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Original Paper

Increase of Kynurenic Acid after Encephalomyocarditis Virus Infection and Its Significances

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Key Words
Picorna • EMCV • Piglets • Depression • Lethality • Heart • Kynurenic acid • Neopterin • β2-microglobulin

Abstract
Background/Aims: The moust symptoms of piglets infected with Encephalomyocarditis virus (EMCV) are related to breeding difficulty, circulation insufficiency, depression and occurrence of high lethality. An increase of tryptophan metabolism in the periphery and in the central nervous system (CNS) in human and non-human subjects with inflammatory diseases has been suggested. We investigated an alterations of tryptophan metabolite i.e. kynurenic acid (KYNA) level in the serum of piglets after EMC virus infection. In addition, we investigated the markers of immune stimulation i.e. neopterin and β2-microglobulin. ***Methods:*** KYNA was determined by high performance liquid chromatography method, while neopterin and β2-microglobulin by ELISA method. Piglets with an age of 8 weeks were infected intranasal and orally with the EMC virus. Blood samples were collected before virus inoculation at day 0 (control) and at 1, 2, 3 and 4 days post inoculation (DPI) and piglets as control subjects were used, too. ***Results:*** In EMCV infected piglets we observed a time dependent alteration of investigated parameters. KYNA level increased significantly and at 3 DPI was 341% of CO, $p<0.001$ and at 4 DPI an enhancement was 242% of CO, $p<0.001$, respectively. Neopterin increased moderately after EMCV infection and at 4 DPI was 130% of CO, $p<0.05$. Serum β2-microglobulin was slightly lowered and at 4 DPI was 86% of CO, $p<0.05$. Present data indicate an marked increase of kynurenine metabolism in the periphery after EMCV infection and an moderate activation of immune system. ***Conclusion:*** A marked increase of KYNA and a moderate enhancement of neopterin indicate sensibility of kynurenine metabolism to EMCV infection. Lowering of ß2-

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microgobulin might relate to development of events leading to the lethality. We suggest that due to viral infection an increase of KYNA might contribute to the inpairment of organs in the periphery and CNS function and might participate by sudden death.

Introduction

The most symptoms of EMCV diseased piglets are depression, breeding difficulty and circulation insufficiency [1, 2]. Clinically, EMCV causes a sudden death syndrome in piglets, and in adults the infection may lead to reproductive failure [1, 2]. EMCV mainly affects heart tissue and the CNS [3, 4].

Tryptophan as an essential amino acid serves as a substrate for several important reactions including kynurenine pathway leading to niacin formation [5]. Activation of tryptophan metabolism has been reported in the periphery and in the CNS in human and non-human subjects with inflammatory diseases due to viral, bacterial, fungal or parasitic infections, and in autoimmune diseases also in meningitis and septicaemia [6-11]. Induction of indoleamine-2, 3-dioxygenase (IDO), the first enzyme of the kynurenine pathway, which converts L-tryptophan to L-kynurenine (L-KYN) takes place by inflammatory events [11].

In the periphery and in the brain kynurenic acid (KYNA) is synthesized from L-KYN by using various kynurenine aminotransferases [12-14]. KYNA is an endogenous ionotropic excitatory amino acid (EAA) receptors antagonist which modulates and disrupts excitatory i.e. glutamate- and acetyl cholinergic amino acid neurotransmission [5, 15]. Our previous data indicated that KYNA dose dependent influences heart mitochondrial function by increasing oxygen consumption and lowering ATP synthesis [16, 17]. We have also shown that a deficit of oxygen leads to a significant elevation of KYNA in CNS [18]. Furthermore, we found that the highest lethality correlated with a peak of KYNA increase and lowering of ATP [18, 19]. Based on the molecular data, the infection of piglets by EMCV is detectable at 4^{th} day after inoculation [20]. It is known that the stage of infection is dose and time dependent and by using the optimal established amount of virus suspension the infection at day 4^{th} and 6^{th} is characterised by relatively low mortality in contrary to day 8^{th} or a longer period of infection. Since no data are available regarding the neurochemical changes *in vivo* we first examined the effect at the 4th day after infection. Since heart tissue effectively synthesizes KYNA [13] and since KYNA may influence the heart mitochondria function [16, 17] we were interested to proof if KYNA in serum is affected after EMCV infection in piglets. Because host immune mediators such as interferon-gamma and tumour necrosis factor alpha may increase IDO activity and L-KYN metabolism [6-9, 11], therefore we analyse the kynurenine metabolite KYNA in the serum of piglets after EMCV infection. In addition, we measured neopterin and β2-microglobulin which are markers of immune stimulation. Subsequently, a correlation study of investigated parameters was performed. A part of the data was presented in an abstract form [21].

Materials and Methods

Chemicals

L-KYN, KYNA, pyruvate, pyridoxal-5'-phosphate and 2-amino-2-methyl-1-propanol (AMPOL) were purchased from Sigma-Aldrich Handel's GmbH, Wien, Austria. All other chemicals used were of the highest commercially available purity.

