Neuroscience Letters 714 (2020) 134576

Contents lists available at ScienceDirect

Neuroscience Letters

journal homepage: www.elsevier.com/locate/neulet

Research article

Impaired metabolism of kynurenine and its metabolites in CSF of parkinson's disease

Kazuhiro Iwaoka*, Chigumi Otsuka, Tetsuya Maeda, Kanako Yamahara, Kanako Kato, Kenta Takahashi, Kai Takahashi, Yasuo Terayama

Division of Neurology and Gerontology, Department of Internal Medicine, School of Medicine, Iwate Medical University, 19-1 Uchimaru, Morioka, Iwate 020-8505, Japan

ARTICLE INFO

Keywords:
Parkinson's disease
Kynurenine pathway
Oxidative stress
Neuroinflammation

ABSTRACT

Aim: The kynurenine (KYN) pathway plays an important role in degrading molecules responsible for oxidative stress in the central nervous system (CNS), but can also have neurotoxic effects. Both 3-hydroxykynurenine (3-HK) and quinolinic acid are neurotoxic metabolites produced from this pathway. In Parkinson's disease (PD), oxidative stress is suspected to represent a key pathogenic mechanism. This study aimed to investigate the function of the KYN pathway and interactions between oxidative stress and neuroinflammation in PD.

Methods: Participants comprised 20 patients with PD and 13 controls. Cerebrospinal fluid (CSF) levels of KYN and 3-HK were measured using high-performance liquid chromatography coupled with an electrochemical detector. CSF levels of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and interferon (IFN)-γ were measured with an enzyme-linked immunosorbent assay, and results were statistically compared between PD patients and controls.

Results: Median CSF levels of KYN and 3-HK were 49.0 nM and 4.25 nM in PD and 30.5 nM and 1.55 nM in controls, respectively, showing significantly higher levels in PD ($p < 0.05$). CSF levels of measured cytokines showed that TNF-α and IL-1β were significantly higher in PD patients than in controls. No positive correlation between 3-HK and TNF-α was seen in PD.

Conclusion: Dysfunction of the KYN pathway may induce oxidative stress in the CNS in PD, and may also induce cytokine-mediated neuroinflammation. Functional amelioration of the KYN pathway may facilitate modification of neurodegenerative processes in PD.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder characterized as the cardinal motor features such as tremor at rest, muscle rigidity, akinesia and postural instability. Recently, PD has been rediscovered as neuropsychiatric [1] or systemic disorder because of frequent and variable nonmotor symptoms including autonomic dysfunctions, mood disorders, sleep disorders, cognitive dysfunctions and sensory problems [2]. The mechanism is unknown but some etiological candidates have been postulated, which are inflammatory reactions [3], oxidative stress [4], mitochondrial dysfunction [5], proteotoxic stress [6], dysfunction of kinases [7] and others. Overlapping of these pathogenic conditions can induce progressive and irreversible neuronal cell deaths in PD [8, 9]. Neuroinflammation is induced by inflammatory cytokines [10–12] associated with activated microglia in the central nervous system under pathogenic condition. In particular, microglial activities are intensively investigated using with *in vivo* positron emission tomography, as the facilitation of [11C](*R*)-PK11195 uptake into pons, basal ganglia and frontal and temporal cortical regions is reported in PD [13,14]. Elevation of some inflammatory cytokines, such as IL-6, IL-1β, TNF-α, and IFN-γ are known in the cerebrospinal fluid (CSF) or brain tissue in PD [15,16]. It is suggested that these cytokines can be derived from activated microglia and be an ignition key of those regional neuroinflammation in PD.

Serotonin is well known as an important neurotransmitter

Abbreviations: PD, Parkinson's disease; CSF, cerebrospinal fluid; TRP, tryptophan; KYN, kynurenine; 3-HK3-, hydroxykynurenine; KYNA, kynurenic acid; QA, quinolinic acid; TNF-, αtumor necrosis factor-α; IL-1, βinterleukin-1β; IL-6, interleukin-6; IFN-γ, interferon-γ

* Corresponding author.
E-mail addresses: kiwaoka@iwate-med.ac.jp (K. Iwaoka), chigohtsuka@gmail.com (C. Otsuka), maeda@iwate-med.ac.jp (T. Maeda), kkonno@iwate-med.ac.jp (K. Yamahara), kanakana117421@yahoo.co.jp (K. Kato), ktakahashi1009@gmail.com (K. Takahashi), sea.t.0926@gmail.com (K. Takahashi), surabe@iwate-med.ac.jp (Y. Terayama).

