

## **Prostaglandin E2-Induced Fever in Young and Old Long-Evans Rats**

### **Introduction**

As rats age, they tend to show a reduced fever response to infections. Response to fever consists of a cascade of chemical responses within the body, and it is not currently clear which of these events is negatively affected by the aging process. This decrease response to fever-causing agents implies that the body's mechanisms for controlling body temperature may become defective with age.

The body's response to fever can be studied by injecting them with certain chemicals. Two chemicals that are commonly used to achieve this effect are lipopolysaccharides (LPS) and proinflammatory cytokines. When injected into young rats, these chemicals are effective in inducing a fever response but they are ineffective when injected into older rats. In naturally occurring fever responses, one of the initial steps involves release of proinflammatory cytokines into the peripheral circulation. There is evidence that proinflammatory cytokines do increase normally after older rats are injected with LPS, even when the LPS injections fail to induce fever. Also, direct injection of proinflammatory cytokines bypasses this first step, yet still fails to produce fever in older rats. Therefore, the blunted fever response of older in spite of normal levels of proinflammatory cytokines (whether naturally occurring or artificially administered) indicates that the problem with fever response in older rats is somewhere after the first step.

One of the next steps in the fever response cascade involves the release of prostaglandin E (PGE), a chemical produced by the body in response to proinflammatory cytokines. It is possible that the blunted fever response of old rats occurs because (1) proinflammatory cytokines fail to cause an increase in the secretion of PGE and/or (2) the neurons in the brains of older rats responsible for controlling body temperature are insensitive to the increased secretion of PGE and do not respond in the same way as in younger animals. This second possibility can be tested in rats by measuring the fever response (increase in body temperature) that directly follows experimental administration of PGE into the third ventricle of the brain. The third

ventricular is a site near the area of the brain that controls body temperature and is known to be highly sensitive to PGE.

### **Study Objectives and Hypotheses to be Tested**

The objective of this study is to determine whether the neurons in the brain of the older rat respond normally to PGE.

**H<sub>0</sub>:** There are no differences in the fever responses of old and young rats following intra-ventricular PGE treatment. The increase in body temperature measured in old rats does not differ from that measured in young rats.

**H<sub>A</sub>:** Old rats show a decreased fever response compared to young rats following intra-ventricular PGE treatment. The increase in body temperature measured in old rats is significantly less than that measured in young rats.

### **Methods**

Subjects will be young (3-5 months old) and old (24-26 months old) Long-Evans male rats. All rats will have cannulas surgically implanted into the third ventricle of the brain using standard techniques. This cannula will provide a means of introducing PGE into the brain. The rats will then be allowed to recuperate for a period of 14 days. Each rat will then receive two treatments in sequence. First, rats will be administered 0.05% ethanol in saline solution at a rate of one ml/min for 30 min. This solution is the solvent into which the PGE is dissolved, and represents a control for the administration of PGE. Three days after administration of the control solution, each rat will receive 100 ng of PGE, administered at the same rate (ml/min for 30 min).

Body temperature will be monitored for 120 minutes following each treatment using a telemetric device implanted in the abdomen of each rat at the time of cannula implantation. This device measures core body temperature at 5-min intervals and transmits this information to a receiver. The body temperature data is then relayed to a PC computer for analysis. The change in body temperature observed following PGE treatment will be compared to the changes in body temperature following the control treatment using Analysis of Variance (ANOVA). In addition, ANOVA will be used to compare the responses of young and old rats.

## **Expected Results And Interpretation**

I expect that young rats will show a significant increase in body temperature within 120 minutes of administration of PGE and no such response following administration of the control solution. If the brains of old rats are still as responsive to PGE as the brains of young rats, then the old rats should also show an increase in body temperature within 120 minutes of PGE administration, and there should be no significant difference between old and young rats in the amount of the increase in body temperature. If the brains of old rats are less responsive to PGE, then old rats will show a significantly lower response to PGE administration than young rats and may show no difference in body temperature between treatments (control solution vs. PGE).

If old rats are unable to increase their body temperatures in response to intra-ventricular PGE treatment, it will indicate that the brain areas that regulate body temperature cease to respond normally as animals age. If, on the other hand, the old rats show the same response to intra-ventricular PGE treatment as do young rats, it will suggest that the lack of fever in response to infections and chemical treatments in older rats is due to a defect in another part of the cascade of physiological events that result in fever.