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RESEARCH ARTICLE

EFFECT OF EXERCISE INDUCED GLUTAMINE ON IMMUNE FUNCTION.

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Abstract

Rapidly dividing and proliferating cells required high rates of glutaminolysis. It is not only for energy but also for the precursor of many biosynthetic pathways used for macromolecule synthesis. In response to antigenic challenge, lymphocytes also utilize glutamine at high rate for rapid multiplication and proliferation. Skeletal muscle play the major role in glutamine homeostasis as it is the major site of glutamine synthesis to maintain the plasma glutamine concentration. Mononuclear cells cannot synthesize glutamine due to absence of its intracellular glutamine synthase but they possess a high-intracellular activity of glutaminase. So, lymphocytes must be supplied with glutamine from the plasma to accomplish its metabolic requirements. Heavy exercise decreases plasma glutamine concentration that may causes immune depression due to reduced supply of glutamine to lymphocytes. However, glutamine supplement was unable to abolish the exercise induced decline in salivary IgA. Though glutamine supplementation decreases the number of upper respiratory tract infection (URTI) in athletes. Glutamine supplementation abolished exercise induced decrease in plasma glutamine but not exercise-induced impaired lymphocyte functions.

Introduction:-

Regular exercise is an interval stressor. The magnitude of changes during exercise outcomes in a wide range of specific adaptations; depending largely on the intensity, duration, the force or load (pathological and psychological; metabolic and mechanical) and the body's initial level of fitness (Manley 1996). Acute bout of intense exercise can alter host defence, leading to changes in disease susceptibility and severity (Walsh et al 2011). One important mechanism for such changes is alterations in immune functions. Moderate exercise may have predominance over immunity via anti-inflammatory and immunomodulatory effects (Wasinski et al 2014), whereas high intensity exercise raises the concentration of anti-inflammatory cytokines, leading to cause infection by intracellular microorganisms as well as alterations in endocrine system and metabolic regulation (Mondal and Chatterjee 2018). Exercise modulates immune function in a variety of ways through complex interaction of hormones, cytokines, and metabolic changes. Plasma glutamine level alteration may one of the route through which such exercise induced cellular metabolic changes modulate immune functions (Frederick et al 2014). The major cellular components of the immune system are lymphocyte, macrophages and neutrophils which highly utilizes both glucose and glutamine for its metabolic requirements (Newsholme 1994; Krzywkowski et al 2001). Glutamine is an imperative non-essential amino acid for rapidly dividing cells. There is an abundance of epidemiological evidence and clinical data to advocate that nutritional deficiencies can mobilize immunocompetence and increase the risk of infection and even

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medically harmless infections may significantly affect athletic performance (Newsholme and Parry-Billings 1990; Gleeson and Bishop 2000; Krzywkowski et al 2001; Frederick et al 2014). Metabolic changes during physical activity may serve a declined glutamine concentration in plasma to persuade lymphocyte activity (Newsholme and Parry-Billings 1990; Krzywkowski et al 2001). Glutamine is also utilized by many other tissues within the body, like the kidneys, gut, and some cells of the cellular immune system (Hiscock et al 2002). To accomplish the high demands for glutamine in the body, glutamine is synthesized by several organs, like skeletal muscle, kidneys, liver, lungs, and heart. Among them skeletal muscle plays a vital role in glutamine homeostasis as it is the major site of glutamine synthesis and also release glutamine into the bloodstream at a high rate (Krzywkowski et al 2001, Hiscock et al 2002, Nieman 2001). High rate of glutamine utilization also provides specific immune-stimulatory properties through production of metabolic intermediates for purine and pyrimidine biosynthesis (Parry-Billings et al 1992). Similarly, dwindle in glutamine concentration results in a reduction of phagocytosis via macrophages (Parry-Billings et al 1990). Henceforth this review is a consequence of the matter, related to exercise induced alteration in glutamine utilization by lymphocytes and resultant modification of immune functions.

