

Coronavirus-induced severe acute respiratory syndrome (sars) as a possibile expression of fatty acid amide hydrolase (faah) hyper-activation and possible therapeutic role of faah inhibitors in covid19-induced sars.

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Abstract

It has appeared that the acute respiratory distress induced by COVID 19 is mainly depending on the excessive host inflammatory response, consisting of an inappropriate secretion of several inflammatory cytokines, namely IL-17A, IL-6 and TNF-alpha, rather than to a direct viral-induced tissue damage. Moreover, it is known that the inflammatory response is physiologically under a neuroendocrine regulation, namely played by the endogenous cannabinoid system. COVID 19-related cannabinoid reduced activity would be due to a virus-induced activation of the enzyme responsible for cannabinoid degradation, the fatty acid amide hydrolase (FAAH). Then, FAAH inhibitors could exert a therapeutic role in COVID 19 infection.

Key Words: Cannabinoid system; COVID 19; Fatty acid amide hydrolase (FAAH); FAAH inhibitors

Introduction

The endocannabinoid system (ECS) represents an endogenous defense complex to protect against an exaggerated inflammatory biological reaction in both tumor growth and cardiovascular disorders (1). The ECS may produce both CB1 and CB2 agonists, and non-cannabinoid agents (2,3). The main endogenous cannabinoid agonists are the arachidonyl-ethanol-amide (AEA) and the 2-arachidonyl-glycerol (2-AG) (1-3), while the main non-cannabinoid agonists are the palmitoyl-ethanol-amide (PEA), and the oleoyl-ethanol-amide (OEA) (4), which may be considered as the endogenous equivalents of the non-cannabinoid agonist and the non-psychoactive agent of Cannabis, the cannabidiol (CBD) (1-3). The main enzyme involved in the metabolic destruction of cannabinoids is the fatty acid amide hydrolase (FAAH), as well as monoacylglycerol lipase (MAGL) (1-3). Moreover, it has been shown that both CBD and PEA, even though they are not cannabinoid agonists, may allow an increase in the endogenous content of cannabinoid agonists by acting as FAAH inhibitors. Finally, it has been demonstrated that a hyper-activation of FAAH activity may allow to an enhanced inflammatory response, as well as to an increased predisposition to cancer onset and development (5). FAAH cellular concentrations would increase with age, then this finding could explain the tendency to an exaggerated inflammatory response against several causes, including the viral infections (1-3). The higher immunobiological response in aged subjects would be also to age-related increase in TH17 lymphocyte activity (6),

with a consequent enhanced inflammatory reactivity, in association with a decline in that of regulatory T lymphocytes (T reg) (7), which in contrast counteract the inflammatory response. The inhibitory action of FAAH inhibitors on the intensity of the inflammatory response may be amplified by the pineal hormone melatonin (MLT) (8), by suggesting the existence of a functional axis between brain cannabinoid system and pineal gland (9).

Coronavirus-Endocannabinoid System Interactions

It is known that the ECS plays a fundamental role in the perception of pleasure, including that related to the taste (1-3). Moreover, it is a common evidence that one of the main early COVID 19-related symptoms is the loss of taste. Then, the loss of taste induced by the infection of COVID 19, also called SARS-COV-2, could depend on an acute ECS deficiency. Finally, it is known that the spike glycoprotein of COVID 19, which is located on the outer envelope of the virion and constituted by two subunits, binds to host receptor angiotensin-converting enzyme-2 (ACE-2) through its receptor binding domain (RBD)(10). Then, Coronavirus infection would allow an exaggerated immune-inflammatory response (11). Since FAAH hyper-activation may also allow an excessive immune-inflammatory responses, coronavirus infection might induce an excessive inflammatory response by determining an ECS deficiency. In other words, viral spike glycoprotein-ACE-2 interactions would allow a hyper-stimulation of FAAH activity,

with a consequent failure in ECS function, which has been proven to predispose to cardiopulmonary complications (12). In more detail (5), FAAH hyper-activation would allow a down-regulation of tissue inhibitor of matrix metalloproteinase-1 (MP-1), with a consequent enhanced MP-1-induced alterations of the intercellular matrix and a stimulation of the angiogenic processes (5).

Possible Block of Covid 19-Induced Inflammatory Response By A Neuroimmune Approach

If the main problem of COVID 19 infections is the control of host excessive inflammatory response, namely due to TNF-alpha, IL-6 and IL-17A hyper-production, because of the fundamental role of FAAH activity in the generation of the inflammatory response, one simple way to reduce host exaggerated inflammatory response could consist of the inhibition of FAAH activity, which may be achieved by the same endogenous FAAH inhibitors, such as PEA (4), by CBD (1-3), or by the most recent FAAH inhibitors, including arachidonoylglycerol (AA-5HT), URB597 (5), and SA-57, which may inhibit both FAAH and MAGL (13). Mu-opioid agonists would also inhibit FAAH (13). Doses and schedule of administration will be established by controlled clinical studies.

Conclusions

COVID-19 infection may be interpreted as an in vivo dramatic examination of the immunological knowledgements of the human Sciences, since the terrible lethality induced by its infection is the consequence of a profound alteration of the interactions between host immune-inflammatory response and its neuroendocrine regulation. The lacked evolution of the Immunology into the Psycho-neuro-immunology is the main cause of the inappropriate therapeutic response to COVID 19 infection and the consequent acute inflammatory respiratory failure.

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