Bellwether Magazine

Volume 1
Number 55 *Winter 2002*

Article 16

Winter 2002

Effects of Early Exposure to MSG and Phenobarbital

Effects of early exposure to MSG and Phenobarbital

Newspaper and television ads extol the benefits of a multitude of drugs and supplements, diet products, and flavor enhancers. People take herbal remedies to fight everything from a cold to depression, if those don't work, they obtain a prescription for one of the many drugs to elevate or alter their mood. Nobody knows yet the long-term effects of all these substances on the human body, and in particular on the highly vulnerable perinate. What may be therapeutic or safe for the mother, could be toxic to the fetus and nursing infant. Many of these compounds are too new to have been studied for a long period of time.

There are two substances that have been widely available for many years, and they, for 25 years, have been one of the subjects of **Dr. Bernard Shapiro's** funded research. Shapiro, professor of biochemistry, has studied the influence of MSG on prenatal and perinatal development. Fifteen years ago, he added the drug phenobarbital to his investigations. Why those two? MSG, commonly known as monosodium glutamate, is a food additive that cannot be avoided. It's in prepared foods, and has been widely used in the United States since the 1940s as a flavor enhancer—it is estimated that Americans consume 200 million lbs. of MSG or related products annually. Phenobarbital, a barbiturate, is frequently prescribed to infants in intensive care and to pregnant women for a variety of commonly occurring maladies, among them convulsive disorders that complicate one out of every 200 pregnancies. Prescriptions for pregnant women were particularly common between the 1950s and 1970s exposing more than 23 million children in the United States alone. Neither MSG nor phenobarbital produce visible birth defects, however, it is thought that they interfere with the production of a number of liver enzymes, known as CYPs that are vital to the body's ability to metabolize drugs and other potentially toxic substances.

The expression of these drug metabolizing enzymes is controlled by growth hormone produced by the pituitary. Levels of the hormone in males and females are different as males secrete the hormone in an episodic on-off rhythm with periods where the hormone cannot be detected. Women produce growth hormone continuously and it is always present in circulation. Because of these profiles, the levels of drug metabolizing enzymes are different in males and females; this may in part explain the difference in response to drugs, for example women take longer to emerge from anesthesia

than men. To complicate matters, levels of growth hormone decline as a person ages.

In earlier studies, Dr. Shapiro's group had shown that neonatal administration of normal, exposure-like levels of both phenobarbital and

Extracorporeal High Energy Shock Wave Therapy

Lithotripsy, the fragmentation of bladder-stones by shock waves, is an established treatment in human medicine. Now these shock waves are utilized in equine medicine to help heal specific ligament and bone injuries. **Dr. Olga Seco**, lecturer in sports medicine and imaging, and other ultrasound specialists at the Allam Center for Equine Sports Medicine at New Bolton Center are compiling data on horses they are treating with Extracorporeal High Energy Shock Wave Therapy (ESWT).

The Scott Equine Sports Medicine Building houses the ESWT equipment. Horses with suspensory ligament desmitis and stress fractures, and other musculoskeletal problems are treated with ESWT. In the condition known as suspensory ligament desmitis, the ligament originating in the palmar/plantar aspect of the canon bone has sustained an injury. This injury can affect only the ligament, or have an associated avulsion fracture (piece of bone pulled up at the area of attachment of the ligament by the stress caused by the pulling on the ligament). A stress fracture is an incomplete fracture that occurs as the result of repetitive overload and microfractures in one area of the bone. They frequently occur in the dorsal aspect of the canon bone in thoroughbred racehorses.

ESWT is thought to speed healing as well as relieve pain. Pulsated pressure waves (shock waves; not electric) are sent to the targeted area via a probe contained in a head that also incorporates an ultrasound transducer that helps localize the area of injury during the treatment and focus very accurately in the area of interest. Horses with soft tissue injuries usually receive three treatments at three weeks intervals. For bony injuries, there is usually one treatment, but sometimes depending on the response to the treatment, there can be additional sessions. Each treatment usually consists on 2,000 shocks delivered to the area of injury. Horses received this treatment under sedation as the shock waves cause some pain while being administered.

Many chronically lame horses become sounder with ESWT treatment, although no one knows with any degree of certainty why the treatment seems to work. It is thought that increased blood flow may help with the healing process.

Dr. Seco and **Dr. Virginia Reef** will present their findings at the Sports Medicine Symposium in the spring of 2003.

