бактериальной терапии, которую получали новорожденные во время пребывания в стационаре. Было выявлено, что количество схем варировало от 4-х до 17, а длительность лечения составляла 22-19 суток. Наиболее часто применялись препараты из группы карбапенемов, гликопептидов. а также цефалоспоринов III поколения и аминогликозидов.

რეზიუმე

ანტიბაქტერიული თერაპიის გამოყენების შეფასება დღენაკლულ ახალშობილებში ნეონატალური პერიოდის თავისებურებების გათვალისწინებით

[1]ნ.კობეშავიძე, [2]დ.ჩიკვილაძე, [2]ხ.გაჩეჩილაძე, [2]მ.მიქელაძე

[1]შპს "იმედის კლინიკა" თბილისი; [2]თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, მიკრობიოლოგიის დეპარტამენტი, საქართველო

სტატიაში წარმოდგენილია შედეგები, რომლებიც მიღებული იყო დღენაკლული ახალშობილების 3 ბიოტოპიდან – სასუნთქი გზების, შარდგამომყოფი სისტემის და მსხვილი ნაწლავის ლორწოვანი გარსებიდან გამოყოფილი მიკრობული შტამების ანტიბიოტიკომგრძნობელობა/რეზისტენტობის შესახებ. მიკრობიოლოგიური გამოკვლევები უტარდებოდათ ახალშობილებს დაბადებიდან პირველ 72 საათში, მე-14 და 30-ე დღეებზე. კვლევის პერიოდში გამოყოფილი იყო 677 სხვადასხვა სახეობის მიკრობული შტამი, მათ შორის გრამდადებითი მიკროფლორა (386 შტამი) თითქმის 1,5 ჯერ პრევალირებდა გრამუარყოფით მიკროფლორაზე (291 შტამი). ანტიბიოტიკომგრძნობელობა/რეზისტენტობა ტარდებოდა ორი მეთოდით – დისკო-დიფუზური და სერიული განზავებების მეთოდით მყარ საკვებ ნიადაგებზე.

ნეონატალური პერიოდის მიმდინარეობის თავისებურებების შესწავლისას შეფასებული იყო ანტიბაქტერიული თერაპიის გამოყენების ხანგრძლივობა, რომელსაც ღებულობდნენ დღენაკლული ახალშობილები სტაციონარში ყოფნისას. გამოვლინდა, რომ სამკურნალო სქემების რაოდენობა ვარირებდა 4-დან 17-მდე, და თერაპიის ხანგრძლივობა შეადგენდა 22-91 დღე-ღამეს. ყველაზე ხშირად იყენებდნენ კარბაპენემების, გლიკოპეპტიდების, III თაობის ცეფალოსპორინების და ამინოგლიკოზიდების ჯგუფის პრეპარატებს.

ENDOCANNABINOIDS RECEPTORS MEDIATED CENTRAL AND PERIPHERAL EFFECTS (REVIEW)

Ghonghadze M., Pachkoria K., Okujava M., Antelava N., Gongadze N.