Nutrients metabolism and lymphocytic functions:-

Although lymphocytes are able to use glucose, glutamine, ketone bodies and fatty acids (FA), glucose and glutamine are quantitatively the most important fuel for activated lymphocytes (Curi et al 1999). Lymphocytes consume both the glucose and glutamine at high rates in a function dependent manner, though glutamine is utilized at a considerably higher rate than that of glucose (Newsholme et al 1985). In activated lymphocytes glucose retained in the cell by phosphorylation into glucose-6-phosphate by hexokinase (HK) (Frederick et al 2014, Ganeshan et al 2014). Glucose 6 phosphate is then used either by aerobic glycolysis or by pentose phosphate pathway (PPP). Through PPP, it generate ribose for DNA and RNA synthesis and NADPH for fatty acid synthesis but through aerobic glycolysis, pyruvate is produced (Calder et al 2007; Ganeshan et al 2014). This pyruvate is finally converted to either lactate or acetylcholine or be fully oxidized through TCA cycle (Curi et al 1999). Very small percentage of glucose 6 phosphate is fully oxidized in lymphocyte (Curi et al 1999). Due to the removal of citrate (pyruvate converted to acetyl-CoA plus oxaloacetate) from the tricarboxylic acid (TCA) cycle for biosynthetic reactions, it become necessary to replenishing intermediates to maintain the cycle operative (Frederick et al 2014, Ganeshan et al 2014). Thus activated lymphocytes also have to increase the uptake of glutamine and convert it to glutamate, which is then converted to α-ketoglutarate by glutamate dehydrogenase (Curi et al 1999). Some of the glutamine in lymphocytes is also converted to aspartate and ammonia for providing biosynthetic precursors of purine and pyrimidine (Curi et al 1999). Finally, a limited percentage of glutamine is fully oxidized or be converted to lactate (Curi et al 1999; Frederick et al 2014).

In different functional states, lymphocytes reprogram their glucose and glutamine metabolism to balance their requirement for ATP and macromolecule production (Frederick et al 2014). Therefore the inability of cell metabolism to congregate the energetic and biosynthetic demands of lymphocytes may upset immune functionality (Caro-Maldonado et al 2012; Wasinski et al 2014). Mononuclear cells have a high-intracellular activity of glutaminase but they cannot synthesize glutamine due to lack of glutamine synthase. So, lymphocytes must be supplied with glutamine in the plasma to accomplish the metabolic requirements of these cells. Studies demonstrated that metabolic reprogramming and lymphocyte activation are closely linked (Fredrick et al 2014). T lymphocytes adopt a metabolic program for their energetic and biosynthetic needs in specific states, viz; resting to memory cell conversion. Resting lymphocytes migrate through secondary lymphoid tissues to maintain immune surveillance prior to activation and need to rely on the oxidative metabolism of glucose, amino acids and lipids (Gerriets and Rathmell 2012). During antigenic challenge, lymphocytes need metabolic substrates to attempt dramatic increase in metabolism (Calder et al 2007) for rapid burst in cellular proliferation, biosynthetic and secretory activities (Pearce et al 2013). Thus the cell has to replaces its previous efficient ATP production (resting state) with efficient and rapid macromolecule biosynthesis (activated state) (Maciver et al 2013).

Lymphocyte function and differentiation is depended on the patterns of “fuel usage” and transcriptional and posttranscriptional factors, controlling metabolism in the various activated T cell lineages (Maciver et al 2013). Inability of lymphocytes hereafter produces several pathologies under a given condition to meet their nutrient demands for energetic and biosynthetic purpose (Caro-Maldonado et al 2012). For example, the inhibition of glycolysis suppresses cell proliferation and cytokine production and also compromise effector T cell differentiation (Michalek et al 2011). In diet-induced obesity (DIO) model, resident inflammatory lymphocyte population increases by reduction in the T regulatory (Treg) and T helper2 (Th2) cell populations (Anderson et al 2013). There are three possible outcomes of insufficient fuel usage in T lymphocytes. The first is altered or inhibited Th1, Th2, and Th17

differentiation. The second is the inhibition of proliferation or induction of cellular senescence and the third is the induction of cell death (Frederick et al 2014).

