constant temperature. The experiment has been approved by the IACUC, protocol A0910-006, which was approved on September 29, 2009. All mice are food restricted within 85% of their free-feeding weight to maintain the primary motivation for food. 8-10 mice of each genetic strain will be used in each part of the experiment. Two breeding pairs will be used to breed a new cohort of mice made up of all three genetic strains as well. Each mouse in the new cohort is to be genotyped by Dr. Thomas Shafer’s laboratory.

Our progressive ratio schedule increases by a value of 2 after each reinforcer. The mouse must press the lever 2 times to receive the first reinforcer, and then must press 4 times, then 6, 8, 10, and etc. The session will stop if the mouse does not press the lever for over three minutes or has received 30 pellets. All experimental sessions will be conducted in operant chambers in another sound-attenuating room separate from the colony room. The chambers present no stress or discomfort to the animals, and are used primarily to record behavior under the control of a
schedule of reinforcement. All of the chambers are controlled by computers in yet another control room. Data is saved to a database that will later be analyzed by using the statistical software SPSS.

**Description of the Product**

In order to fulfill the requirements for the Undergraduate Departmental Honors thesis, I will create and execute my own experiment. After the data is appropriately analyzed, I will then write a paper conclusively explaining the results of the experiment. I then must defend my paper in front of a committee consisting of Dr. Ruth Hurst, Dr. Raymond Pitts, and Dr. Thomas Shafer. Ultimately, my thesis will be catalogued in the UNCW library. In addition, this thesis will be presented in a poster both on the UNCW campus and at least one professional conference.
Works Cited


modeling of major neurobehavioral syndromes. *Neuroscience and Biobehavioral Reviews, 33*, 560-572.


Teuting et al. (1999). The phenotypic characteristics of the heterozygous reeler mouse. *NeuroReport, 10*, 1329-1334