Tbilisi State Medical University, Department of Medical Pharmacology, Georgia

Endocannabinoids are endogenous lipid based retrograde neurotransmitters that as natural ligands bind to corresponding cannabinoid receptors [7, 8, 9, 28, 45]. Endocannabinoids (ECS) include [17, 19, 22, 24, 27, 56] arachidonoylethanolamide (anandamide), 2-arachidonoylglycerol (2-AG) and palmitolethanolamide (PE). Anandamide is a partial agonist for CB_1 and CB_2 receptors providing more affinity for CB_1 receptors, while 2-AG reveals agonistic properties to both of them in contrast to PE, which may bind to a unidental "CB_2-like"receptors [8, 17, 27, 31, 45, 46]. CB_1 receptors are distributed in the central and peripheral nervous system. They have been identified in the greatest amount in the cortex, basal ganglia, spinal cord, cerebellum, hippocampus and olfactory areas owing for the modulatory action of cannabinoids on cognitive function, memory, behaviour, emotion and locomotor activity [2, 8, 9, 11, 12, 13, 34, 35, 51, 56, 60]. Their existence in the periaqueductal grey matter (PAG) and dorsal horn of the spinal cord may explain their involvement in pain-sensation and modulation [3, 4, 6, 55, 63, 64, 66, 70], while lack of respiratory depression after the administration of cannabinoids may due to CB_1 receptors low density in the brainstem [68, 74]. CB_1 receptors are overlapping with the oroxinergic projection system colocallized for example in the lateral hypothalamus where the CB_1 and orexin receptor (OX1) joining together form the CB_1- OX_1 receptor heterodimer [54, 67, 68] indicating about their implication in feeding behaviour [68]. CB_2 receptors were found in the cells of immune system [53], especially in the spleen and macrophages [15, 45, 46]. ECS are also involved in the regulation of fertility and pre- and postnatal development [65]. It was shown that aside from CB_1 and CB_2 receptors certain orphan receptors may bind endocannabinoids [4, 6, 17]. It was also shown that anandamide is a vanilloid receptors (VR1) agonist [6, 57, 66].

Cannabinoid receptors have been discovered on the pre-synaptic membrane belonging to G-protein coupled receptors [7, 8, 19, 27, 28, 68]. Their stimulation results in decrease in cAMP concentration via inhibition of adenylylcyclase (AC) and an increase in the concentration of mitogen-activated protein kinase (MAPK). Diminished amount in cAMP is accompanied by phosporylation and subsequent activation along with MAPK also the PI3/PKB and MEK/ERK signalling pathways [19, 55, 59]. At the same time the stimulation of CB_1 receptors is associated with an increase in the activity of transcription factors like c-Fos and Krox-24 [7, 9, 10, 11, 12, 27, 42, 68].

The activation of CB_1 and CB_2 receptors through inhibition of cAMP production modulates channel activity (27, 28, 46), leading to neurones hyperpolarisation by activating K^+ channels and by closing voltage-dependent Ca^{2+} channels [7, 20, 22, 59]. Experimental studies showed co-localization of CB_1 receptors with a family of potassium channels such as GIRK and Kv14 indicating about their physiological interaction [68]. CB_1 receptors are involved in neuronal excitability by decreasing synaptic input [12, 17, 19]. The underlying mechanism implies retrograde transmission and presynaptic inhibition when postsynaptic neuron produces endocannabinoids that bind on the presynaptic terminal resulting in reduction of neurotransmitter release and consequently diminished effects on the postsynaptic neuron

[22, 27, 28, 29]. A number of studies suggests the involvement of CB_1 receptors in non-ion channel mechanism of regulation of neurotransmitter release by reduction in AC and protein kinase A activity through Gi/O-protein associated inhibition [7, 9, 10, 14, 17]. Recent evidence shown the possible concomitant implication of glutamate NMDAR ionotropic and mCLUR metabotropic receptors along with CB1 receptors in antinociceptive modulatory reactions which underlying mechanism requires to be clarified [23, 48, 55, 61]. ECS synthesis is associated with increase in intracellular Ca2+ during which 2-AG and anandamide are not co-synthesized. It was found that in the bed nucleus of the stria terminals calcium influx through voltage sensitive Ca^{2+} channels results in L-Type current leading in 2-AG release, while stimulation of metabotropic $mGLUR_1/5$ receptors facilitates the synthesis of anandamide [20, 21, 22]. The first step of ECS synthesis involves conversion of membrane phospholipid-phospatidylethanolamine into N-acyl-phosphatidylethanolamine (NAPE), which is cleaved by phospholipase D, leading to anandamide formation mediating by bile acids [41]. The released Anandamide and 2-AG are removed from the extracellular space by saturable uptake process presenting in neurons and astrocytes [13]. ECS after taken up by a transporters on the glial cell undergo to breakdown by fatty acid amide hydrolase (FAAH) with resulting cleavage of anandamide into arachidonic acid and ethanolamine or monoacylglycerol lipase (MAGL), and 2-AG into arachidonic acid and glycerol. It is suggested that FAAH has significant role in clearance and inactivation of ECS after their reuptake [7, 19, 69].

