260

Molecular docking study of cassia seed compounds to identify amylase and lipase inhibitors for weight management

Heidi Yuen [1,*], George Lenon [1], Andrew Hung [2], Angela Yang [1]

[1] *School of Health and Biomedical sciences, RMIT University, Bundoora, VIC, Australia*
[2] *School of Science, RMIT University, Melbourne, VIC, Australia*

Background: The epidemic of obesity has become a major challenge to health globally. Current pharmacological treatments for obesity are limited by their efficacy and side effects. Cassia seed (CS) is an herb commonly used for weight management in China. However, the bioactive compounds in CS with anti-obesity properties have not been identified and the relevant mechanisms of action are not clear.

Aim: To identify promising active compounds in CS as amylase and lipase inhibitors for weight management with molecular modelling and docking studies.

Methods: Autodock Vina [1] was the molecular docking software used in this study. The selected ligands were orlistat (a drug designed to treat obesity) and 27 compounds reported to be present in CS. Seven amylases and lipases were used as protein targets. Every ligand was docked against each target and the binding affinity of the pair was calculated by Autodock Vina. The binding affinity indicates the strength of interaction between the ligand and target.

Results: The preliminary molecular docking study has shown that CS compounds emodin, alaternin, rubrofusarin gentiobioside and ononitol are comparable, in terms of binding affinity and efficiency, to orlistat. Predicted binding affinity values suggest that rubrofusarin exhibits similar affinity to lipase compared to orlistat; while emodin has substantially (> 20%) higher affinity, indicative of the latter's potential to act as an inhibitor with greater efficacy than orlistat.

Conclusion: The results suggest that some chemical compounds in CS may interact with amylase and lipase via a similar mechanism to orlistat. Further studies, with Biovia Discovery Studio [2], are recommended to identify ligand-receptor interactions at the binding sites to confirm if there is any inhibitory action.

References

[1] Trott, O, Olson, AJ. AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. Journal of Computational Chemistry. 31(2) 455–61.
[2] BIOVIA, D.S. BIOVIA Discovery Studio. 2017 [cited 2018 23 Aug]; Available from: http://accelrys.com/products/collaborative-science/biovia-discovery- studio/.

https://doi.org/10.1016/j.orcp.2018.11.183

261

Metabolic detection of energy deficit by Crat in AgRP neurons links hunger with reward

Alexander Reichenbach [1,*], Robyn Brown [2], Zane B. Andrews [1]

[1] *Monash University, Clayton, VIC, Australia*
[2] *Florey Institute of Neuroscience & Mental Health, Melbourne, Australia*

Obese individuals show increased activation of brain reward regions (mesolimbic and mesocortical dopamine projections from the ventral tegmental area [VTA]), and fasting increases the desire to eat in obese more than lean humans. It remains unclear how the brain receives, senses and integrates metabolic information that reinforce food value and motivate feeding behaviours. For example, *does inappropriate sensing of metabolic need drive greater activation of brain pathways underlying motivation and reward*? Agouti-related peptide (AgRP) neurons in the arcuate nucleus of the hypothalamus are one key neuronal population that link homeostatic detection of hunger with dopamine pathways in the brain that control motivation and reward. To assess the role of metabolic sensing in AgRP neurons and the effects on reward and motivation, we studied mice lacking carnitine acetyltransferase (Crat) in AgRP neurons. Previous studies show that Crat in AgRP neurons plays a crucial role during the metabolic shift from fasting to refeeding and thus we hypothesised that it might couple the detection of metabolic state with food reward value and motivated behaviours.

We show that Crat in AgRP neurons is important for sensing of the caloric value of sweet solutions since fasting increases sucrose consumption during states of fasting in WT more than in KO mice. Moreover, during fasting WT mice will still consume sucrose spiked with quinine (unpleasant tastant) in order to consume calories as required, whereas KO mice do not. Intriguingly KO mice continually consume more saccharin despite changes in metabolic state due to fasting. Current studies using operant conditioning to examine motivation to work for caloric versus non-caloric sweet solutions are underway. These studies highlight that Crat in AgRP neurons is crucial for the caloric assessment of sugar solutions and may link the detection of energy deficit with increased food reward and motivation.

https://doi.org/10.1016/j.orcp.2018.11.184

262

Gastric band tubing causing caecal volvulus

Joseph Do Woong Choi [1,*], T. Michael D. Hughes [1,2], Nicholas K. Ngui [1]

[1] *Sydney Adventist Hospital, Wahroonga, NSW, Australia*
[2] *Sydney Adventist Hospital Clinical School, University of Sydney, Sydney, NSW, Australia*

Introduction: Obesity is a major public health issue, with increasing prevalence in western societies. Since 1993, Laparoscopic Adjustable Gastric Band (LAGB) is gradually being replaced in many institutions by other surgical techniques for weight loss, due to high inherent complications.The authors present a rare case of caecal volvulus caused by LAGB inserted 11 years prior. Methods: A 65 year old lady presented with a one day history of abdominal pain. Her past medical history included a LAGB placed 11 years prior, which achieved 11 kg weight loss, 3.8 kg/m^2 body mass index (BMI) reduction, 9.17% weight loss, and 23.04% excess weight loss during this time. For several months prior, she also described of intermittent abdominal bloating and colicky abdominal pain. Her abdomen was mildly distended, and tender in the periumbilical and lower quadrants with no peritonism. Her inflammatory markers were normal. Computed Tomography scan demonstrated a cecal volvulus with displacement of cecum towards the upper abdomen with dilatation of up to 10 cm, with twisting of the ascending colon and terminal ileum inferior to the cecum from the LABG tubing. Major Findings: Laparotomy demonstrated a cecal volvulus associated with the LAGB tubing, which had wrapped and twisted around the cecal mesentery. Macroscopically, the cecum appeared chronically dilated, with no acute compromise to the bowel wall. A limited right hemi-colectomy, and removal of gastric band and port was performed. Histopathology demonstrated benign reactive changes.