https://doi.org/10.1016/j.neulet.2019.134576
Received 31 January 2019; Received in revised form 15 October 2019; Accepted 19 October 2019
Available online 22 October 2019
0304-3940/

associating with depression in patients with PD [17], which is catalyzed from tryptophan via 5-hydroxytryptophan with tryptophan hydroxylase and aromatic L-amino acid decarboxylase [18]. In the human brain, most of tryptophan is converted into kynurenine (KYN) under indolamine 2,3-dioxigenase [19] which can influence physiological functions such as behavior, sleep, thermo-regulation, and pregnancy. These two metabolic pathways are representative in tryptophan metabolism. KYN pathway finally makes nicotinamide adenosine dinucleotide (NAD) and contributes redox reaction [20,21]. KYN is converted into two main compounds, one of which is kynurenic acid (KYNA) catalyzed by kynurenine-oxoglutarate transaminase and the other of which is 3-hydroxykynurenine (3-HK), catalyzed by KYN hydroxylase. 3-HK is converted into quinolinic acid (QA). These two key regulatory enzymes are activated by pro-inflammatory cytokines, such as tumor necrosis factor (TNF)-α and interferon (IFN)-γ. KYNA is an endogenous antagonist of glutamate ionotropic excitatory amino acid *N*-methyl-D-aspartate (NMDA) receptors in the nervous system and works neuroprotectively [22], whereas 3-HK and QA are NMDA receptor agonists and works neurotoxically [23,24]. 3-HK is a strong inducer of neurotoxic radicals as well [25]. Therefore, dysfunction of KYN pathway can exacerbate neurodegeneration process via oxidative stress and/or inflammatory reactions. In several neurological diseases including PD [26], pathogenic association of dysfunction of KYN pathway has been reported.

The purpose of the present study was to investigate the function of KYN pathway and interactions between oxidative stress and neuroinflammation in PD.

2. Results

We could enroll 20 patients with PD and 13 age-matched healthy controls ($p = 0.135$). The details are shown in Table 1. Eighteen patients had no antiparkinsonian medication and 2 patients were under medication whose levodopa equivalent doses were 375 and 200 mg per day. Age-matched healthy controls included 2 healthy volunteers and 11 patients who received lumbar anesthesia in our hospital, including antepartum (n = 1) and others (n = 10).

We detected cerebrospinal fluid (CSF) levels of KYN and its metabolites in both PD patients and controls. Five CSF samples from four patients with PD showed cytokine levels below the minimum level of detection for the enzyme-linked immunosorbent assay (ELISA); these samples were considered undetectable. All of measured values are shown in Table 2. These values were statistically compared between PD patients and controls as shown in Table 3. No differences in CSF levels of tryptophan were identified. CSF levels of KYN were significantly higher in PD patients than controls ($p = 0.036$). In metabolites of the KYN pathway, CSF levels of 3-HK were significantly higher in PD patients than controls ($p = 0.011$), but no difference in CSF levels of KYNA or QA was identified. In cytokines in the CSF, CSF levels of TNF-α and IL-1β were significantly higher in PD patients than controls ($p = 0.020$ and 0.015, respectively). No differences in CSF levels of IL-6 or IFN-γ were seen between groups. In PD group, we found no significant correlation between clinical background characteristics such as age, sex, disease duration or Unified PD rating scale (UPDRS) part III [27] and CSF levels of cytokines, KYN, or KYN metabolites. A positive correlation was observed between CSF levels of 3-HK and TNF-α in the PD group with the analysis using Spearman's rank correlation coefficient ($r = 0.48$), whereas no significant difference was seen between CSF levels of KYN and any cytokines.

Table 1
Clinical characteristics of Parkinson's disease patients and controls.

	PD	C
Number, male:female	20, 9:11	13, 9:4
Age, y	69.0 ± 6.4	69.0 ± 16.7
Disease duration, m	29.6 ± 20.3	–
H&Y stage	2.5 ± 0.5	–
stage 2, n	10	–
stage 3, n	10	
UPDRS part III	25.2 ± 9.5	–
MMSE	27.8 ± 2.2	–

PD; Parkinson's disease, C; control, y; years, m; months, H&Y; Hoehn and Yahr, n; number, UPDRS; unified Parkinson's disease rating scale, MMSE; mini-mental state examination.
Some values are described as mean ± standard deviation.

