2020

medicina

BUENOS AIRES VOL. 80 Supl. V - 2020

MEDICINA

Volumen 80, Supl. V, Págs. 1-207

in CBE treated hearts, both compared to NIC. The content of CB1 increased ~ 140 % and CB2 decreased ~ 40 % in IC hearts. Opposite changes were observed in CBE treated hearts: CB1 decreased ~ 60 % y CB2 increase up to 150 %. These data demonstrate that CBE reduces cell death and myocardial post-ischemic contractile dysfunction. These beneficial effects appear mediated by Akt/PKCε/eNOS-dependent pathways activated through CB2 receptors.

FLAVONOIDS AT THE GASTROINTESTINAL TRACT: IMPACT ON OBESITY-RELATED METABOLIC DISORDERS

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The gastrointestinal (GI) tract plays a central role in the absorption, distribution, metabolism, and excretion of flavonoids. Flavonoids and/or their metabolites can modulate events at the GI tract that can have both local and systemic impact. At the GI tract, they can modulate nutrient absorption, GI barrier permeability, the activity of luminal enzymes, neutralize luminal toxins and oxidant species, and mitigate dysbiosis, tumorigenesis and intestinal inflammation. Such local effects have systemic extra-intestinal consequences, e.g. on inflammation, glucose homeostasis, lipid and energy metabolism. Overnutrition and the associated obesity, negatively impact GI functions. This contributes to the development of insulin resistance and type 2 diabetes (T2D), steatosis, non-alcoholic liver disease (NAFLD), and several other co-morbidities. Taking the flavan-3-ol (-)-epicatechin (EC) as an example of flavonoid, we observed in rodent models of high fat- or high sugar-induced obesity and dysmetabolism, that EC exerts beneficial effects at the GI tract mitigating also the development of T2D and NAFLD. At the GI tract, EC and/or its oligomers, the procyanidins were able to : i) regulate lipid absorption; ii) maintain the intestinal barrier integrity and prevent endotoxemia; iii) regulate the synthesis/secretion of gut hormones that have GI trophic actions and modulate glucose/lipid metabolism, iv) inhibit inflammation and oxidative stress; v) exert anti-colorectal cancer activity. These effects were associated with decreased systemic inflammation improved insulin sensitivity and mitigation of steatosis. NADPH oxidase and redox-regulated signaling cascades (NF-κB, JNK1/2, ERK1/2) emerge as central targets of EC's actions. This can in part explain EC capacity to mitigate GI barrier permeabilization, liver/adipose tissue endoplasmic reticulum stress, inflammation and inhibition of the insulin pathway. Some of the described effects/mechanisms are also exerted by other structurally-related flavonoids. In summary, further understanding of the mechanisms mediating the effects of flavonoids at the GI tract is of critical importance given the relevance of the GI tract in sustaining overall health and of the widespread recommendations of increasing the intake of plant bioactives. *Supported by NIFA-USDA*.

BURNING FAT: ROLE OF POLYPHENOLS IN WHITE ADIPOSE TISSUE BROWNING

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Obesity is one of the main public health concerns worldwide. White adipose tissue (WAT) is an endocrine organ that stores energy excess as triglycerides. Increased adiposity, mainly visceral WAT, is strongly associated with insulin resistance, type 2 diabetes and cardiovascular disease, among others. In contrast to WAT, brown adipose tissue (BAT) has the ability to dissipate energy in the form of heat due to the presence of the uncoupling protein 1 (UCP-1), a key determinant of mitochondrial thermogenesis. Interestingly, "brown-like" adipocytes can be observed in WAT and are characterized by the presence of multilocular lipid droplets and high number of mitochondria which are associated with a reduction of total adiposity and improvement of metabolic alterations. WAT browning can be triggered by different stimuli such as cold, exercise or pharmacological treatment, such as β-adrenergic stimulation or peroxisome proliferator activated receptor-γ (PPARγ) agonists. In addition, bioactive compounds such as polyphenols had been recently implicated in the emergence of brown-like cells in WAT. Polyphenols are bioactive compounds widely distributed in fruits and vegetables with an important role in preventing and managing increased adiposity and its comorbidities. We observed in rodent models of high fat-induced increased adiposity and metabolic alterations that supplementation with grape pomace extract (GPE), rich in polyphenols, stimulate the expression of the main transcriptional regulators of brown-like cell development, i.e., PPARγ-coactivator-1α (PGC-1α), PPARγ, PR domain containing 16 (PRDM16), and UCP-1 reducing adipose hypertrophy and inflammation in WAT and insulin resistance. GPE and two of the major GPE flavonoids, quercetin and (-)- epicatechin, enhanced the expression of transcriptional regulators of browning and UCP-1 through the up-regulation of the β-adrenergic receptor downstream cascade in 3T3-L1 adipocytes treated with palmitate. Overall, this finding highlights the potential utilization of bioactive grape-derived compounds to prevent/attenuate adiposity associated pathologies.