ECS may produce the different central effects including analgesia. In animal models of acute pain using radiant heat tail-flick test, nerve damage or administration of inflammatory substances, cannabinoides reduce behavioural response to noxious stimuli. A number of evidence suggests that cannabinoids mediate their antinociceptive effects by stimulation of CB_1 and CB_2 or CB_2-like receptors [4, 6, 55]. Activation of CB_1 receptors may inhibit nociceptive stimuli on the level of spinal cord and supraspinal level involving ventro-postero-lateral (VPL) nucleus of the thalamus, which was proofed by prevention of the analgesic action of different cannabinoid receptor agonists after blocking of the CB_1 receptors with its antagonist SR141716A [59]. It was established the existence of CB_1 receptors on the central and peripheral terminals of small and large diameter primary afferent sensory neurones. Because large diameter primary afferent fibers are more densely populated with cannabinoid than with μ-opioid receptors, CB_1 receptors agonists in comparison with opioids may produce more efficacy to inhibit neuropathic than acute pain [3, 6].

Some studies have revealed the participation of α_2-adrenoceptors in analgesic effects of cannabinoids, because injection of α_2-adrenoceptors antagonist yohimbine into the lumbar region of the spinal cord reduced tail-flick latency which was increased after intravenous injection of δ-9THC (Tetrahydrocannabinol) [6, 55, 58]. It should be noted the synergistic antinociceptive interaction of cannabinoids with opioid receptor agonists including both-spinal and supraspinal components undergoing to attenuation with cannabinoid and opioid receptors blocking agents [17, 50, 55]. Cannabinoids at the spinal cord may inhibit responses of neurons in the dorsal horn induced by noxious stimulus by modulating descending norepinephrine input from the brainstem [6]. Because many of these fibers are primarily GABA-ergic, cannabinoid stimulatory action in the spinal column leads to disinhibition followed by increase of norepinephrine production, resulting in reduction of noxious stimuli associated events in the periphery and dorsal root ganglion [73]. Recent evidence showed that for PE which is the most investigated ECS regarding its antinociceptive action the significant receptors are the PPAR-alpha, TRPV and GPR_{55} receptors in contrast to early conception implying that antinociception producing by PE is mediated by its predominant binding with CB_1 and CB_2 receptors [4, 6, 55, 62].

Some analgesic and anti-inflammatory effects of cannabinoids instead of their action on cannabinoids receptors is associated with predominant inhibition of cyclo-oxygenase-2 (COX-2) rather than COX-1 [25]. In experimental studies performed in rats that have been made hyperalgesic after intradermal injection of capsaicin cannabinoids have revealed ability to suppress responses induced by thermal and mechanical irritation, as well as in a model of neuropathic pain they reversed mechanical allodynia, cold and thermal hyperalgesia caused by chronic constriction of the sciatic nerve [6, 25, 32, 55]. In this experiments antagonists of CB_1 receptors by reducing response thresholds on the injured but not the contralateral side have exacerbated the nociception suggesting about modulatory antihyperalgesic action of cannabinoids during different models of pain initiation [3, 51, 71, 72, 76].