3. Discussion

3.1. Kynurenine and its metabolites in CSF

This case-control study obtained the following findings using CSF samples obtained from PD patients. Whether the KYN pathway in the CNS of PD is changed has remained unclear, but our results provide a partial answer because we directly analyzed CSF levels of KYN and its metabolites. Among any other biological samples, CSF most likely reflects phenomena occurring in the CNS. CSF levels of KYN and 3-HK were increased in PD. We simultaneously analyzed CSF levels of inflammatory cytokines and observed elevated TNF-α and IL-1β in PD. These results revealed that dysfunction of the KYN pathway may be associated with inflammatory cytokines and may induce oxidative stress in the CNS of PD patients.

Tohgi and his colleagues have reported a different result from ours [28,29]. We could not know the precise reason why our results differed from the works, but can find a few different points in the methods between ours and Tohgi's works. Their study was designed focusing on the serotonin metabolism primarily, besides in de novo patients. Our study primarily targeted on the functional changes of the KYN pathway in patients with PD. We recruited controls as healthy subjects satisfied some originally defined criteria. All Tohgi's controls had minor surgeries and no details in clinical backgrounds were described in their papers. Onset ages of PD patients were different between ours and Tohgi's works, which was younger in Tohgi's works than ours. Furthermore, we recruited also patients with PD under antiparkinsonian medication as PD group. We know that antiparkinsonian agents can make some changes in the results. Fortunately, one of Tohgi's papers has confirmed that levodopa can't change the CSF levels of KYN and 3-HK. We also confirmed that reevaluation analysis could show no change in results even when excluding PD patients under medication.

3.2. Oxidative stress and neurotoxicity of 3-HK

3-HK is not only directly but also indirectly harmful to neuronal cells due to oxidative stress in the CNS. 3-HK itself is oxidized during specific physiological conditions such as in the presence of copper and iron, and can be neurotoxic due to production of hydrogen peroxide and highly concentrated reactive hydroxyl radicals as in the self-oxidation process [30,31]. Lower concentrations of 3-HK can enzymatically induce oxidative stress due to the activity of endogenous xanthine oxidase, whereas higher concentrations of 3-HK can induce cell death nonenzymatically via oxidative stress in the extracellular space [32]. The excitotoxic effects of 3-HK can also be enhanced by low-dose QA [33]. Selective neurotoxicity of 3-HK was shown using cell cultures derived from striatal and cortical cells of rat fetuses [32]. Indirectly, 3-HK can also induce oxidative stress via QA and/or NAD + derived from 3-HK in the KYN pathway. We detected elevation of KYN and 3-HK, but no elevation of QA or KYNA. Together with this prior evidence, our results suggest that 3-HK may play an important role in neurodegenerative processes associated with oxidative stress in the striatum of PD patients.

Table 2
Individual cerebrospinal fluid levels of kynurenine metabolites and inflammatory cytokines in Parkinson's disease patients and controls.