Effect of Exercise on Lymphocyte's Metabolism and Its Functions:-

Evidence suggests that one of the modulatory way through which exercise induce modification of immune function is the alteration of nutrient metabolism (glucose, glutamine, ketone bodies, fatty acids etc.), particularly glucose and glutamine metabolism of lymphocytes (Curi et al 1999; Frederic et al 2014). Enzymes of glucose and glutamine metabolism are the crucial targets for the modulatory effect of chronic exercise in alteration of lymphocytic functions. Chronic exercise induces modification in lymphocyte functionality and substrate metabolism (Frederic et al 2014). During exercise or antigenic challenge, to meet the new bioenergetic and biosynthetic demands imposed by activation, lymphocytes increase the maximal activity of enzymes hexokinase (HK), glucose-6-phosphate dehydrogenase (G6PDH) and phosphate-dependent glutaminase (GLUTase), which are key enzymes in the glycolysis, pentose-phosphate and glutaminolysis pathways respectively. Mitochondrial TCA cycle enzyme citrate synthase (CS) is also affected (Ardawi et al 1985). T lymphocytes also increase glutamine utilization through through shifting its metabolism to aerobic pathway by exercise induced maximal activities of (GLUTase) and (CS) in T lymphocytes (Navarro et al 2013). Concomitantly, these cells reduce their glucose consumption and lactate production levels (Navarro et al 2013; Frederick et al 2014). In contrast, although both the glucose and glutamine consumption were increased in B lymphocytes, only glutamine aerobic metabolism was increased. In spite of GLUTase and CS, maximal activities of HK and G6PDH were also augmented in B lymphocytes in response to chronic exercise (Navarro et al 2013). Exercise-induced changes in the hormonal environment also influence the metabolism of glutamine in the lymphocytes. For example, adrenaline concentration increases at workloads over 60% VO2max (Webb et al 2008). Increased adrenaline then augments the maximal activities of HK, GLUTase as well as glucose and glutamine consumption of lymphocytes (Rosa 1997) and may thus uplift the immune status in moderate exercise.

Exercise and Plasma Glutamine Concentration:-

The effect of acute exercise on plasma glutamine concentration depends largely on exercise duration and intensity. Release of glutamine from skeletal muscle is thought to be the main source of plasma glutamine as skeletal muscle possesses high activities of branched-chain amino acid (BCAA) transaminase and glutamine synthase, the key enzymes of glutamine synthesis (Hiscock et al 2002). Prolonged exhaustive exercise in humans, increase the glutamine release from muscle which result in decrease in muscle glutamine concentration and an increase in plasma glutamine concentration (Castell 1997, Parry-Billings 1992). Prolonged, intensive exercise also increases the plasma glucocorticoid concentrations which contribute to a change in glutamine metabolism by increasing glutamine synthase activity and its mRNA expression (Galbo 1983). It causes decrease in intramuscular glutamine stores and maintains maximum glutamine supply, even at lowered intramuscular glutamine levels (Rowbottom et al 1996; Hiscock et al 2002). However, these changes may still be insufficient to balance an increased rate of glutamine overutilization by other organs, resulting in decrease in plasma glutamine concentrations (Castell et al 1997). Increased plasma level of cortisol and glucagon in prolonged exercise increase the uptake of glutamine by liver for gluconeogenesis and acute phase protein synthesis (Galbo 1983; Walsh et al 2000). Increased glutamine uptake by the activated lymphocytes also contributes to the decrease of plasma gutamne level in prolonged exercise (Mackinnon et al 1996, Walsh et al 2000). Whereas intermittent, high-intensity, short-duration bouts either decrease plasma glutamine concentration (Walsh et al 1998, Keast et al 1995) or result in no significant change (Sewell et al 1994, Parry-Billings 1992). *In vivo* decrease in plasma glutamine concentration in relation to exercise is 100 M, depending on the type and duration of the exercise (Rohde et al 1995). Streneous exercise decrease plasma glutamine levels but its plasma level increase in chronic moderate-intensity exercise (Agostini and Biolo 2010).

