Pointing the Finger at Proton Pump Inhibitors

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This issue of the *Biomedical Journal* welcomes articles from a wide range of disciplines. We take a look at the optimization of surgical techniques in rabbits and visit some of the medical wonders of stem cell technology. In particular, we highlight Sasmita Biswal's discussion of an emerging link between the use of proton pump inhibitors and hospital-acquired *Clostridium difficile* infections, in addition to intriguing data showing that environmental enrichment protects hippocampal neurons from damage in stressed, diabetic rats. *(Biomed J 2014;37:165-168)*

Key words: clostridium difficile, proton pump inhibitors, diabetes, environmental enrichment, hippocampus

SPOTLIGHT ON REVIEWS – Balancing Risk: Proton Pump Inhibitors and *Clostridium Difficile* Infection

Hospital-acquired infections involving the commensal bacterium *Clostridium difficile* are commonly blamed on the overuse of antibiotics and poor hygiene. In this issue of the *Biomedical Journal*, Sasmita Biswal discusses an emerging culprit responsible for these potentially life-threatening infections, a class of drugs called proton pump inhibitors (PPIs).[1]

C. difficile is a Gram-positive, anaerobic bacterium that resides naturally in the gut in a small proportion of the adult population [Figure 1]. It exists in two forms, vegetative and spore-forming, and may cause problems in colonized individuals following alteration of the normal gut flora by antibiotics. This bacterium produces exotoxins that inhibit Rho GTPases, thus increasing epithelial permeability and causing colitis. Furthermore, the overgrowth of *C. difficile* may lead to the superinfection pseudomembranous colitis (PMC), which can be life-threatening.

The transmission rate of *C. difficile* among hospitalized patients is alarming. One study estimated that patients admitted to hospital for more than 4 weeks have a 50% risk of acquiring the bacterium.[2] The main risk factors for colonization are antibiotics, age, duration of stay, severe illness, cytotoxic chemotherapy, and immunosuppressive therapy.[3] However, studies over the past few years have added a new factor to this list, PPIs, which are designed to limit the production of gastric acid.[4,5] Those exposed to PPIs have a 1.4–2.75 fold higher risk of developing a *C. difficile* infection (CDI) than those not taking PPIs.

PPIs are commonly prescribed to limit the damage caused by gastric acid to sensitive tissues in people suffering from gastroesophageal reflux or stomach ulcers. PPIs impair the secretion of gastric acid and elevate its pH. However, it is precisely this property that makes gastric acid an excellent first line of defense against invading pathogens, because any potential colonizer must survive a bath in gastric acid at a pH as low as 1.5. At pH 4, gastric acid is highly bactericidal, but at pH 6 it is totally ineffective.[6] Thus, PPIs increase susceptibility to bacterial infections.

Although the link between PPIs and CDI is fairly strong, Dr. Biswal points out one unresolved issue in the story. Spores, which are commonly responsible for transmission, are not killed by gastric

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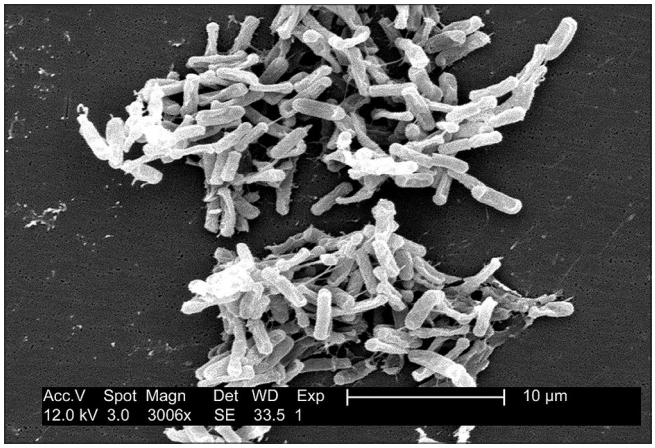

Figure 1: Micrograph of Clostridium difficile (Adapted from the Wikipedia).

acid.[7] New theories have emerged in light of this realization which may help to explain the link between PPIs and CDI. Notably, a recent studyshowed that basic pH favors the production of the highly potent toxin A.[8] Thus, PPIs may promote infection by altering the expression of bacterial toxin genes.

The stance of the Food and Drug Administration (FDA) on this issue is clear. On February 8, 2012, it issued a safety announcement for PPIs stating that "patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated."[9] Biswal concludes that vigilance must be urged in prescribing PPIs, particularly for patients already taking antibiotics, in order to tackle this global problem.

SPOTLIGHT ON ORIGINAL ARTICLES – Environmental Enrichment Limits Damage to Stressed Neurons

Both diabetes and prolonged exposure to stress lead to neuroplastic changes in the hippocampus. Environmental enrichment (EE) may help to prevent such changes, report Pamidi and Nayak in this issue of the *Biomedical Journal*.[10]

The latest figures from the World Health Organization show that a staggering 347 million people worldwide have diabetes mellitus.[11] Hyperglycemia may result in several secondary complications affecting many organs including the eyes, kidney, heart, and notably the brain. A surge of recent studies have focused on the neurological consequences of diabetes and, in particular, structural alterations of the hippocampus, which is highly sensitive to stress and disease. Both the proliferation and dendritic arborization of hippocampal neurons are impaired in animal models of diabetes.[12,13] Environmental stress leads to similar perturbations.[14] Alterations to neuronal plasticity caused by diabetes and the stress associated with this disorder may explain why depression and anxiety are highly prevalent in diabetic patients.