Subjects	Sex	Age (y)	H&Y stage	TRP (μmol/L)	KYN (nmol/L)	3-HK (nmol/L)	KYNA (nmol/L)	QA (nmol/L)	TNF-α (pg/mL)	IL-1β (pg/mL)	IL-6 (pg/mL)	IFN-γ (pg/mL)
PD 1	F	71	3	2.81	23.13	2.66	1.88	0.13	1.29	0.17	UD	1.48
PD 2	F	69	3	2.54	30.73	0.42	0.88	0.39	1.11	0.18	0.90	1.60
PD 3	M	72	3	2.55	31.90	1.68	2.29	0.09	UD	0.19	UD	1.82
PD 4	M	76	3	2.57	37.91	3.97	1.36	0.17	1.18	0.22	1.04	2.16
PD 5	F	73	2	2.22	36.83	0.20	0.56	0.08	1.22	0.26	0.81	UD
PD 6	M	69	3	2.71	61.91	5.59	1.06	0.16	1.14	0.18	1.14	2.24
PD 7	F	70	3	2.40	42.76	8.64	1.26	0.16	1.89	0.18	0.92	2.49
PD 8	F	79	3	2.15	50.22	6.99	2.91	0.50	2.07	0.19	1.29	1.81
PD 9	F	67	3	2.04	62.13	3.29	1.51	0.07	0.94	0.17	1.43	1.75
PD 10	M	57	2	2.28	52.97	3.82	0.80	0.24	1.48	0.17	0.81	1.96
PD 11	M	74	3	2.04	90.30	9.11	1.98	0.06	1.56	0.17	1.23	1.60
PD 12	F	59	2	1.95	36.56	13.26	1.10	0.27	1.30	0.18	2.21	1.96
PD 13	M	59	2	2.01	44.38	6.28	2.02	0.07	1.03	0.21	1.31	3.05
PD 14	F	71	2	1.98	47.77	2.17	0.78	0.11	UD	0.26	2.08	1.99
PD 15	M	66	2	2.11	22.60	4.52	0.62	0.17	1.56	0.18	1.40	2.06
PD 16	M	63	3	1.78	65.99	4.90	0.69	0.28	1.62	0.27	1.33	1.64
PD 17	F	67	2	2.37	79.65	7.50	0.69	0.12	1.34	0.22	0.99	1.86
PD 18	F	74	2	2.09	73.79	3.96	0.93	0.32	1.32	0.16	1.26	1.97
PD 19	M	80	2	2.44	62.30	5.89	1.18	0.34	1.27	0.17	0.97	1.72
PD 20	F	65	2	1.89	52.47	1.68	2.56	0.14	1.21	0.24	0.94	2.15
C 1	F	72	–	2.26	46.13	1.89	2.36	0.38	UD	UD	1.01	2.47
C 2	M	68	–	2.38	51.40	1.44	2.60	0.18	0.96	UD	UD	UD
C 3	M	63	–	2.49	25.25	0.53	0.52	0.19	UD	UD	0.26	UD
C 4	F	43	–	2.75	35.72	1.65	0.85	0.16	1.24	UD	UD	3.22
C 5	F	79	–	2.70	20.58	3.96	2.45	0.14	1.99	0.22	UD	2.89
C 6	M	78	–	0.94	9.49	0.01	0.37	0.11	UD	0.11	UD	UD
C 7	F	73	–	1.82	22.11	1.55	1.78	0.13	1.64	0.21	UD	2.42
C 8	M	23	–	2.44	35.23	1.11	0.61	0.24	2.39	0.19	3.24	1.69
C 9	M	75	–	2.51	30.51	2.08	1.03	0.21	UD	0.31	1.14	UD
C 10	M	78	–	2.63	38.27	1.33	1.60	0.08	0.61	0.09	1.34	UD
C 11	M	81	–	1.89	39.20	1.75	1.78	0.17	0.03	0.13	1.43	UD
C 12	M	81	–	1.96	10.31	2.01	1.66	0.11	UD	0.09	2.27	UD
C 13	M	83	–	2.54	31.12	1.45	0.85	0.28	0.89	0.16	2.37	1.06

PD; Parkinson's disease, C; Control, F; female, M; male, y; years, H&Y; Hoehn and Yahr, KYN; kynurenine, TRP; tryptophan, 3-HK; 3-hydroxykynurenine, KYNA; kynurenic acid, QA; quinolinic acid, TNF-α; tumor necrosis factor-α, IL-1β; interleukin-1β, IL-6; interleukin-6, IFN-γ; interferon-γ, UD; undetectabl.

3.3. Elevated cytokines and neuroinflammation

Inflammatory cytokines are important players in the neurodegenerative mechanisms of PD [12, 33]. In our study, CSF levels of TNF-α and IFN-1β were elevated in PD. KYN monooxygenase (KMO) is a regulatory enzyme in the KYN pathway and catalyzes the reaction producing 3-HK from KYN. Because KMO is activated by inflammatory cytokines such as TNF-α and IFN-γ released from microglia [21,24], inflammatory cytokines can activate both oxidative stress mediated by 3-HK and the above-mentioned neurotoxicity via activation of NMDA receptors in the KYN pathway. In addition, TNF-α facilitates the release of glutamate from activated microglia [34] and induces activation of NMDA receptors. This activation of NMDA receptors followed by an increase in the calcium ion concentration gradient can initiate chain reactions of variable intracellular molecules and result in neuronal death [35,36]. Our study also suggested that TNF-α may play an important role in these processes, along with IFN-1β. We could detect an obvious correlation coefficient between CSF levels of TNF-α and 3-HK levels. CSF levels of IFN-γ were also not different between PD and control groups in our study. We recognize that the number of patients is one limitation of this study. A larger-scale study in the future will address this problem.

3.4. Therapeutic potential of modification of the KYN pathway

From a clinical perspective, our study suggests that functional amelioration of the KYN pathway may contribute to modification of the neurodegenerative process of PD. First, reducing 3-HK is a potential

Table 3
Comparison of cerebrospinal fluid levels of kynurenine pathway components and cytokines between Parkinson's disease patients and controls.

