Taylor & Francis
Taylor & Francis Group

Annals of Medicine

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iann20

Modulation of the initial stages of systemic inflammation by intervention in the NFkB signalling pathway

Ângela Amaro-Leal

To cite this article: Ângela Amaro-Leal (2021) Modulation of the initial stages of systemic inflammation by intervention in the NFkB signalling pathway, Annals of Medicine, 53:sup1, S3-S4, DOI: 10.1080/07853890.2021.1894004

To link to this article: https://doi.org/10.1080/07853890.2021.1894004

Published online: 28 Sep 2021.

[a]SCERG – Stem Cell Engineering Research Group, IST – Taguspark, Porto Salvo, Portugal; [b]Instituto de Medicina Molecular, Faculdade de Medicina da Universidade de Lisboa, Avenida Prof. Egas Moniz, Lisboa, Portugal; [c]Centro de Investigação Interdisciplinar Egas Moniz (CiiEM), Egas Moniz Cooperativa de Ensino Superior, Caparica, Portugal; [d]The Discoveries Centre for Regenerative and Precision Medicine, Lisbon Campus, IST – Taguspark, Porto Salvo, Portugal; [e]Laboratório de Ciências Forenses e Psicológicas Egas Moniz, Campus Universitário – Quinta da Granja, Caparica, Portugal

ABSTRACT

Phytocannabinoids are psychotropic substances found in cannabis that bind to the endocannabinoid receptors regulating a variety of physiological processes in human body, including synaptic activity in the central nervous system and metabolic effects in the peripheric nervous system among many others [1,2]. Synthetic cannabinoids emerged as popular alternative to cannabis. Most of these substances are synthetic analogues of Δ^9-THC, the psychotropic compound of cannabis, binding with higher affinity to the endocannabinoid receptor CB_1 and eliciting a stronger and long-lasting effect on brain cells. Molecular structure of synthetic cannabinoids is always changing escaping the control by authorities and increasing the hazard for general population. The popularity of cannabis and its derivatives may lead, and often does, to child's exposure to cannabinoids both in utero and through breastfeeding by a drug-consuming mother. Prenatal exposure to cannabis has been associated with higher risk of newborn morbidity [2,3], altered rate of mental development and significant changes in nervous system functioning [4,5]. However, direct evidence that these effects are mediated through the binding of cannabinoids to endocannabinoid receptors is still lacking. Thus, it is paramount to better understand the psychoactive effects of natural and synthetic cannabinoids on the developing human brain.

We conveyed a pilot study in which human induced pluripotent stem cells (hiPSCs) were induced into neural differentiation and treated with a non-psychotropic component of cannabis, cannabidiol, known to bind the CB_2 receptor, and two synthetic Δ^9-THC analogues, THJ-018 and EG-018. Neuronal differentiation and functional maturation were assessed by immunofluorescence, qRT-PCR and single cell calcium imaging. Our results indicate that all three substances have profound impact on the differentiation, maturation and functioning of developing CNS neurons, providing a new evidence for the importance of thorough research of the impact of pre-natal exposure to natural and synthetic cannabinoids.

References

[1] Wu C-S, Jew CP, Lu H-C, et al. Lasting impacts of prenatal cannabis exposure and the role of endogenous cannabinoids in the developing brain. Future Neurol. 2011;6(4):459–480.

[2] Metz TD, Stickrath EH. Marijuana use in pregnancy and lactation: a review of the evidence. Am J Obstetr Gynecol. 2015; 213(6):761–778.

[3] Hurd YL, Wang X, Anderson V, et al. Marijuana impairs growth in mid-gestation fetuses. Neurotoxicol Teratol. 2005; 27(2):221–229.

[4] Fried PA. Conceptual issues in behavioral teratology and their application in determining long-term sequelae of prenatal marihuana exposure. J Child Psychol Psychiatry. 2002;43(1):81–102.

[5] Gray KA, Day NL, Leech S, et al. Prenatal marijuana exposure: effect on child depressive symptoms at ten years of age. Neurotoxicol Teratol. 2005;27(3):439–448.

DOI: 10.1080/07853890.2021.1893997

Modulation of the initial stages of systemic inflammation by intervention in the NFkB signalling pathway

Ângela Amaro-Leal

Faculty of Medicine of Lisbon (FMUL), Cardiovascular Autonomic Function (CAF) Lab of the Cardiovascular Center of the University of Lisbon (CCUL)

ABSTRACT

Sepsis is a systemic inflammatory state mediated by the innate immune system resulting in an excessive cellular response to severe infection, with high levels of morbidity and mortality. Furthermore, patients who survive sepsis, have long-term cognitive and functional impairment. Animal models are essential to clarify the pathophysiological mechanisms of sepsis. Herein, we characterise an animal model of lipopolysaccharide (LPS)-induced inflammation, evaluating neural and cardiac function, during the initial stages of infection. Male Wistar rats (12–20 wks, $n = 24$) were injected with LPS (E. coli serotype O127:B8; tail vein) and divided into 3 groups: LPS6 (6 mg/kg), LPS12 (12 mg/kg) and Sham (NaCl 0.9%; 0.1 ml/100g). At 6 and 24 h after LPS injection, an autonomic evaluation was performed in both conscious animals, with continuous