MSG to laboratory animals can produce delayed, but permanent defects in hormone secretion and drug metabolism, contributing to long-term, serious health consequences. Another of their studies found that prenatal administration of either one of the two substances can result in a multitude of long-term reproductive, growth, hepatic and neural dysfunctions. One finding, in particular, is disturbing: neonatal administration of phenobarbital can induce a delayed but permanent elevation in the activities of several hepatic drug metabolizing enzymes. These enzymes break down specific substances, when their activities are elevated, these drugs are broken down faster. One would expect such elevated activity right after administration of phenobarbital, but not much later. However, it appears that at sexual maturity, when gender dependent differences in drug metabolism appear, the hepatic drug metabolizing enzymes are induced again and remain overexpressed for the rest of life. In rats exposed as neonates to phenobarbital this results in a shorter lifespan, and a great increase in tumor formation.

Neonatal exposure to MSG has a different effect on growth hormone production. It causes a permanent reduction in the secretion of growth hormone which leads to a reduced production of the drug-metabolizing enzymes. This hampers the metabolization of drugs and toxic substance. The reduced quantity of growth hormone leads to stunted growth and irreversible obesity. Like phenobarbital, defects resulting from neonatal exposure to MSG are not apparent until adulthood.

Dr. Shapiro and his group are currently working to answer these questions: How do the chemicals induce the defects? How are the defects expressed? The group has observed that, when the production of growth hormone is disturbed, the level of drug metabolizing enzymes is affected. They found that in male and female rats, prenatally exposed to phenobarbital, there were permanent defects in the expression of these enzymes. The mechanism by which the abnormal profile of growth hormone disrupts the enzyme expression is not known, and the group proposes to investigate it.

It is known that men, exposed perinatally to phenobarbital, have a considerable higher incidence of delayed puberty, undescended testes, and genital abnormalities. In women this exposure leads to irregular menstrual cycles and problems during pregnancy. Both sexes score lower on IQ tests as adults. Further, phenobarbital is a known carcinogen that induces the overexpression of selected hepatic enzymes that can increase the metabolism of innocuous compounds into carcinogenic and toxic metabolites. Perinatal exposure to the barbiturate has been reported to subsequently increase the risk of cancer in adult rats and children.

Phenobarbital and MSG are just two substances that can have an impact on drug metabolism. There are many other compounds that are in drugs or food and their impact on human metabolism is unknown. One of these, aspartame, is used widely as a sweetener. "Our studies with rats have shown that the sweetener, containing an amino acid like MSG, could produce subtle developmental defects in growth hormone secretion," explains Dr. Shapiro. "It is estimated that children consume almost 100 mg of aspartame per kg of body weight per day, a level approaching the adverse doses found in animal studies. Children under the age of five are particularly vulnerable, their hepatic and neuroendocrine differentiation are still incomplete and early constant exposure to low levels of food additives could permanently alter hormone secretion, the expression of hepatic drug metabolizing enzymes and/or their responses to inducing agents. Such effects could unknowingly affect the efficacy of drug therapy or the susceptibility to chemically-induced cancers in adulthood."

Sports Medicine Symposium for Equine Practitioners

Saturday, March 22 and Sunday, March 23, 2003

Registration/participation fee: $175 Saturday only; $200 Saturday plus Sunday wet labs.

March 22: Lecture Topics

Performance problems in the Race Horse—Dr. Ben Martin
Performance problems in the Sport Horse—Dr. Elizabeth Davidson
Cardiovascular Problems in the Equine Athlete—Dr. Virginia Reef
Obscure Lameness Problems in the Equine Athlete—Dr. Mike Ross
Exercise Physiology: What You Need to Know—Dr. Ric Birks
Evaluation of Cardiac Output and Myocardial Function in Exercising Horses—Dr. Mary Durando
Muscular Problems associated with Poor Performance—Dr. Jill Beech
Motion Correction for Standing Equine MRI—Dr. Lexi Lawrence
Suspensory desmitis and its response to treatment with high energy extracorporeal shock wave therapy—Dr. Olga Seco
Where we stand and where we are moving toward with respiratory surgery—Dr. Eric Parente
All presenters with exception of Dr. Mary Durando are New Bolton Center faculty/clinicians

March 23: Wet Labs

Station A - High speed treadmill demonstration
Station B - Endoscopic evaluation of upper airway dysfunction detected at speed
Case discussions at 2 stations - half of participants in each group
Station C - Lameness videos
Station D - Scintigraphic case evaluations

CE credits: 8 hours
Registration limited to 80 for Saturday sessions, 60 (max.) for Sunday wet labs

Saturday Sessions will be held in Woerner Amphitheatre, George D. Widener Hospital for Large Animals, New Bolton Center, Kennett Square, Pa.

Wet Labs to be held in the new Scott Equine Sports Medicine Building, Jeffords Treadmill Building, Scintigraphy station, New Bolton Center.

Please contact Office of Development, New Bolton Center, for detailed information and registration forms. Tel: 610-444-5800. ext. 2500 or email Patricia Hall at <phall@vet.upenn.edu>