	PD mean ± SD (range)	C	p value
TRP (μmol/L)	2.25 ± 0.28 (1.78-2.81)	1.95 ± 0.63 (0.94-2.75)	0.334
KYN (nmol/L)	50.31 ± 18.08(22.60-90.30)	36.06 ± 13.07(9.49-51.40)	0.036
3- HK (nmol/L)	4.83 ± 3.14(0.20-13.26)	2.29 ± 1.27(0.01-3.96)	0.011
KYNA (nmol/L)	1.35 ± 0.68(0.56-2.91)	1.37 ± 0.74(0.37-2.60)	0.957
QA (nmol/L)	0.19 ± 0.12(0.06-0.50)	0.20 ± 0.09(0.11-0.38)	0.573
TNF-α (pg/mL)	1.23 ± 0.49(0.94-2.07)	0.75 ± 0.82(0.00-2.39)	0.020
IL-1β (pg/mL)	0.20 ± 0.03(0.16-0.27)	0.11 ± 0.10(0.00-0.31)	0.015
IL-6 (pg/mL)	1.16 ± 0.51(0.81-2.21)	1.01 ± 1.05(0.00-3.24)	0.964
IFN-γ (pg/mL)	1.86 ± 0.55(1.48-3.05)	1.06 ± 1.24(0.00-3.22)	0.061

PD; Parkinson's disease, C; control, SD; standard deviation, TRP; tryptophan, KYN; kynurenine, 3-HK; 3-hydroxykynurenine, KYNA; kynurenic acid, QA; quinolinic acid, TNF-α; tumor necrosis factor-α, IL-1β; interleukin-1β, IL-6; interleukin-6, IFN-γ; interferon-γ.

therapeutic intervention for suppression of neurodegenerative progression. Inhibition of TNF-α is expected to reduce CNS levels of 3-HK. A clinical trial using an inhibitor of TNF-α in brain injury cases has already been reported [37]. Inhibition of inflammatory cytokines may also directly suppress neuroinflammation. However, TNF-α inhibitor cannot pass through the blood-brain barrier, so further development is needed. Amelioration of the balance in KYN metabolism may also prove beneficial to modify neurodegenerative processes due to a reduction in 3-HK and an increase in KYNA, because in this situation the KYN pathway would work in a neuroprotective manner. A KMO inhibitor decreased 3-HK, increased KYNA, and attenuated post-ischemic neuronal damage in cultured hippocampal slices [38]. In experiments using model mice, this KMO inhibitor prevented functional and morphological changes in transgenic models of Alzheimer's disease and also extended the life span in models of Huntington's disease [39]. Together with these lines of evidence, our results suggest that KMO may represent a therapeutic target for some neurodegenerative diseases.

3.5. Limitations

Our study has some limitations, including the small sample size already mentioned above. In the current study, the results in CSF levels of KYN and 3-HK were different from previous study. We found an obvious relationship between CSF levels of TNF-α and 3-HK, but we could not conclude finally. The inevitable varieties of personal backgrounds could also make some fluctuations of CSF levels of KYN and its metabolites. These issues should be addressed using larger-scale replication studies. Investigation of the relationship between clinical factors and functional abnormalities in the KYN pathway may contribute to the exploration of practically accessible surrogate markers and the identification of useful new biomarkers. The exclusion criteria in this study were insufficient, because antepartum subject should not be included because of the different metabolism from other controls hormonally or biochemically. Pregnancy is known as a fluctuating factor of KYN metabolism. As a result, there was no change in statistical significance in all items associating with KYN metabolism and cytokines, and our results did not change even if one antepartum subject was excluded. Finally, because we adopted the United Kingdom PD Society Brain Bank (UKBB) criteria [26] as research criteria, the UKBB criteria prescribes the diagnostic accuracy also in this study as other previous studies were.

4. Conclusion

The KYN pathway is functionally impaired in PD. Some metabolites derived from this abnormal pathway can enhance oxidative stress and increase certain inflammatory cytokines that may subsequently induce neuroinflammation in the CNS in PD. These neurotoxic conditions may be one factor that promotes clinical progression of PD. From a therapeutic point of view, functional amelioration of the KYN pathway may contribute to beneficial modification of the neurodegenerative process of PD.

5. Methods and materials

5.1. CSF sampling and study approval

PD patients were neurologically examined by movement disorder experts and fulfilled the UKBB criteria. Clinical severities were evaluated with H&Y stage [40] and UPDRS part III [41]. Age-matched healthy controls who showed no neurological abnormalities according to medical records, laboratory examinations, neurological examinations, and structural neuroimaging were established. Controls showing neurological disorders or severe illnesses were also joined in this study.