radio-telemetry recording of blood pressure (BP) and heart rate (HR), and in anaesthetised animals (induction: sodium pentobarbital, 60 mg/kg, ip; maintenance: 20% solution, v/v) with BP, ECG, HR, tracheal pressure, respiratory frequency (RF) and body temperature continuously monitored. Baro and chemoreflex were evaluated with phenylephrine (0.2 ml, 25 μg/ml; iv) and lobeline (0.2 ml, 25 μg/ml; iv), respectively. Behavioural changes were also evaluated through the elevated-plus maze, open-field and Y-maze tests. Immunohistochemistry and RT-PCR were executed to determine heart and brain inflammatory state. Serum biomarkers levels for organ disfunction were also measured. Overall our results show a rise in BP and HR, and elevated RF due to increased chemoreflex sensitivity. 24 h following LPS injection, all groups have a significantly decreased baroreflex ($p < 0.05$), however, 6 h post-injection, LPS12 show a statistically significant increase in baroreceptor reflex ($p < 0.05$). At both time-points, the two LPS groups present an anxiety-like behaviour, associated with less locomotor/exploratory activity and highly significant cognitive impairment ($p < .0001$). The autonomic evaluation of the anaesthetised LPS12 group results in an increase of the autonomic tone at 6 h post-LPS followed by a decrease at 24 h. The LPS6 group shows the opposite profile. Interestingly, conscious animals reveal a slightly different profile in both groups, with a continuous increase in autonomic tone for LPS12 and a decrease 24 h post-LPS in LPS6 group. The molecular studies show reactive astrogliosis and microgliosis, due to inflammatory processes in the hippocampus, as well as, an upregulation of pro-inflammatory factors in the heart and brain. Serum analysis yielded higher levels of biomarkers for renal and liver dysfunction ($p < .05$) and pancreatic and neuromuscular injury ($p < .05$), in the LPS12 group. Concluding, LPS administration induces strong modifications in both cardiac and neurological systems, during the early stages of the systemic inflammatory response. Being a good model for further pathophysiological and pharmacological studies related to Sepsis.

DOI: 10.1080/07853890.2021.1894004

Molecular biomarkers associated with respiratory insufficiency in amyotrophic lateral sclerosis

Ana Catarina Pronto-Laborinho[a], Catarina S. Lopes[a], Nuno C. Santos[a], Filomena A. Carvalho[a] and Mamede de Carvalho[a,b]

[a]Instituto de Medicina Molecular, Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal; [b]Departmento de Neurociências e Saúde Mental, Hospital de Santa Maria-Centro Hospitalar Lisboa Norte, Lisboa, Portugal

ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a devastating and fatal neurodegenerative disorder.Death typically occurs within 3–5 years after disease onset. The main cause of death in ALS is respiratory failure (RF). No effective treatment is available and no molecular biomarker related to respiratory outcome and to early ventilatory dysfunction was described so far. The club-cell protein (CC-16) is a biomarker associated with respiratory distress and lung inflammation.

The aim of this work is to test if CC-16 and IL-6 could be new biomarkers of ALS for early signs of respiratory insufficiency and disease progression. Additionally, we intend to study morphological and viscoelastic changes of the erythrocytes' membrane associating them with ALS patients' clinical profile.

Eighty-one ALS patients and 30 matched controls were included. Functional capacity and respiratory function (forced vital capacity) were evaluated. CC-16 and IL-6 were quantified by ELISA and multiplex technology, respectively. Morphological and viscoelastic properties of the erythrocytes were analysed by Atomic Force Microscopy (AFM).

CC-16 levels were significantly raised in ALS patients. In 17% of them, CC-16 level was above the upper cut-off value. On these patients, the risk of non-invasive ventilation was greater in the following 6 months and they tend to have higher mortality in the following 30 months. IL-6 values were not different in ALS population as compared with controls.

ALS patients have higher erythrocyte maximum height, area and volume, decreased erythrocyte membrane roughness and increased membrane stiffness than the control group. These results indicates abnormal erythrocyte structure and possible changes on membrane lipid composition on ALS patients.

We propose that increased CC-16 levels could be a marker of lung inflammatory response, associated with ventilatory insufficiency and related to impending respiratory failure, which are not fully predicted by conventional respiratory tests. Moreover, abnormalities in erythrocyte morphology may enhance the risk of tissue hypoxia.

Amyotrophic lateral sclerosis (ALS) is a devastating and fatal neurodegenerative disorder. Death typically occurs within 3–5 years after disease onset. Respiratory failure (RF) is the main cause of death. No effective treatment and no molecular biomarker related to respiratory outcome and to early ventilatory dysfunction are available. The club-cell protein (CC-16) is a biomarker associated with respiratory distress and lung inflammation.

The aim of this work is to test if CC-16 and IL-6 could be new biomarkers of ALS for early signs of respiratory insufficiency and disease progression. Additionally, we intend to study morphological and viscoelastic changes of the erythrocytes' membrane associating them with ALS patients' clinical profile.

Functional capacity and respiratory function (forced vital capacity) were evaluated in 81 ALS patients and 30 matched controls. CC-16 and IL-6 were quantified by ELISA and Multiplex-technology, respectively. Morphological and viscoelastic properties of the erythrocytes were analysed by Atomic Force Microscopy (AFM).