There are controversial data concerning the influence of ECS on cognitive function [30, 31, 32]. Some authors believed that cannabinoids may suppress a long-term memory by worsening of long-term potentiation in the hippocampus [32, 33], while another ones suggest that cannabinoids exacerbate short-term memory [34]. Knockout mices with the absence of CB_1 receptors have showed improved memory and long-term potentiation proofing the significant role of ECS in the disorders of old memories [74]. A number of evidence suggests the facilatory action of ECS in the neurogenesis of hippocampal granule cells. Neural progenitors (NP) in the hippocampus contain FAAH with the expression of CB_1 receptors and utilizing 2-AG [8, 34]. Stimulation of CB_1 receptors by cannabinoids facilitates to NP proliferation and differentiation, which disappeared by CB_1 antagonists or CB_1 knockout animals [16, 59]. In some studies it was shown that Δ^9-THC-caused synaptic and memory impairment is mediated through COX_2, an inducible enzyme facilitating conversion of arachidonic acid to prostanoids-prostaglandins and thromboxane-2 (TX_2) utilizing CB_1 receptors dependent mechanism in contrast to endogenous cannabinoid 2-AG, which provides opposite action by suppression CB_1 receptors dependent COX_2 activity and expression in response to proinflammatory and excitotoxic insults [25]. The authors have concluded that such different action of exogenous and endogenous canabinnoids is associated with intrinsic properties of the CB_1 receptors coupled G protein, because COX_2 induction by Δ^9-THC is linked with G by subunits,whereas its suppression by 2-AG results from the action on $G_{\alpha i}$ subunit [32]. These results are in consistent with data showing that genetic or pharmacological inhibition of COX_2 activity may reduce disorders in hippocampal long-term synaptic plasticity and fear memory, as well as supports improving effects of Δ^9-THC on neurodegenerative processes [17, 33, 38]. Such results indicate that COX_2 signaling pathways is involved in beneficial effect of exogenous cannabinoid Δ^9-THC on cognitive function in case of suppression of this enzyme [38, 39, 41].

Previous investigations showed a rise of PGE_2 levels in the brain and circulation of experimental animals in response to Δ^9-THC cannabinoid administration, which was antagonised by nonselective NSAIDs. This data indicate about participation of both COX-1 and COX-2 in Δ^9-THC-associated elevation in PGE_2 levels [32, 41, 75]. Such results are in agreement with other data providing convincing evidence that pharmacological or genetic

inhibition of COX_2 precludes or reduces cataleptic and locomotor depressive responses induced by Δ^9-THC [8]. It was shown that Δ^9-THC induced increase level of extracellular glutamate is associated with activation of COX-2 and resulting formation of PGE_2, which promotes synaptic and astrocytic production of glutamate [25]. It was concluded that COX-2 and PGE_2 signall may regulate glutamatergic synaptic transmission and plasticity by possible involving of different subtype of PGE_2 receptors [23, 25]. By authors opinion Δ^9-THC may stimulate COX-2 activity via CB 1R-linked G by subunits with resulting implication of the downstream AKt-ERK/MAPK-NF-KB signaling pathway leading eventually to enhance release of PGE_2 from neurons and astroglial cells [13, 27, 28]. Recent evidence shows a link between CB_1R expression in astroglial cells and memory impairment in animals after exposure to cannabinoids [13, 32], suggesting that PGE_2-induced glutamate production and decreases its uptake by glutamate transporters in astrocytes is responsible for extracellular glutamate accumulation. Such sustained increase in glutamate level in response to repeated Δ^9-THC administration may lead to down regulation and internalization of glutamate receptor subunits, reduction in the density of dendritic spines in hippocampal neurons with resulting impairment of long-term synaptic plasticity and cognitive function [34]. The final conclusion of authors regarding this data is that such unwanted effects of cannabinoids can be reduced by concomitant administration of COX-2 inhibitors [26, 38, 39]. In animal model of Alzheimer's disease (AD) conducted in 5XFAD transgenic mice it was observed the significant reduction in brain AB proteins and neurodegeneration in response to Δ^9-THC exposure, with retaining of such beneficial effect in case of COX-2, inhibition [25, 32, 61]. It was revealed that Δ^9-THC faicilitates to marked expression of an important endopeptidase neprilysin for Aβ degradation [33, 34].