Animals

Piglets with an age of 8 weeks were infected intranasally and orally with the EMC Virus (8ml, EMCV strain B279/95, 10^7 TCID 50/ml) (N = 14) or medium (control, CO, N = 6). Clinical examinations were carried out twice a day to verify the infection state. At least once daily internal body temperature was measured and the animals examined for clinical signs (general physical examination, with special respect to heart and

lung status). Blood samples were collected in the morning before virus inoculation at day 0 and at 1, 2, 3 and 4 days post inoculation (DPI). Serum samples were coded to conceal patient's identity of control vs EMCV group and the study was carried out at the Veterinary University Vienna according to Austrian Ethical Regulation.

Determination of KYNA

The measurement of KYNA was performed according to Swartz et al. [22] with modifications described by Baran et al. [18]. KYNA was quantified by a high performance liquid chromatography (HPLC) system coupled with fluorescence detection. KYNA samples were purified on a Dowex 50W cation-exchange column as described by Turski et al. [23] before applied to HPLC.

Determination of neopterin and ß2-microglobuline

The macrophage activation marker neopterin was assayed by ELISA (enzyme-linked immunosorbent assay) using kits available commercially. β2-microglobulin was examined by ELISA employing commercially available kit.

Data analyses

All data are presented as the means ± standard error of the mean. For statistical analyses, one–way ANOVA analysis of variance and a Student's t-test were applied. Each sample was determined in duplicate or triplicate. The level for statistical significance was $P<0.05$; $*P<0.05$, $**P<0.01$ and $***P<0.001$ indicate a significance compared with control group. Linear regression analysis was performed using the least squares methods. Correlation between investigated parameters, e.g. KYNA and time after inoculation or KYNA and neopterin or KYNA and β2-microglobulin was analyzed.

Results

Clinical estimation of piglets after EMCV inoculation

The EMCV group showed an increase of the body temperature up to 42°C. Piglets showed a decreased behaviour activities including loss of appetite and apathy and had a higher degree of cardiac insufficiency, similar as reported by other. Two piglets of the EMCV group died and are not included in chemical investigation.

KYNA, neopterin and β2-microglobulin in the serum of control piglets (CO)

In serum of CO piglets we measured 3.398 ± 0.090 (N = 30) of KYNA (fmol/µl). Neopterin was 0.4136 ± 0.02274 (mg/L) and β2-microglobulin was 0.16600 ± 0.00648 (mg/L) (Table 1).

Table 1. Alterations of neopterin and β2-microglobulin levels in the serum of piglets after EMCV infection. Days post inoculation (DPI). Significance: *P<0.05; **P<0.01 compared with CO. One–way ANOVA analyse of neopterin levels between 5 groups i.e. CO, 0 DPI, 1 DPI, 2 DPI, 3 DPI and 4 DPI revealed no significant differences (F = 1.36664, P = 0.2460). One–way ANOVA analyse of β2-microglobulin between 5 groups i.e. CO, 0 DPI, 1 DPI, 2 DPI, 3 DPI and 4DPI revealed no significant differences (F = 1.63256, P = 0.16125)

Groups	Neopterin (mg/L)	% of CO	β2-microglobulin (mg/L)	% of CO
Control (CO)	0.4136±0.02274 (25)	100	0.16600±0.00648 (25)	100
EMCV 0DPI	0.45833±0.04516 (12)	111	0.16083±0.00908 (12)	97
EMCV 1DPI	0.54167±0.09249 (12)	131	0.16917±0.01104 (12)	102
EMCV 2DPI	0.60000±0.13200 (12)	145	0.15583±0,00499 (12)	94
EMCV 3DPI	0.55000±0.03138 (12)	133**	0.14917±0,00633 (12)	90
EMCV 4DPI	0.53636±0.05604 (11)	130*	0.14273±0.00541 (11)	86*

KYNA in the serum of EMCV piglets

In EMCV infected piglets we observed a time dependent and significant alteration of KYNA levels (Fig. 1). One-way ANOVA analyse of KYNA levels between CO and 0 or 1, 2, 3 and 4 DPI revealed significant differences (F = 3.50182, *P* = 0.00642). At one DPI the serum KYNA level was slightly elevated but not significant (111% of CO, *P* = 0.29441; one–way ANOVA analyse revealed F = 1.12956; *P* = 0.29441). KYNA levels increased significantly after: 2 DPI (192% of CO, *P*<0.001, one–way ANOVA was F = 17.39428, *P* = 1.58483E-4); 3 DPI (341% of CO, *P*<0.01, one-way ANOWA was F = 7.90649, *P* = 0.00759) and 4 DPI with EMCV (242% of CO, *P*<0.001; one-way ANOVA was F = 18.55486, *P* = 1.08032E-4), respectively. Analysis of KYNA levels between CO and 0 DPI revealed no significant differences (*P* = 0.99579).