CSF samples were obtained from participants by lumbar puncture between 09:00 and 10:00 AM after several minutes of left-sided bedrest and before breakfast. CSF samples from controls receiving lumbar anesthesia were obtained by anesthesiologists in the same manner. Venous blood sampling was simultaneously performed in all cases in order to exclude systemic inflammatory diseases including infectious diseases, autoimmune diseases and other diseases. CSF samples were promptly centrifuged at 1700 *g* (3000 rpm) for 10 min at 4 °C, and the supernatants were cryopreserved in a deep freezer at −80 °C until use in the following experiments.

This study was carried out after obtaining approval from the Iwate Medical University School of Medicine Ethical Review Board. Details of this study were explained adequately using hard copies of the protocol, and written informed consent was acquired before enrolment in this study.

5.2. Biochemical detection of KYN metabolic products in CSF

CSF samples (50 μl) were automatically injected into a high-performance liquid chromatography column using an autosampler. The mobile phase consisted of 50 mM disodium phosphate, 25 mM citric acid, and 125 mg low sulfur heavy stock (pH 2.50). The flow rate was set at 700 μl/min. Tryptophan, KYN, 3-HK, QA, and KYNA were separated on a reverse-phase analytical column at 35 °C (Acclaim Polar Advantage II C18, 3 μm, 120 Å, 4.6 × 150 mm; Thermo Fisher Scientific, Kanagawa, Japan) and detected using an electrochemical detection system (Coulochem III; ESA, Bedford, MA). The electrode sets were from a Model 5010 analytical cell (ESA) and a Model 5020 guard cell (ESA), with the potential set at 100 mV, 550 mV, and 600 mV (Guard Cell).

5.3. Immunoassay for cytokines in CSF

CSF levels of cytokines including IL-6, IL-1β, TNF-α, and IFN-γ were measured using commercially purchased ELISA kits (Quantikine ELISA Kit; R&D Systems, Minneapolis, MN), according to the protocol from the manufacturer. Optical density was read at 450 nm using an ELISA reader (Infinite F50R; TECAN, Kawasaki, Japan).

For statistical analysis of inflammatory cytokines, samples with values below the limit of detection were assigned a value of 0, and then statistical analysis was conducted.

5.4. Statistical analysis

We conducted comparisons between PD and control groups using Mann-Whitney's *U* test We performed correlation analysis using Spearman's rank correlation coefficient. These analyses were carried out using StatView version 5.0 software (Abacus Concepts, Inc., Berkeley, CA). The level of significance was set at $p < 0.05$.

Conflict of interest

None.