After an acute bout of cycle ergometry, plasma glutamine concentration significantly decrease from resting levels but blood mononuclear cell (BMNC) glutamine concentration actually increase during recovery because the circulating BMNC count significantly decrease during recovery (Hiscock et al 2002). Thus, even though plasma glutamine concentration is decreased, there is no decrease, and possibly an increase the amount of glutamine available to the circulating BMNCs (Hiscock et al 2002). It is unclear whether this decrease in plasma glutamine concentration observed after acute exercise reduces the availability of glutamine to immune cells and if it is, then, it could be related to immune suppression, whereas its increased level induced by chronic moderate-intensity exercise would induce a positive effect upon immune functions (Agostini and Biolo 2010).

Glutamine is an important tissue culture supplement, necessary for the survival and growth of a variety of mammalian cells and the cells of the immune system. There is much evidence that *in vitro* function of some immune cells is decreased when glutamine concentration is reduced below physiological levels. In humans, glutamine influences the in vitro proliferation of lymphocytes when stimulated with concanavalin A (ConA) (Rohde et al 1996) in a concentration dependent manner and shows optimal proliferation at a glutamine concentration of 600 M (Rohde et al 1995). Incubation with concanavalinA, rate of glutamine utilization by lymphocytes was increased and under this condition, concentrations of glutamine and 2-oxoglutarate are decreased in the lymphocyte. Cultured lymphocytes function equally at the glutamine concentration of postexercise glutamine level (300–400 M) with that of resting glutamine level 600 M. Majority of *in vitro* studies have shown that glutamine concentration has to be less than 100 M to observe a decreased lymphocytic proliferative response (Rohde et al 1995; Rohde et al 1996). Lymphocyte proliferation is associated with enhanced production of interleukin (IL)-2 and interferon (IFN-γ) by phytohemagglutinin-stimulated human BMNCs with glutamine concentration of 600 M. But the production of IL-1, IL-6, or Tumor necrosis factor-α was not influenced by glutamine. Thus it is possible that glutamine may influence the lymphocyte proliferation by inducing the production of IL-2 and IFN-γ (Hiscock et al 2002).

Effect of Glutamine Supplement on Plasma Glutamine Level and Immune Functions:-

Despite the attenuation of the exercise induced decrease in plasma glutamine concentration, glutamine supplementation cannot abolish the post exercise immune suppression characterized by a decrease in lymphocyte concentration, salivary IgA concentration, T-cell proliferation, natural killer (NK) cell count and lymphokine activated killer (LAK) cell activity (Hiscock et al 2002). Though, glutamine supplementation decreases the number of URTI in athletes (Castell et al 1996; Krzywkowski et al 2001). This study does not support that post exercise decrease in salivary IgA is related to plasma glutamine concentrations. But probable explanation should be due to high intensity exercise induced increase of salivary cortisol and a reduced level of interleukin (IL)-21, a cytokine which stimulate immunoglobuline A secreting cells (Moreira et al 2013; Frederic et al 2014). This finding is not likely to be explained by an effect of glutamine on the function of circulating lymphocytes given that glutamine supplementation abolished exercise-induced decrease in plasma glutamine but not exercise-induced impaired lymphocyte function (Rohde et al 1998). However, the excess of systemic catecholamines induced by high-intensity, exhaustive exercise reduces the plasma levels of interferon-α (IFN-α) and an antiviral cytokine (Yano et al 2010). In addition to its antiviral property, IFN-α limit T and B cell proliferation by the suppression of glucose and glutamine metabolism and reduced maximal G6PDH, CS, and GLUTase activities (Bacurau et al 2010). Thus it may be the probable reason of why glutamine supplement can not uplift the impaired functions of lymphocytes after prolonged intensive exercise.

Conclusion:-

Exercise affects the lymphocyte functions by the modulation of glucose and glutamine metabolism. In various physiological and pathological conditions, high rate of glutaminolysis in lymphocytes provide ideal conditions for the fine control of energetic and the rate of use of metabolic intermediates for various biosynthetic pathways. Supplementary glutamine attenuates the exercise induced decrease in plasma glutamine level but unable to abolish exercise induced immune suppression which may be due to negative effect of strenuous exercise induced excess plasma level of catecholamines and glucocorticids and require further detailed investigations to confirm about this mechanism.

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