Neopterin in the serum of EMCV piglets

Neopterin content was moderately and significantly increased 3 and 4 days after EMCV infection, i.e. it was 133% of CO, *P*<0.01 and 130% of CO, *P*<0.05, respectively (Table 1). One-way ANOVA analysis of neopterin levels between CO and 0 or 1, 2, 3 and 4 DPI revealed no significant differences (F = 1.36664, *P* = 0.2460). One-way ANOVA analysis of neopterin levels between CO and 0 DPI revealed no significant differences, F = 0.9802, *P* = 0.3289. At 1 DPI neopterin was 131% of CO, F = 3.2337, *P* = 0.0808; at 2 DPI was 145% of CO, F = 3.7775, *P* = 0.0600; at 3 DPI neopterin was 133% of CO, F = 11.9947, *P* = 0.0014 and at 4 DPI neopterin was 130% of CO, F = 5.97021, *P* = 0.0199, respectively.

β2-microglobulin in the serum of EMCV piglets

β2-microglobulin content was moderately lowered 4 days after EMCV infection and was 86% of CO, *P*<0.05 (Table 1). One-way ANOVA analysis of β2-microglobulin levels between CO and 0 or 1, 2, 3 and 4 DPI revealed no significant differences (F =1.63256, *P* = 0.16125). One-way ANOVA analysis of β2-microglobulin levels between CO and 0 DPI revealed no significant differences, F = 0.2099, *P* = 0.6497. At 1 DPI β2-microglobulin was 102% of CO, F = 0.0689, *P* = 0.79446; at 2 DPI β2-microglobulin was 94% of CO, F = 1.0295, *P* = 0.31724; at 3 DPI β2-microglobulin was 90% of CO, F = 2.6372, *P* = 0.11336 and at 4 DPI β2-microglobulin was 86% of CO, F = 4.95002, *P* = 0.03283, respectively.

Correlations

Linear regression study between KYNA and neopterin levels revealed significant correlation at 4 days (Fig. 2) but not at 1, 2 or 3 days after infection: i.e. at 0 DPI, y = 1.58078 - 3.96975 x, R = 0.3434, *P* = 0.27445; at 1 DPI, y = 3.99696 – 0.42255 x, R = - 0.08161, *P* = 0.81146; at 2 DPI, y = 8.29764 - 2.96787 x, R = - 0.33137, *P* = 0.29272; at 3 DPI, y = 37.53982 - 47.17846 x, R = - 0.31567, *P* = 0.3176; at 4 DPI, y = -6.97754 + 28.36932 x, R = 0.84528, *P* = 0.00105.

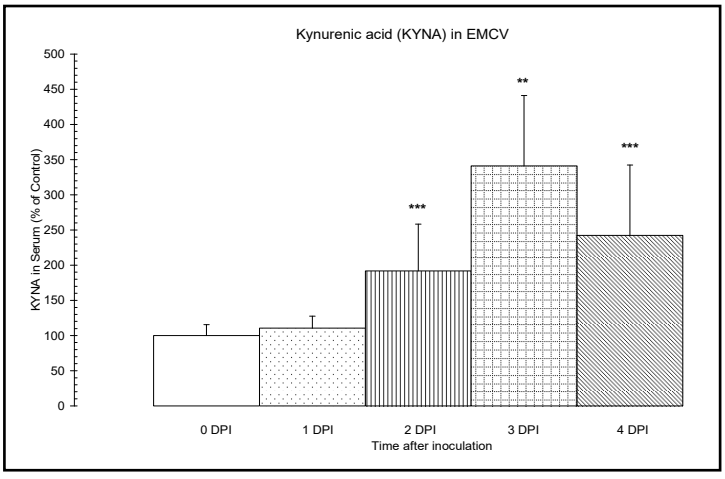

Fig. 1. KYNA level in the serum of EMCV infected piglets. Values represent the mean ± SEM of following: Control (CO, N = 30); EMCV subgroups: O DPI (N = 12); 1 DPI (N = 11); 2 DPI (N = 12); 3 DPI (N = 12); 4 DPI (N = 11). Days post inoculation (DPI). Significance: *P<0.05; **P<0.01; ***P<0.001 compared with CO. One–way ANOVA analyse revealed significant differences in KYNA levels in serum between 5 groups i.e. CO, 0 DPI, 1 DPI, 2 DPI, 3 DPI and 4 DPI (F = 3.50182, P = 0.00642).

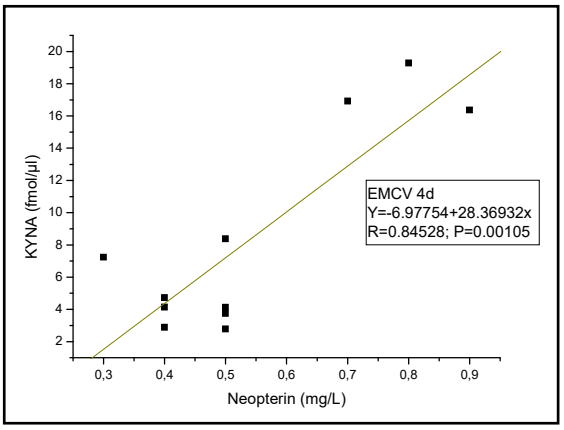

Fig. 2. Correlation between KYNA and neopterin levels at 4th day after inoculation of piglets with EMCV. Linear regression study between KYNA and neopterin levels revealed significant correlation: y = -6.97754 + 28.36932 x, R = 0.84528, P = 0.00105.

