

# Science Digest

Contributed by Michael Legge

## Is your cat secretly into opioids?

For those who have cats and have observed the very strong association with the attraction for the catnip plant it may come as no surprise the euphoric look on the cat's face in the presence of catnip. Catnip (*Nepeta cataria*) is a plant along with silver vine (*Actinida polygoma*) are well known attractants for cats who have, in some cases, demonstrated an intoxicated response following significant exposure including eating the plants. A joint research project between Japan and the UK (1) investigated why cats enjoyed being "spaced out". The effects on cats were first described in the 1700s by Japanese and British botanists, including Japanese folklore story of a battle between cats and mice where the mice won the day by intoxicating the cats with silver vine. More recently (2021) the research team has determined exactly which compounds were responsible for the cat euphoria. The group knew that a group of compounds known as indoids protect plants from aphids but was also of interest to cats. They extracted and isolated a range of specific indoids and over a five-year period tested each compound for cat attractants. They identified that nepetalacrol from silver vine and nepetalactone from catnip were both very strong attractants.

To confirm these results, they tested them on 30 feral cats and a leopard, two lynxes and two jaguars in a zoo. All the cat family were attracted to the compounds but mice and dogs were not. Domestic cats exposed to either of the compounds were shown to have elevated  $\beta$ -endorphins ("happiness hormone") but cats given opioid blockers did not respond. Anecdotal reports from 20 years ago where cats were exposed to mosquitos, with and without plant exposure, indicated that both plants were as good as DEET for an insect repellent. The conclusion was that cats learned to use the plants as a functional insecticide and the heroin-like euphoria was an additional benefit. The researchers have patented the compounds as a new generation of insecticides (presumably for humans as cats get it for free).

## Host citric acid cycle aids *salmonella* survival in the gut

*Salmonella enteritica* is versatile pathogen and a common cause of gastroenteritis. It is thought to be effective by establishing itself in phagosomes of either the intestinal epithelial cells or macrophages to produce inflammation via proinflammatory cytokines and chemokines. As a result of this inflammatory response, the citric acid cycle in macrophages is broken in a number of places. This interference with an important metabolic pathway results in the accumulation of certain metabolites including succinic acid,  $\alpha$ -ketoglutarate and itaconate. All three can act as signaling molecules to promote an inflammatory response.

Recent research from Israel has identified that the three metabolites can promote survival of intracellular *S. enteritica* (2). In a two-step process they first induced the regulation of the *Salmonella* pathogenicity island 2 type III secretion system, which injects a protein into host cells that remodels the phagosome. Then they enhanced expression of the polymyxin regulon that promotes resistance to antimicrobial peptides by promoting modifications to lipopolysaccharides. The researchers identified that succinate alone would induce both of the above steps and that *S. enteritica* lacking receptors for succinate had impaired ability to replicate in macrophages. With the evidence of metabolic 'piggy-backing' the authors propose that the initial infection established a replicative niche and initiates an innate immune response leading to inflammation.

The neutrophil response releasing reactive oxygen species kills the *Clostridia* and *Bacteroidia* but *S. enteritica* is resistant. The depletion of the normal gut flora and their metabolic support for intestinal epithelial cells leads to the intestinal cells making a metabolic switch from oxidative phosphorylation to glycolysis thereby decreasing the consumption of oxygen which passively diffuses in to the intestine lumen enhancing the metabolism of *S. enteritica* including the up regulation of succinate leading to a significant increase in *S. enteritica* replication. The authors conclude that *S. enteritica* can respond to succinate by both using it as a metabolic fuel and in macrophages as a way of metabolically re-programming macrophages. In addition they considered that more research is needed relating to understanding the role of succinate-mediated gene regulation.

## Analytical challenges for faecal immunochemical tests for haemoglobin

Colorectal cancer is one of the most prevalent cancers worldwide and in New Zealand approximately 1200 people/year will die of colon cancer. Historically this cancer has been difficult to diagnose until its later stages and early detection will lead to an improved treatment and outcomes. Historically, faecal occult blood has been a primary indicator. However, the use of the guaiac occult blood test had very variable results with specificity 65 to 99% and sensitivity 19 to 44%. The development of a faecal immunological test for haemoglobin has changed significantly the reliability of this test with a specificity of 89% and a sensitivity of 96% as a screening test. In an overview of the faecal immunochemical test for haemoglobin the International Federation of Clinical Chemistry, Faecal Immunochemical Test Working Group have considered pre-analytical variables and possible quality assurance measures for this test (3).