Several pharmacological and non-pharmacological treatments have been envisaged to correct perturbations to hippocampal neuroplasticity. EE, defined as "modifying the environment of captive animals to enhance their physical and psychological well-being by providing stimuli that meet their specific needs,"[15] stimulates hippocampal cell proliferation and survival in rodent models of diabetes.[16,17] Pamidi and Nayak studied this phenomenon in the dual context of stress and diabetes. They subjected rats with streptozotocin-induced diabetes to stress and/or EE and examined hippocampal neurogenesis after 30 days. Animals in the stress group were made to undergo 6 h of immobilization per day, which, for some fortunate animals, was followed by 6 h of *ad libitum* play with a variety of objects such as rotating wheels, plastic tubes, and toys of different dimensions. The number and types of these toys were changed every day to create a different environment for the animals.

Consistent with previous reports in mice,[16] histological staining of the CA1, CA3, and DH regions of the hippocampus showed that the number of surviving neurons in diabetic rats subjected to EE was significantly higher than in diabetic rats housed in control conditions. These experiments also confirmed the additional burden of stress on hippocampal neurogenesis in the context of diabetes. However, in all regions of the hippocampus studied, twice as many surviving neurons were present in diabetic rats subjected to both stress and EE than in diabetic animals subjected to stress alone.

This study shows that EE limits damage caused by stress and hyperglycemia to the hippocampus. Although the mechanisms involved are unclear, previous studies have shown that EE can stimulate the expression of neural trophic factors[18] and affect immune responses in the brain,[19] which may in turn accelerate synaptogenesis and promote neuron survival. Trials of EE in humans, including those involving aerobic exercise, cognitive training, learning of complex tasks (e.g. juggling balls), and sensory enhancement (e.g. listening to music), have shown that EE improves cognition and memory.[20] Although more work is required, this study suggests that similar non-pharmacological approaches may be relevant to treat depression associated with stress and diabetes.

ALSO IN THIS ISSUE: REVIEWS – Role of the P2x7 Receptor in Infectious Inflammatory Diseases

In this review, Coutinho-Silva and colleagues discuss

new emerging functions for the ubiquitously expressed P2X7 receptor in acute infection and examine the role of ectonucleotidase in the control of P2X7 function.[21]

Systematic Review of the Surgery – First Approach in Orthognathic Surgery

Chen and colleagues discuss how the use of surgery-first approach for the correction of orthognathic abnormalities has changed with time.[22] A systematic review of the literature reveals that both the surgery-first approach and the orthodontics-first approach have similar long-term outcomes but the surgery-first approach has a shorter treatment time.

ORIGINAL ARTICLES – Limiting the Response of Human Airway Smooth Muscle Cells to Pro-Inflammatory Cytokines

Human airway smooth muscle (ASM) cells express inflammatory molecules such as intercellular adhesion molecule (ICAM-1) in response to pro-inflammatory cytokines. Kuo and colleagues show that treatment of human ASM cells with the peroxisome proliferator-activated receptor gamma (PPARγ) receptor agonist ciglitazone impairs the ICAM-1 expression in response to tumor necrosis factor alpha (TNF-α),[23] which may be relevant to control chronic inflammation of the airways that occurs in asthma.

Thromboprophylaxis after Total Knee Arthroplasty

Venous thromboembolism (VTE) is a common complication of total knee arthroplasty (TKA). Wang and coworkers[24] compare the safety and efficacy of the anticoagulants rivaroxaban and enoxaparin in patients undergoing TKA and show that despite a purported risk of bleeding complications associated with rivaroxaban,[25] the occurrence of VTE was comparably low in patients taking either drug.

Neuromuscular Electric Stimulation for Stroke Patients

Neuromuscular electric stimulation (NMES) induces muscle contraction and promotes the perfusion/oxygenation of recipient tissue. Wang and colleagues highlight the interest of this treatment for stroke patients and show that repeated NMES treatment delays stroke-related decline of peripheral vascular function in paretic upper extremities.[26]

Additive Extends the Shelf Life of Platelets

Platelets have a short half-life and are typically viable in plasma at 22 C for only 5 days. Kumar and colleagues test a range of temperatures and storage conditions with the aim of extending this shelf life,[27] and show that the use of additive solution can both prevent contamination and maintain optimal platelet function for up to 7 days.

Hyaluronic Acid Prevents Scarring after Spinal Surgery in Rabbits

Hyaluronic acid (HA) is an anti-adhesive molecule with a wide range of clinical applications. Chen and colleagues potentially add to this list with their animal study of spinal surgery and show that an HA-based gelatin effectively limits scarring and postlaminectomy adhesion between the dural sac and surrounding tissues in rabbits.[28]

Optimal Visualization of the Fetal Spinal Cord by Magnetic Resonance Imaging

In this report, Chang and coworkers investigate the optimal parameters for prenatal magnetic resonance imaging of the normal spinal cord.[29] They show that the balanced fast field echo (bFFE) sequence provides a higher signal contrast ratio of cerebrospinal fluid to spinal cord and, hence, better visualization of the spinal cord than the single-shot turbo spin-echo (SSh-TSE) sequence.

CORRESPONDENCE: Stem Cells Repair Damaged Limbs

In this correspondence, Trevedi and coworkers report a remarkable case of pioneering technology in action.[30] They harvested adipose tissue derived mesenchymal stem cells from a patient with post-traumatic brachial plexus injury from an accident that occurred 16 years ago. They then differentiated these cells into neuronal stem cells and infused them, in combination with hematopoietic stem cells derived from bone marrow, into the right brachial plexus sheath. The patient showed a sustainable recovery with re-innervation over a follow-up period of 4 years, including a regain of pain sensation, finger movement, and muscle mass. These findings show that stem cell therapy can provide hope of functional recovery, even for patients with very old injuries.

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