Linear regression study between KYNA and β2-microglobulin levels revealed no significant correlation at any time point of infection: i.e. at 0 DPI, y = 6.5996 - 19.8925 x, R = - 0.34615, *P* = 0.27038; at 1 DPI, y = 4.88579 - 6.53687 x, R = - 0.14775, *P* = 0.66463; at 2 DPI, y = -7.75785 + 91.60278 x, R = 0.38691, *P* = 0.21405; at 3 DPI, y = 59.95474 - 324.22 x, R = - 0.43768, *P* = 0.15475; at 4 DPI, y = 6.05367 + 15.30932 x, R = 0.04402, *P* = 0.8977.

Discussion

In respect to investigated parameters in the serum of control piglets, i.e. KYNA, neopterin and β2-microglobulin, the levels were lower in comparison to human, indicating species differences [7-9, 24].

The most notable finding of the study is the marked increase of KYNA in the serum of piglets after EMCV infection. The peak of an enhancement of KYNA was time dependent, the highest value of 341% of CO was seen at 3rd day after inoculation and at 4th day the levels were moderately declined to 242% of CO. The level of neopterin, a marker of immunoreactivity, was increased by 145% of CO at 4th day after infection and the levels of β2-microglobulin were slightly lowered, by 86% of CO at 4th day after infection. Revealed data indicate that infection with EMCV causes significant alteration of investigated parameters in piglets in the periphery, with different pattern of changes. Neopterin and β2-microglobulin were moderately altered in the blood of EMCV infected piglets up to 4 days after inoculation in comparison to marked enhancement of KYNA. We suggest that the alteration of L-tryptophan metabolism might play a pivotal role during acute period of infection and probably later, too. At 4th day after inoculation significant correlation between an enhancement of KYNA and neopterin was revealed and this observation is in the line with data observed in human after immunodeficiency virus type-1 (HIV-1) infection [7, 8]. Whereas in human after HIV-1 infection the content of β2-microglobulin was increased [8], it was lowered in the blood of piglets after EMCV infection. Lowering of β2-microglobulin in serum of piglets at 4th day after the EMCV infection might suggest the development of infectious mortality. Recently, an association between lower serum β2-microglobulin levels and worse survival in incident of peritoneal dialysis patients has been described [25]. At day 4th the infection of piglets with EMCV is characterised by moderate reduction of β2-microglobulin and correlate with low mortality [20].

A disturbance of L-tryptophan metabolism along kynurenine pathway was found in human HIV-1 [6-9] and after influenza A virus infection, too [10]. Some reports described lowered L-tryptophan, elevated L-KYN, KYNA and quinolinic acid levels in the CSF of HIV-1 patients [6-10]. In our previous work we have shown a significant enhance of KYNA synthesis in the human brain after HIV-1 infection [26]. Interestingly, study in the brain homogenate of piglets after EMCV infection revealed an increase of KYNA formation, too [27, 28].

Breathing difficulty, bronchopneumonia, lobar pneumonia, oedema of the lung or even tuberculosis occurs after various infections i.e. EMCV, HIV-1, influence A or Corona virus [1-4, 29-32]. Notably, a high mortality in infected mammalians including human has been reported [20, 28, 29, 33]. A significant observation on marked increase of KYNA synthesis was revealed in the brain of human suffering from bronchopneumonia [34]. Therefore, would be reasonable to consider the importance of kynurenine metabolism activation during events related impaired abilities of oxygen consumption. In the line, a marked increase of KYNA in the brain has been found due to a deficit of oxygen in case of asphyxia [18]. In this work, a particular of interest was the observation that the longer the period of oxygen deficit, the higher the observed peak of KYNA in the brain and the higher the lethality rate, too [18]. Lowering of ATP synthesis correlated significantly with duration of asphyxia, too [18, 19].

Experimental work *in vivo* study has shown that administration of KYNA (icv) into the rats resulted in ataxia and stereotypy, in a dose-dependent manner (0.025-1.6 μmol) [35]. Importantly, authors demonstrated that administration of 0.8 μmol of KYNA resulted in sleeping and in an approximate 25% mortality of the animal and at a dose of 1.6 μmol all of the animals died within 2-5 min from cardiorespiratory failure [36]. These data would suggest that spontaneous synthesis of KYNA in the brain due to infection and/or unknown reason might lead to the cardiorespiratory impairment followed by per acute death. In the line, our preliminary data indicated that the kynurenine metabolism is activated after EMCV infection in the brain, as well [27, 28]. We believe that this increase might be responsible for the incidence of cardiorespiratory dysfunction and sudden death. However, this proposed mechanism need further investigation.