Author contributions

This study was conceived and designed by C.O. Patient groups were examined by C.O., K.Y., K.K., K.T., and K.I. Data were sampled and analyzed by O.C. and K.I. Preparations and contributions to this article were written by K.I. and T.M. All authors have approved the final article.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] E. Oikonomou, T. Paparrigopoulos, Neuropsychiatric manifestations in Parkinson's disease, Psychiatriki 26 (2015) 116–130.
[2] R.G. Cury, R. Galhardoni, E.T. Fonoff, S. Perez Lloret, M.G. Dos Santos Ghilardi, E.R. Barbosa, M.J. Teixeira, D. Ciampi de Andrade, Sensory abnormalities and pain in Parkinson disease and its modulation by treatment of motor symptoms, Eur. J. Pain 20 (2016) 151–165.
[3] K.U. Tufekci, R. Meuwissen, S. Genc, K. Genc, Inflammation in Parkinson's disease, Adv. Protein Chem. Struct. Biol. 88 (2012) 69–132.
[4] P. Jenner, Oxidative stress in Parkinson's disease, Ann. Neurol. 53 (2003) S26–36 discussion S36-8.
[5] J.T. Greenamyre, G. MacKenzie, T.-I. Peng, S.E. Stephans, Mitochondrial dysfunction in Parkinson's disease, Biochem. Soc. Symp. 66 (1999) 85–97.
[6] J.L. Eriksen, Z. Wszolek, L. Petrucelli, Molecular pathogenesis of Parkinson disease, Arch. Neurol. 62 (2005) 353–357.
[7] M.R. Cookson, The role of leucine-rich repeat kinase 2 (LRRK2) in Parkinson's disease, Nat. Rev. Neurosci. 11 (2010) 791–797.
[8] U. Ungerstedt, 6-Hydroxy-dopamine induced degeneration of central monoamine neurons, Eur. J. Pharmacol. 5 (1968) 107–110.
[9] M.F. Beal, Experimental models of Parkinson's disease, Nat. Rev. Neurosci. 2 (2001) 325–334.
[10] T. Nagatsu, M. Sawada, Inflammatory process in Parkinson's disease: role for cytokines, Curr. Pharmac. Design. 11 (2005) 999–1016.
[11] S. Phani, J.D. Loike, S. Przedborski, Neurodegeneration and inflammation in Parkinson's disease, Parkinsonism Relat. Disord. 18 (2012) 207–209.
[12] M. Sawada, K. Imamura, T. Nagatsu, Role of cytokines in inflammatory process in Parkinson's disease, J. Neural Transm. Suppl. 70 (2006) 373–381.
[13] Y. Koshimori, J.H. Ko, R. Mizrahi, P. Rusjan, R. Mabrouk, M.F. Jacobs, L. Christopher, C. Hamani, A.E. Lang, A.A. Wilson, S. Houle, A.P. Strafella, Imaging striatal microglial activation in patients with Parkinson's disease, PLoS One 18 (2015) e0138721, , https://doi.org/10.1371/journal.pone.0138721.
[14] A. Gerhard, N. Pavese, G. Hotton, F. Turkheimer, M. Es, A. Hammers, K. Eggert, W. Oertel, R.B. Banati, D.J. Brooks, In vivo imaging of microglial activation with [11C](R)-PK11195 PET in idiopathic Parkinson's disease, Neurobiol. Dis. 21 (2006) 404–412.
[15] M. Mogi, M. Harada, P. Riederer, H. Narabayashi, K. Fujita, T. Nagatsu, Tumor necrosis factor-alpha (TNF-alpha) increases both in the brain and in the cerebrospinal fluid from parkinsonian patients, Neurosci. Lett. 3 (1994) 208–210.
[16] M. Mogi, T. Kondo, Y. Mizuno, T. Nagatsu, p53 protein, interferon-gamma, and NF-kappaB levels are elevated in the parkinsonian brain, Neurosci. Lett. 27 (2007) 94–97.
[17] R. Mayeux, Y. Stern, M. Sano, J.B. Williams, L.J. Cote, The relationship of serotonin to depression in Parkinson's disease, Mov. Disord. 3 (1988) 237–244.
[18] E.L. Sainio, K. Pulkki, S.N. Young, L-tryptophan: biochemical, nutritional and pharmacological agents, Amino Acids 10 (1996) 21–47.
[19] D. Zadari, P. Klivenyi, E. Vamos, F. Fulop, J. Toldi, L. Vecsei, Kynurenines in chronic neurodegenerative disorders: future therapeutic strategies. J Neural Transmneurodegenerative disorders: future therapeutic strategies, J. Neural Transm. 116 (2009) 1403–1409.
[20] R. Schwarcz, Metabolism and function of brain kynurenines, Biochem. Soc. Trans. 21 (1993) 77–82.
[21] N. Braidy, G.J. Guillemin, R. Grant, Effects of kynurenine pathway inhibition on NAD+ metabolism and cell viability in human primary astrocytes and neurons, Int. J. Tryptophan Res. 4 (2011) 29–37.
[22] M.N. Perkins, T.W. Stone, An iontophoretic investigation of the actions of convulsant kynurenines and their interaction with the endogenous excitant quinolinic acid, Brain Res. 247 (1982) 184–187.
