Pharmacology 2018: Administration of 1-Deoxynojirimycin Attenuates Hypothalamic Endoplasmic Reticulum Stress and Regulates Food Intake and Body Weight in Mice with High-Fat Diet-Induced Obesity

Eun-Young Yun,

Sejong University, Republic of Korea

Abstract

Obesity is increasingly becoming a public ill health worldwide . it's caused by an energy imbalance characterized by high energy intake relative to energy expenditure, also as established risk factors like type 2 diabetes, disorder, atherosclerosis, stroke, and Dyslipidemia . within the central Nervous System (CNS), the hypothalamus plays a critical role because the primary regulator of feeding behaviour and energy homeostasis by regulating appetite-related neuropeptides and neuronal excitations. Dysfunction of the hypothalamus results in energy imbalance, which has been recognized as a possible pathogenic mechanism of obesity.

Research suggests that hypothalamic endoplasmic reticulum (ER) stress causes hypothalamic dysfunction and neuronal apoptosis, which results in feeding behaviour disorders related to obesity and diabetes . Indeed, hypothalamic ER stress and leptin resistance are related to increased energy intake and weight. the 2 factors are closely linked: Hypothalamic ER stress has been shown to play a causal role within the development of leptin resistance and obesity. Moreover, in vitro and in vivo treatment with ER stress inducers are shown to market hypothalamic ER stress and attenuate leptin-induced phosphorylation of signal transducer and activator of transcription 3 (STAT3) proteins, important because phosphorylation of STAT3 at Try1138 plays a key role in mediating the consequences of leptin on energy balance .

Leptin, a substance primarily synthesized and secreted by white fat, is vital for regulating food intake and energy expenditure within the CNS . Leptin receptors (LepRs) are densely packed within the hypothalamus. The binding of leptin to LepRs results in phosphorylation of Janus-activated kinase 2 (JAK2), which successively phosphorylates several tyrosine residues of LepR, thus activating different signaling pathways and physiological functions.The α-glucosidase inhibitor, 1-deoxynojirimycin (DNJ), has been isolated from the leaves and roots of the mulberry (Morus alba), also as silkworm (Bombyx mori) larvae and a number of other microorganisms including Bacillus subtilis and Streptomyces. 1-Deoxynojirimycin is being investigated for potential antidiabetic and antiobesity effects because it reduces weight and serumHyperglycemia and enhances carbohydrate metabolism and insulin tolerance.

All of those effects improve diabetic conditions by inhibiting α-glucosidase activity and preventing absorption of glucose within the small intestinal brush border. Researchers have recently reported that DNJ has significant antiobesity effects in Otsuka Long Evans Tokushima Fatty (OLETF) rats and diet-induced obese mice. 1-Deoxynojirimycin also reportedly stimulates the assembly of adiponectin in cultured 3T3-L1 adipocytes and increases expression of adiponectin mRNA in adipose tissues. 1-Deoxynojirimycin (DNJ) and N-alkylated DNJ [N-butyl DNJ (NB-DNJ) and N-nonyl DNJ (NN-DNJ)] were the main iminosugars. The hydrophilic DNJ may be a potent α-glucosidase inhibitor as compared to the more hydrophobic NB-DNJ and NN-DNJ compounds [38, 39], and DNJ was far less toxic than the lipophilic NB-DNJ. The above contents are explained within the manuscript. N-Butyldeoxy nojirimycin (NB-DNJ), an inhibitor of α-glucosidases, reduces weight and food intake via central appetite suppression. Orally administered NB-DNJ has been shown to cross the blood brain barrier.