In our previous study we have investigated an impact of elevated L-tryptophan metabolism on mitochondrial function of various organs [16, 17]. We demonstrated significant dose dependent effect of L-tryptophan metabolites i.e. KYNA, 3-OH-kynurenine or 3-OH-anthranilic acid on respiratory parameters of rat brain, heart and liver mitochondria [16, 17]. We have shown that high KYNA levels lowered oxygen consumption of the heart mitochondria and ATP synthesis, but not of brain or liver mitochondria, whereas 3-OH-kynurenine, 3-OH-anthranilic acid affected heart, liver and brain mitochondria respiratory parameters [17]. These findings support the suggestion that activation of L-KYN metabolism might have an impact on different organs, particularly influence the heart cell function, causing an impairment of cardiovascular processes and leading to congestive cardiac dysfunction. In the line, an enhancement of KYNA levels of a stroke patient has been described and its significance for involvement of an impairment of cardiovascular system has been suggested [37, 38]. Ouinolinic acid, an endogenous neurotoxin, has been suggested also to play a role concerning the development of dementia after HIV-1 infection and might participate by induction of death [39], but does not affect respiratory parameters in rat heart, liver or brain mitochondria [17].

In respect to various data and presently developed pandemic due to Corona virus infection it is important to discuss this topic intensively. Patients infected with Corona virus are showing clinically depression, impairment of smell, breathing difficulty and might develop severe pathological conditions including high frequency of death cases, as well [32]. Although, none data are available on KYNA levels of Corona infected patients yet, our previous and present studies strongly suggest that an increase of KYNA levels is likely to appear in the periphery and CNS due to Corona infection. It is obvious that KYNA content in the periphery and/or CNS results from accumulation of events related to activation of KYNA synthesis. An influence of aging process on KYNA levels was observed in different forms of hydrocephalus [40]. Notable, in the line a high lethality rate due to Corona infection has been observed in older animals, in rhesus macaque model of COVID-19, or in older human patients (age >70 years), as well as in patients with other health problems [41-43]. The role of the aging process by CORONA infections has been described [42] and an age dependent increase of KYNA in the cerebrospinal fluid of clinically healthy persons has been shown [24]. Only marginal synthesis of KYNA in the brain was found in the CNS of young animals and significant age-dependent increase was revealed in adult and older animals [44, 45].

A study in terms of sex including risk of mortality by COVID-19 amongst adult patients revealed that male sex is an important risk factor for mortality [46]. Interestingly, study on the synthesis of KYNA in human saliva suggests a higher ability to form KYNA in saliva of males [47] and this should be proved with high number of investigated cases.

An enhancement of KYNA content in CNS has been described in patients with HIV-1, Alzheimer's disease, bronchopneumonia, stroke, hydrocephalus, Down's syndrome and many others diseases including aging and its involvement in development of depression, impairment of memory and cognition was suggested [9, 24, 26, 34, 37, 40, 48-50].

Recently, the high incidence of the sudden death due to Corona infection has been reported in patients with Down's syndrome [51]. Interestingly, the involvement of high KYNA levels in the brain tissue of patients suffering from Down's syndrome might be relevant for the incidence of high lethality. Indeed, the average age of patients with Down's syndrome is about 40-50 years and these patients have a high level of KYNA over 300% of CO in the brain [49]. Importantly, it is also reasonable to question if elevated KYNA metabolism in the brain of patients with Down's syndrome, in general, might contribute to a short spam of life.

Anti-dementia agent Cerebrolysin or D-cycloserin [52, 53] and herbal extracts like Jerusalem Balsam or Hawthorn, all of them are able to lower KYNA formation [54-57]. D-cycloserine was even used in earlier time for tuberculosis treatment [53]. In respect to that we suggest that blockade of KYNA synthesis could be a part of therapeutic measure to increase the efficiency of drugs for viral diseases. Indeed, recently published study demonstrated improvement of clinical symptoms of COVID-19 due to natural herbal medicine and authors suggest that it may be effective in treating COVID-19 [58, 59]. Also evaluation of the adjuvant efficacy of natural herbal medicine on COVID-19 revealed a positive effect regarding therapeutic success of COVID-19 patients [60].

Conclusion

The present data demonstrates a significant enhancement of KYNA levels in piglets after Picorna virus infection and suggests activation of L-tryptophan degradation along kynurenine pathway. Immune marker neopterin and β2-microglobulin were less affected than KYNA supporting the physiological role of L-tryptophan metabolism during acute period of infection. Measurement of KYNA levels in the blood and/or searching an ability of saliva to form KYNA might represent important marker for the stage of disease and probably of lethality. We suggest that conditions related to respiratory deficits, dementia and lethality might share dose dependent involvement when it comes to the increased KYNA metabolism observed. This observation might have an impact on EMCV infected piglets and patient infected with others virus including Corona virus, as well. We suggest that modulation of KYNA content by lowering its synthesis might support the cardio-respiratory system and acts, at least in part, as an anti-dementia agent and might lower incidence of lethality not only in animals but also in humans. In the near future further studies should evaluate an impact of oxygen impairment and KYNA accumulation in humans.

Abbreviations

ANOVA (analysis of variance); CNS (central nervous system); CO (control); DPI (days post inoculation); EAA (excitatory amino acid); HIV-1 (human immunodeficiency virus type-1); icv (intra cerebra ventricular); KYNA (kynurenic acid); N (numbers).