[23] T.W. Stone, M.N. Perkins, Quinolinic acid: a potent endogenous excitant at amino acid receptors in CNS, Eur. J. Pharmacol. 10 (1981) 411–412.
[24] T. Ogawa, W.R. Matson, M.F. Beal, R.H. Myers, E.D. Bird, P. Milbury, S. Saso, Kynurenine pathway abnormalities in Parkinson's disease, Neurology. 42 (1992) 1702–1706.
[25] S.J. Pearson, G.P. Reynolds, Increased brain concentrations of a neurotoxin, 3-hydroxykynurenine, in Huntington's disease, Neurosci. Lett. 14 (1992) 199–201.
[26] A.J. Hughes, S.E. Daniel, L. Kilford, A.J. Lees, Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases, J. Neurol. Neurosurg. Psychiatry 55 (1992) 181–184.
[27] S. Fahn, C.D. Marsden, M. Goldstein, D.B. Calne, Unified parkinsons disease rating scale, Recent Developments in Parkinsons Disease 2 (1987), pp. 153–163.
[28] H. Tohgi, T. Abe, S. Takahashi, J. Takahashi, H. Hamato, Concentrations of serotonin and its related substances in the cerebrospinal fluid of parkinsonian patients and their relations to the severity of symptoms, Neurosci. Lett. 5 (1993) 71–74.
[29] H. Tohgi, T. Abe, S. Takahashi, J. Takahashi, H. Hamato, Alterations in the concentration of serotonergic and dopaminergic substances in the cerebrospinal fluid of patients with Parkinson's disease, and their changes after L-dopa administration, Neurosci. Lett. 3 (1993) 135–138.
[30] C.L. Eastman, T.R. Guilarte, Cytotoxicity of 3-hydroxykynurenine in a neuronal hybrid cell line, Brain Res. 495 (1989) 225–231.
[31] L.E. Goldstein, M.C. Leopold, X. Huang, C.S. Atwood, A.J. Saunders, M. Hartshorn, J.T. Lim, K.Y. Faget, J.A. Muffat, R.C. Scarpa, L.T. Chylack Jr, E.F. Bowden, R.E. Tanzi, A.I. Bush, 3-hydroxykynurenine and 3-hydroxyanthranilic acid generate hydrogen peroxide and promote alpha-crystallin cross-linking by metal ion reduction, Biochemistry. 39 (2000) 7266–7275.
[32] S. Okuda, N. Nishiyama, H. Saito, H. Katsuki, Hydroxykynurenine, an endogenous oxidative stress generator, causes neuronal cell death with apoptotic features and region selectivity, J. Neurochem. 70 (1998) 299–307.
[33] P. Guidetti, R. Schwarcz, 3-hydroxykynurenine potentiates quinolinate but not NMDA toxicity in the rat striatum, Eur. J. Neurosci. 11 (1999) 3857–3863.
[34] R. Kuno, Y. Yoshida, A. Nitta, T. Nabeshima, J. Wang, J. Kawanokuchi, H. Takeuchi, T. Mizuno, A. Suzumura, The role of TNF and its receptors in neurotrophic factor production by astrocytes, Brain Res. 1116 (2006) 2–18.
[35] C. Wersinger, A. Sidhu, Inflammation and Parkinson's disease, Curr. Drug Targets Inflamm. Allergy 1 (2002) 221–242.
[36] A. Hald, J. Lotharius, Oxidative stress and inflammation in Parkinson's disease: is there a causal link? Exp. Neurol. 193 (2005) 279–290.
[37] E. Shohami, R. Gallily, R. Mechoulam, R. Bass, T. Ben-Hur, Cytokine production in the brain following closed head injury: dexanabinol (HU-211) is a novel TNF-alpha inhibitor and an effective neuroprotectant, J. Neuroimmunol. 72 (1997) 169–177.
[38] R. Carpenedo, E. Meli, F. Peruginelli, D.E. Pellegrini-Giampietro, F. Moroni, Kynurenine 3-mono-oxygenase inhibitors attenuate post-ischemic neuronal death in organotypic hippocampal slice cultures, J. Neurochem. 82 (2002) 1465–1471.
[39] D. Zwilling, S.Y. Huang, K.V. Sathyasaikumar, F.M. Notarangelo, P. Guidetti, H.Q. Wu, J. Lee, J. Truong, Y. Andrews-Zwilling, E.W. Hsieh, J.Y. Louie, T. Wu, K. Scearce-Levie, C. Patrick, A. Adame, F. Giorgini, S. Moussaoui, G. Laue, A. Rassoulpour, G. Flik, Y. Huang, J.M. Muchowski, E. Masliah, R. Schwarcz, P.J. Muchowski, Kynurenine 3-monooxygenase inhibition in blood ameliorates neurodegeneration, Cell. 10 (2011) 863–874.
[40] M.M. Hoehn, M.D. Yahr, Parkinsonism: onset, progression and mortality, Neurology. 17 (1967) 427–442.
[41] C.G. Goetz, B.C. Tilley, S.R. Shaftman, G.T. Stebbins, S. Fahn, P. Martinez-Martin, W. Poewe, C. Sampaio, M.B. Stern, R. Dodel, B. Dubois, R. Holloway, J. Jankovic, J. Kulisevsky, A.E. Lang, A. Lees, S. Leurgans, P.A. LeWitt, D. Nyenhuis, C.W. Olanow, O. Rascol, A. Schrag, J.A. Teresi, J.J. van Hilten, N. LaPelle, Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results, Mov. Disord. 15 (2008) 2129–2170.