Currently there are variable threshold limits set for both qualitative and quantitative tests and there are approximately 47 different testing systems commercially available. The expert review group identified three main pre-analytical issues relating to the use of the immunochemical tests. First, the comparability of the measurement results especially setting threshold levels and the relationship of calibration techniques to an international reference preparation. There is a lack of harmonization of the results between the different systems and results. There has been a call to develop universal measurement units and proposed that the expression of results should be  $\mu\text{g Hb/g faeces}$  and this has been generally accepted although they indicate the pre-analytical phase uncertainty ranges between 16 and 31%. Second, the pre-examination (pre-analytical) variables, in particular the variable design of the sampling probe between manufacturers coupled with variable sampling instructions. Both these variables have been shown to affect the quality of the specimen. There are also issues relating to specimen transport particularly temperature and buffer composition with positive results declining after for days in transit at 20°C. The different use of polyclonal antibodies by various manufacturers who do not specify what each antibody is detecting in relation to the globin moiety including haemoglobin variants. Variability of results has also been reported from chemicals used in the toilet. Third, the availability of a third party internal quality control (IQC) for the assay is lacking. Although the kit manufacturers provide IQC, studies have indicated that when tested on different systems there was no agreement, primarily due to lack of standardization. The authors consider the development and use of external quality control systems (EQC) and propose a number of methods to develop

an EQC system as well as the issues relating to their development. In conclusion the authors express concern that there will be grey areas relating to manufacturers reagent changes, transferability of results and the interpretation of results that are above the examinational limit but below the threshold limit for follow-up.

### Basophils and eczema itch

Eczema (atopic dermatitis) is one of the most common chronic itch disorders with approximately 10% of adults and 20% of children suffering from this disorder, which can cause inability to focus and loss of sleep. While there is no direct connection between eczema and typical allergens, it quite often is associated with the development of food allergies, allergic rhinitis and asthma with what has been termed the 'atopic march'. The itches result in broken skin barriers and a consequential exposure to allergens then associated with an increase in allergen-specific IgE and sensitization. The mechanisms behind the 'itch flares' in some individuals and not others have previously been unknown.

In a collaborative research between USA, China, Japan, and South Korea the investigators have determined that when eczema suffers have an associated high level of allergen-specific IgE that there is a basophil interaction with sensory neurons which is the trigger for the 'itch-flares' (4). In the next experimental stage they used a mouse model and sensitized the mice with ovalbumin which mimics the human eczema and while the IgE response was identical to humans the mast cells were found to be not responsible for the 'itch flares'. The final set of investigations used the previous patient samples and compared circulating immune cells. Patients with eczema and 'itch flares' were found to have a unique subset of basophils that had a high affinity IgE for  $Fc_{\epsilon}R1$  and CDC203c. They indicate that a group of circulating basophils become primed for enhanced response and mediate the itch flares and following allergen-exposure locate with an elongated morphology alongside free nerve endings. Degranulation in this locale transmit itch signals and signal the release of inflammatory mediators. In this response the investigators identified leukotriene C4 which activate CysLTR2 on sensory neurons which drives the 'itch flares', thus identifying a new role for basophils in atopic 'itch flares'.

### Salicylate poisoning

This is an excellent review of the issues relating to salicylate poisoning and indicates that the first signs and symptoms are

often overlooked as in Emergency Departments. Salicylate poisoning often presents with symptoms similar to viral (including COVID-19) infections. Interestingly there is reasonable evidence from retrospective analysis of autopsy reports that some of the 1918-1919 flu epidemic deaths were caused by salicylate poisoning, which was a recommended treatment at the time. The review considers the historic use of salicylates and importantly identifies the large number of over-the-counter medicines that contain salicylates and the variable concentrations. For example, topical liniments and solutions used in vapour therapy may contain up to 1400 mg of salicylate.

The review describes the metabolic pathways of salicylate metabolism as well as the metabolic issue relating to salicylate poisoning. It is well illustrated and takes a logical progression from metabolism to poisoning and finally options for treatment, indicating that there is no specific antidote for salicylate poisoning. The review is very well referenced, some of which provide interesting historical insights in to both the use and the issues relating to salicylate as well as the up to date current understanding of this common medication (5).

### AUTHOR INFORMATION

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