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Author Contributions

Conceived and designed the Experiments: HB. Experimental work: MD. Analysed the data: MD, HB. Developed the structure and arguments for the paper: HB. Contributed to the writing of the manuscript: MD, CK, BK. Agree with manuscript results and conclusions: HB, MD, CK, BK. All authors reviewed and approved the final manuscript.

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Disclosure Statement

The authors declare that no conflicts of interest exist.

References

1 Murnane TG, Craighead JE, Mondragon H, Shelokov A: Fatal disease of swine due to encephalomyocarditis virus. Science 1960;131:498-499.

2 Noack K, Lieberman H: Die Enzephalomyokarditis virus-infektion beim Schwein. Ein Überblick. Tierarztl Umsch 1992;47:16-23.

3 Brewer LA, Lwamba HCM, Murtaugh MP, Palmenberg AC, Brown C, Njenga MK: Porcine Encephalomyocarditis Virus Persists in Pig Myocardium and Infects Human Myocardial Cells. J Virol 2001;75:11621-11629.

4 Canelli E, Luppi A, Lavazza A, Lelli D, Sozzi E, Martin AMM, Gelmetti D, Pascotto E, Sandri C, Magnone W, Cordioli P: Encephalomyocarditis virus infection in an Italian zoo. Virol J 2010;64:1-7.

5 Stone TW: Neuropharmacology of quinolinic and kynurenic acids. Pharmacol Rev 1993;45:309-379.

6 Fuchs D, Forsman A, Hagberg L, Larsson M, Norkrans G, Reibnegger G, Werner ER, Wachter H: Immune activation and decreased tryptophan in patients with HIV-1 infection. J Interferon Res 1990;10:599-603.

7 Fuchs D, Möller AA, Reibnegger G, Stöckle E, Werner ER, Wachter H: Decreased serum tryptophan in patients with HIV-1 infection correlates with increased serum neopterin and with neurologic/psychiatric symptoms. J Acquir Immune Defic Syndr 1990;3:873-876.

8 Heyes MP, Brew BJ, Saito K, Quearry BJ, Price RW, Lee K, Bhalla RB, Der M, Markey SP: Inter-relationships between quinolinic acid, neuroactive kynurenines, neopterin and beta 2-microglobulin in cerebrospinal fluid and serum of HIV-1-infected patients. J Neuroimmunol 1992;40:71-80.

9 Heyes MP, Saito K, Crowley JS, Davis LE, Demitrack MA, Der M, Dilling LA, Elia J, Kruesi MJP, Lackner A, Larsen SA, Lee K, Leonard HL, Markey SP, Martin A, Milstein S, Mouradian MM, Pranzatelli MR, Quearry BJ, Salazar A, et al.: Quinolinic acid and kynurenine pathway metabolism in inflammatory and non-inflammatory neurological disease. Brain 1992;115:1249-1273.

10 Holtze M, Asp L, Schwieler L, Engberg G, Karlsson H: Induction of the kynurenine pathway by neurotropic influenza A virus infection. J Neurosci Res 2008;86:3674-3683.

11 Sage LK, Fox JM, Mellor AL, Tompkins SM, Tripp RA: Indoleamine 2,3-Dioxygenase (IDO) Activity during the primary immune response to influenza infection modifies the memory T cell response to influenza challenge. Viral Immunol 2014;27:112–123.