She made an uneventful postoperative recovery. Conclusion: LAGB accounts for only 5.5% of all bariatric surgeries. This has largely been due to reported removal rates of up to 40% after 7 years secondary to complications. Only four other case reports of cecal volvulus from LAGB have been described. Surgeons should have a high index of suspicion of a volvulus in a patient with an acute abdomen as a late complication of LAGB.

https://doi.org/10.1016/j.orcp.2018.11.185

263

Persistent leptin signalling in the arcuate nucleus reduces insulin's capacity to suppress hepatic glucose production in obese mice

Eglantine Balland*, Weiyi Chen, Garron Dodd, Gregory Conductier, Tony Tiganis, Michael A. Cowley

Biomedical Discovery Institute, Department of Physiology, Monash University, Clayton, Melbourne, Victoria, Australia

Since the discovery of leptin 23 years ago, a major challenge to weight loss strategies in obesity is leptin resistance. The lack of response to exogenous leptin administration in obesity is not only an obstacle to energy homeostasis regulation, but it could also be involved in the type 2 diabetic phenotype associated with obesity.

Our previous work *in vivo* and *ex vivo* with diet-induced obese mice (DIO) suggested that contrary to expectations, leptin signalling remains functional and is permanently activated in arcuate nucleus of the hypothalamus (ARH) neurons of DIO mice. This state of constant response to endogenous leptin underpins the lack of response to exogenous leptin. The obese phenotype of DIO mice is also associated to glucose intolerance, caused by a decreased sensitivity to insulin. The immunohistochemistry study of combined leptin and insulin signalling leads us to conclude that there is a common pool of ARH neurons responding to both leptin and insulin.

We then hypothesized that the constant activation of LepRb-neurons in the ARH of DIO mice could prevent insulin signalling in these neurons, leading to impaired glucose homeostasis and type 2 diabetes.

Accordingly, immunohistochemistry and hyperinsulinemic euglycemic clamps experiments demonstrated that antagonizing central leptin signalling in DIO mice restores hypothalamic insulin signalling and decreases hepatic glucose production. Using icv injection of inhibitors and ARH specific gene deletion, we identified protein phosphatase 1B (PTP1B) as the main mechanism by which the constant leptin signalling inhibits insulin response in ARH neurons of DIO mice.

Altogether our results bring new insights in obesity-linked central insulin resistance and open a potential new path of therapeutic strategy to treat type 2 diabetes in obese patients.

https://doi.org/10.1016/j.orcp.2018.11.186

264

Crosstalk between hypothalamic leptin and insulin signalling in obesity

Christine Ishak*, Eglantine Balland, Michael Cowley

Biomedical Discovery Institute, Department of Physiology, Monash University, Clayton, Melbourne, Australia

Obesity is characterised by increased adiposity, high leptin levels, and leptin resistance. Plasma leptin concentration is positively correlated with fat mass. Fasting decreases body fat and consequently decreases leptin levels. Obesity is a risk factor for type 2 diabetes mellitus (T2DM). T2DM is characterised by increased fasting glycaemia and impaired glucose tolerance. Insulin resistance is a common feature between obesity and T2DM. Leptin and insulin act on the same neuronal population within the arcuate nucleus of the hypothalamus (ARH). Our previous work demonstrated that Diet-induced obese (DIO) mice show no response to insulin, but still demonstrate leptin signalling in the ARH. Pharmacological blockade of leptin signalling in the CNS restores insulin signalling in DIO mice, thereby improving glucose homeostasis. However, utilising fasting to decrease leptin level and exert a physiological rescue of insulin signalling has not been investigated yet. We hypothesised that decreasing endogenous leptin level using a 48-hour fasting could reduce leptin response in the ARH and promote the restoration of insulin signalling and glucose tolerance in DIO mice. Mice are fed with chow diet or high-fat diet for 20 weeks, followed by a baseline glucose tolerance test (GTT). After a two-week recovery, the DIO mice will then be divided into two groups: 'DIO fed' mice, fed *ad libitum*, or 'DIO F48' mice, fasted for 48 h prior to the final GTT undergone by all mice. Following the final GTT, mice received either saline or insulin for histological signalling studies. Brain slices will be immuno-stained for phosphorylated signal transducer and activator of transcription-3 (pSTAT3) and phosphorylated protein kinase-B (pAkt). pSTAT3/pAkt co-localisation is used a marker of leptin receptor activation, while pAkt-alone a marker of insulin action. This will determine whether reducing leptin level will decrease endogenous leptin signalling and possibly restore insulin action in the ARH of DIO mice.

https://doi.org/10.1016/j.orcp.2018.11.187

300

Descriptive analysis of adult patients referred to the nepean family obesity service in the first six months of service operation

Jeff Ahn[1,2,*], Verene Chua[2], Yu-Fang Wu[1], Sally Badorrek[1], Sarah Lam[1], Annette Macdonald[1], Sharon Yeoh[1,2], Kathryn Williams[1,2]

[1] *Nepean Hospital, Kingswood, NSW, Australia*
[2] *Nepean Clinical School, University of Sydney, Kingswood, NSW, Australia*

The Nepean Blue Mountains Family Obesity Service (NFOS) was set up in 2016 to deliver multidisciplinary healthcare to those with obesity across the lifespan. This file audit was carried out to identify the demographics, clinical characteristics and basic health outcomes of adult patients referred to the NFOS in the first six months of operation. Of the 83 patients referred to NFOS, 71 were included in the audit (8 patients did not attend any appointments, 2 attended the initial group session only, 1 was outside our local health district