However, the mechanisms by which centrally administered DNJ affects leptin and ER stress have yet to be studied. Therefore, we investigated whether centrally administering DNJ into the hypothalamus of high-fat diet- (HFD-) fed obese mice would scale back ER stress and cause anorexigenic effects that attenuate diet-induced obesity (DIO).Non-steroidal anti-inflammatory drugs (NSAIDs) are one among the foremost commonly prescription drugs in post-operative period worldwide. Their nephrotoxic effects are documented and accounts for around 15.5% of all cases of drug induced kidney failure. Acute kidney failure following NSAIDs usage are reported in volume depleted

patients which is further precipitated by co-morbid conditions like hypertension and various drug interactions that increase plasma level of NSAIDs and worsens the condition. This highlights the importance of hydration in post-operative period also as assessment of co-morbid conditions before administration of NSAIDs to stop acute kidney failure.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are one of the most commonly prescribed drugs and their nephrotoxic effects are well known. Diclofenac is widely used as analgesic and anti inflammatory drug. Reports of renal dysfunction have been documented mostly in volume decompensated patients and are favoured by various drug interactions.

Renal dysfunctions are more prominent in geriatric population with falling renal functions. We would like to report a case of diclofenac induced acute renal failure which was favoured by the presence of co-morbid conditions namely, hypertension, falling renal function due to aging and drug interaction during a already volume decompensated patient.Non-steroidal anti-inflammatory drugs alter renal functions through their effects on renal prostaglandins resulting in reversible renal ischemia. Although NSAIDs related hypertension, salt and water retention, edema and hyperkalemia are highly infrequent but they continue to be a priority in patient who are in danger and may develop acute kidney failure.

Prostaglandins don't play a physiologic role in maintaining renal blood flow in normal subjects; but it plays a task in maintaining glomerular filtration rate (GFR). In intravascular depleted states, renal plasma flow is maintained by a balanced between the vasoconstrictor influence of the renin–angiotensin system and therefore the vasodilatory effects of prostaglandins. In fluid depleted states, prostacyclin (PGI2) mostly affects renal homeostatic mechanisms. PGE2 and PGD2 cause dilatation of the renal vascular bed along side the lowering of renal vascular resistance. Thus, it enhances renal perfusion with redistribution of blood be due the cortex to nephrons within the juxta-medullary region. So,

Prostaglandins become critical in maintaining GFR in volume depleted states. Hence, when the assembly of prostaglandins is blocked thanks to NSAIDs, it's going to cause hyperkalemia, peripheral edema, increased vital sign, weight gain and acute kidney failure.

In this case, the patient had no pre-existing renal disease but he was a known case of hypertension and received diuretic therapy before diclofenac administration. Age-related decline in renal blood flow in hypertensive person and volume depletion thanks to diuretics are further worsened by NSAIDs.[2] This was clinically evident in our case as this patient belonged to the geriatric population so he was more vulnerable to nephrotoxic drugs together with his ageing kidneys. On presentation, his vital sign was within normal range but he had marked pedal edema and decreased frequency of micturition. There was sudden rise of plasma creatinine, urea and potassium. He also had low urine output, low sodium excretion and low urinary osmolality which signifies kidney's decreased ability to concentrate urine.

In the above setting, course with NSAIDs therapy i.e., tablet diclofenac 50 mg 3 times each day (150 mg/day) was sufficient to precipitate acute kidney failure as this dose appears to impair the renal blood flow and glomerular filtration rate. Diclofenac has antagonizing effect on atenolol which decreased its antihypertensive effect which further precipitates ARF. This interaction may have had occurred during this case. Thus, the hemodynamically mediated acute kidney failure caused by NSAIDs was further exacerbated with interaction with anti-hypertensive drug. consistent with Naranjo adverse drug reaction probability scale, diclofenac is that the evidence of this hemodynamically mediated acute kidney failure.

Hemodynamically-medicated acute kidney failure thanks to NSAIDs in volume depleted patients is reversible and is usually associated with the dose and duration of exposure. In our case, patient's plasma creatinine and urea began to decline after 7 days of drug discontinuation and his pedal edema subsided subsequently with improvement in urine output. Within one month, on subsequent visit to outpatient department his investigation came within the traditional range.

Biography

Tae-Won Goo has his expertise in mass production of recombinant proteins using transgenic silkworms and functional analysis for materials isolated from various insects. Recently, he was interested in entomophage, and registered three kinds of insects as novel foods on Korean Food Standards Codex through evaluation of toxicity and nutritional components. And then, he has been analyzed

anti-obesity, anti-diabetes, anti-dementia, and so on using various cell lines, mice, and transgenic flies.

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