12 Noguchi T, Minatogawa Y, Okuno E, Nakatani M, Morimoto M, Kido R: Purification and characterization of kynurenine-2-oxoglutarate aminotransferase from the liver, brain and small intestine of rats. Biochem J 1975;151:399–406.
13 Baran H, Amann G, Lubec B, Lubec G: Kynurenic acid and kynurenine aminotransferase in heart. Pediatr Res 1997;41:404-410.
14 Okuno E, Nakamura M, Schwarcz R: Two kynurenine aminotransferases in human brain. Brain Res 1991;542:307-312.
15 Hilmas C, Pereira EFR, Alkondon M, Rassoulpour A, Schwarcz R, Albuquerque EX: The brain metabolite kynurenic acid inhibits α7-nicotinic receptor activity and increases non-α7-nicotinic receptor expression: Physiopathological Implications. J Neurosci 2001;21:7463–7473.
16 Baran H, Staniek K, Kepplinger B, Stur I, Draxler M, Nohl H: Kynurenines and the respiratory parameters in rat heart mitochondria. Life Sci 2003;72:1103-1115.
17 Baran H, Staniek K, Bertignol-Spörr M, Attam M, Kronsteiner C, Kepplinger B: Effect of various kynurenine metabolites on respiratory parameters of rat brain, liver and heart mitochondria. Int J Tryptophan Res 2016;9:17-29.
18 Baran H, Kepplinger B, Herrera-Marschitz M, Stolze K, Lubec G, Nohl H: Increased kynurenic acid in the brain after neonatal asphyxia. Life Sci 2001;69:1249-1256.
19 Lubec B, Marx M, Herrera-Marschitz M, Labudowa O, Hoeger H, Gille L, Nohl H, Mosgoeller W, Lubec G: Decrease of heart protein kinase C and cyclin-dependent kinase precedes death in perinatal asphyxia of the rat. FASEB J 1997;11:482-492.
20 Maurice H, Mnielen M, Stegeman JA, Vanderhallen H, Koenen F: Transmission of encephalomyocarditis virus (EMCV) among pigs experimentally quantified. Vet Microbiol 2002;88:301-314.
21 Baran H, Kepplinger B, Lang Ch, Draxler M, Schmoll F, Strasser A, Schuh M, Nowotny N: Enhancement of kynurenic acid (KYNA) and neopterin levels in serum of piglets after encephalomyocarditis virus (EMCV) infection. Proceedings of the 18th International Pig Veterinary Society Congress 2004;1:364.
22 Swartz KJ, Matson WR, MacGarvey U, Ryan EA, Beal MF: Measurement of kynurenic acid in mammalian brain extracts and cerebrospinal fluid by high-performance liquid chromatography with fluorometric and coulometric electrode array detection. Anal Biochem 1990;185:363-376.
23 Turski WA, Nakamura M, Todd WP, Carpenter BK, Whetsell WO Jr, Schwarcz R: Identification and quantification of kynurenic acid in human brain tissue. Brain Res 1988;454:164-169.
24 Kepplinger B, Baran H, Kainz A, Ferraz-Leite H, Newcombe J, Kalina P: Age-related increase of kynurenic acid in human cerebrospinal fluid - IgG and beta-2 microglobulin changes. Neurosignals 2005;14:126-135.
25 Chang TI, Lim H, Park ChH, Park KS, Park JT, Kang EW, Yoo TH, Kang SW, Han SH: Lower serum beta-2 microglobulin levels are associated with worse survival in incident peritoneal dialysis patients. Nephrology Dialysis Transplantation 2019;34:138–145.
26 Baran H, Hainfellner JA, Kepplinger B, Mazal PR, Schmid H, Budka H: Kynurenic acid metabolism in the brain of HIV-1 infected patients. J Neural Transm 2000;107:1127-1138.
27 Baran H, Draxler M, Kalbacher H, Nowotny N, Schmidt P, Kepplinger B, Url A, Schuh M, Hofecker G: Kynurenine aminotransferase I and II (KAT I and KAT II) in piglet's brain after Encephalomyocarditis (EMCV) infection. Soc Neurosci 2003; Abstr 33:215.8.
28 Baran H, Draxler M, Kepplinger B, Kahlbacher H, Nowotny N, Schmidt P, Url A, Schuh M, Hofecker G: Kynurenine metabolism in piglet brain due to EMCV infection. Pharmacology 2003;69:212-217.
29 Peters CE, Carette JA: Return of the neurotropic enteroviruses: Co-opting cellular pathways for infection. Viruses 2021;13:1-23.
30 Gordin FM, Roediger MP, Girard PM, Lundgren JD, Miro JM, Palfreeman A, Rodriguez-Barradas MC, Wolff MJ, Easterbrook PJ, Clezy K, Slater LN: Pneumonia in HIV-infected persons: increased risk with cigarette smoking and treatment interruption. Am J Respir Crit Care Med 2008;178:630-636.
31 Kerr-Pontes LR, Oliveira FA, Freire CA: Tuberculosis associated with AIDS: the situation in a Northeastern region of Brazil. Rev Saude Publica 1997;31:323-329.
32 Peng QY, Wang XT, Zhang LN, Chinese Critical Care Ultrasound Study Group (CCUSG): Findings of lung ultrasonography of novel corona virus pneumonia during the 2019–2020 epidemic. Intensive Care Med Letter 2020;46:849-850.

33 Lucas SB, Hounnou A, Peacock C, Beaumel A, Djomand G, N'Gbichi JM, Yeboue K, Hondé M, Diomande M, Giordano C, Doorly R, Brattegaard K, Kestens L, Smithwick R, Kadio A, Ezani N, Yapi A, De C, Kevin M: The mortality and pathology of HIV infection in a West African city. AIDS 1993;7:1569-1579.
34 Baran H, Hainfellner JA, Kepplinger B: Kynurenic acid metabolism in various types of brain pathology in HIV-1 infected patients. Int J Tryptophan Res 2012;5:49-64.
35 Vécsei L, Beal MF: Intracerebroventricular injection of kynurenic acid, but not kynurenine induces ataxia and stereotyped behaviour in rats. Brain Res Bull 1990;25:623-627.
36 Vécsei L, Beal MF: Comparative behavioral and pharmacological studies with centrally administered kynurenine and kynurenic acid in rats. Eur J Pharmacol 1991;196:239-246.
37 Kepplinger B, Sedlnitzky-Semler B, Eigner S, Kalina P, Berger P, Baran H: Stroke patients after repetitive transcranial magnetic stimulation (rTMS) – Alterations of tryptophan metabolites in the serum. Int J Neurorehabil 2014;1:1-11.
38 Urbańska EM, Luchowski P, Luchowska E, Pniewski J, Woźniak R, Chodakowska-Zebrowska M, Lazarewicz J: Serum kynurenic acid positively correlates with cardiovascular disease risk factor, homocysteine: a study in stroke patients. Pharmacol Rep 2006;58:507-511.
39 Guillemin GJ, Wang L, Brew BJ: Quinolinic acid selectively induces apoptosis of human immunodeficiency virus type-1 astrocytes potential role in AIDS dementia complex. J Neuroinflammation 2005;2:16.
40 Kepplinger B, Baran H, Kronsteiner C, Reuss J: Increased levels of kynurenic acid in the cerebrospinal fluid in patients with hydrocephalus. Neurosignals 2019;27:1-11.
41 Yu P, Qi F, Xu Y, Li F, Liu P, Liu J, Bao L, Deng W, Gao H, Xiang Z, Xiao C, Lv Q, Gong S, Liu J, Song Z, Qu Y, Xue J, Wei Q, Liu M, et al.: Age-related rhesus macaque models of COVID-19. Animal Model Exp Med 2020;3:93–97.
42 Niu S, Tian S, Lou J, Kang X, Zhang L, Lian H, Zhang J: Clinical characteristics of older patients infected with COVID-19: A descriptive study. Arch Gerontol Geriatr 2020;89:104058.
43 Cabibbo G, Rizzo GEM, Stornello C, Craxì A: SARS-CoV-2 infection in patients with a normal or abnormal liver. J Viral Hepat 2021;28:4–11.
44 Baran H, Schwarcz R: Regional differences in the ontogenetic pattern of kynurenine aminotransferase in the rat brain. Brain Res Dev 1993;74:283-286.
45 Gramsbergen JB, Schmidt W, Turski WA, Schwarcz R: Age-related changes in kynurenic acid production in rat brain. Brain Res 1992;14:1-5.
46 Kelada M, Anto A, Dave K, Saleh SN: The Role of sex in the risk of mortality from COVID-19 amongst adult patients: A systematic review. Cureus 2020;12:e10114.
47 Baran H, Kronsteiner C, Kepplinger B: Kynurenine Aminotransferases I, II and III Are Present in Saliva. Neurosignals 2020;28:1-13.
48 Baran H, Jellinger K, Deecke L: Kynurenine metabolism in Alzheimer's disease. J Neural Transm 1999;106:165-181.
49 Baran H, Cairns N, Lubec B, Lubec G: Increased kynurenic acid levels and decreased brain kynurenine aminotransferase I in patients with Down syndrome. Life Sci 1996;58:1891-1899.
50 Erhardt S, Schwieler L, Nilsson L, Linderholm K, Engberg G: The kynurenic acid hypothesis of schizophrenia. Physiol Behav 2007;92:203-209.
51 Clift K, Coupland CAC, Keogh RH, Hemingway H, Hippisley-Cox J: COVID-19 mortality risk in Down Syndrome: results from a cohort study of 8 million adults. Ann Intern Med Letters 2020;21:1-4.
52 Xiao S, Yan H, Yao P, the Cerebrolysin Study Group: The efficacy of cerebrolysin in patients with vascular dementia: results of a chinese multicentre, randomized, double-blind, placebo-controlled trial. Hong Kong J Psychiatry 1999;9:13-19.
53 Chaturvedi SK, Zaidi N, Alam P, Khan JM, Qadeer A, Siddique IA, Asmat S, Zaidi Y, Khan RH: Unraveling Comparative Anti-Amyloidogenic Behavior of Pyrazinamide and D-Cycloserine: A Mechanistic Biophysical Insight. PLoS One 2015;10:e0136528.
54 Baran H, Kepplinger B: Cerebrolysin lowers kynurenic acid formation-an *in vitro* study. Eur Neuropsychopharmacol 2009;19:161-168.
55 Baran H, Kepplinger B: d-Cycloserine lowers kynurenic acid formation—new mechanism of action. Eur Neuropsychopharmacol 2014;24:639-644.
56 Baran H, Pietryja MJ, Kronsteiner C, Kepplinger B: Jerusalem balsam lowers kynurenic acid formation: an *in vitro* study. J Tradit Med Clin Natur 2017;6:224.

57 Baran H, Kepplinger B: Hawthorn berry extract lowers kynurenic acid and anthranilic acid formation. Clin Pharmacol Biopharm 2017; DOI: 10.4172/2167-065X-C1-026.
58 Zhao CN, Meng X, Li Y, Li S, Liu Q, Tang GY, Li HB: Fruits for prevention and treatment of cardiovascular diseases. Nutrients 2017;9:598.
59 Zheng S, Baak JP, Li S, Xiao W, Ren H, Yang H, Gan Y, Wen C: Network pharmacology analysis of the therapeutic mechanisms of the traditional Chinese herbal formula Lian Hua Qing Wen in Corona virus disease 2019 (COVID-19), gives fundamental support to the clinical use of LHQW. Phytomedicine 2020;79:153336.
60 Zhang HT, Huang MX, Liu X, Zheng XC, Li XH, Chen GQ, Xia JY, Hong ZS: Evaluation of the adjuvant efficacy of natural herbal medicine on COVID-19: A retrospective matched case-control study. Am J Chin Med 2020;48:779-792.