In other studies it was shown the possible involvement of microglial M1/M2 polarization in relapse and remission of schizophrenia and major depressive disorder [5, 36]. M1 polarized microglia may play significant role in the dysfunction of CNS by facilitating to production of reactive oxygen species (ROS), NO and proinflammatory cytokines-IL-1B, IL-6 and TNF-α, while anti-inflammatory cytokines –IL-4,10,13 are associated with activation and polarization of M2. Recent investigations showed an increased levels of IL-1B, IL-6, Il-8 and THF-α in the cerebrospinal fluid (CSF) or peripheral blood in patients with schizophrenia as compared with healthy volunteers reflecting their possible role in M1 microglia polarization in the CNS [36, 37] and relapse of psychiatric disorders [37, 40]. It has been also reported that TNF-α may promote glutamate release from astrocytes resulting in upregulation of TNFα release by microglia [36, 43]. Abovementioned indicate possible relationship between M1 microglia polarization and glutamate production [36, 37, 52]. Other findings reveal marked increase in IL-10and IL-13 in the CSF and blood obtained from patients suffered with schizophrenia. Such results may presumably indicate that the release of anti-inflammatory cytokines can be associated with M2 polarization of microglia in the CNS in patients with schizophrenia [40, 43]. In clinical trials combine use of neuroleptic drugs and COX-2 inhibitors in schizophrenia patients provides the marked improvement of symptoms, while according experimental results, COX-2 inhibitor (celecoxib) decreases the IL-1 B levels and the amount of polarized microglia induced by centrally administered LPS (24). To summarize data concerning influence of pro- and anti-inflammatory cytokines it can be concluded that celecoxibe beneficial effect in schizophrenia is related to inhibition of pro-inflammatory cytokines production by M1, while IL-10may account for M2 microglia polarization resulting in remission in schizophrenia patients.

In clinical trial was demostrated that cannabinoids may improve symptoms of schizophrenia [1] resulting from inhibition of endocannabinoid-degrading enzyme by cannabidiol. On the other hand it was shown the negative relationship between endocannabinoids levels in the CSF and symptoms of schizophrenia [18, 44] suggesting potential role of ECS and their corresponding receptors in M1/M2 microglial polarization and probable involvement in psychiatric disorders [36, 43]. As it was established CB_1 cannabinoid receptor is in abundant in neural cells, while CB_2 receptor is found predominantly in immune cells [44]. It seems that CB_1 agonist mediates the pro-inflammatory events of macrophages associating with ROS production, negatively regulated by CB_2 receptors. It is believed that CB_1 agonists facilitate the polarization of M_1 microglia. At the same time it is thought that endocanabinoid-2 AG downregulates CB_1 and upregulates CB_2 receptors suggesting the inhibitory interaction between their function [45]. A number of evidence suggest that 2-AG-CB_1 axis in involved in polarization of M_1 microglia in contrast to 2-AG- CB_2 axis facilitating to swith from M1 to M2 polarization of microglia [47, 48]. CB_2 activating agents cause the phosphorilation of AMPK (AMP-activated protein kinase), indicating about significant role of CB_2 in AMPK-induced antioxidative and cytoprotective action [47, 49, 53].

Conclusion. Endocannabinoids as natural ligands for CB_1 and CB_2 receptors are involved in the production of wide spectrum of pharmacological effects. They participate in the: regulation of neurotransmitters release, modulation of nociception in different models of pain, cognitive function, synaptic transmission, plasticity, relapse or remission of psychiatric disorders and diseases, suggesting that their receptors site may become an interesting targets for therapeutic intervention.

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SUMMARY

ENDOCANNABINOIDS RECEPTORS MEDIATED CENTRAL AND PERIPHERAL EFFECTS (REVIEW)

Ghonghadze M., Pachkoria K., Okujava M., Antelava N., Gongadze N.

Tbilisi State Medical University, Department of Medical Pharmacology, Georgia

The present article is devoted to the action of endocannabinoids via stimulation of their corresponding receptors. It is well established the existence of three type of endocannabinoids (ECS) such as anandamide (AA), 2-arachidonoylglycerol (2-AG) and palmitoylethanolamide (PE) providing their effects by activation of CB_1 and CB_2 ECS receptors. AA is a partial agonist for both receptors, having more affinity for CB_1 receptors, while 2-AG reveals an equal agonistic properties to both of them in contrast to PE, which may bind to a unidental "CB_2-like" receptors. CB_1 receptors are distributed in the central and peripheral nervous system being identified in the greater amounts in the brain cortex, basal ganglia, spinal cord, cerebellum, hippocampus and olfactory areas, owing for the modulatory action of ECS on cognitive function, memory, behaviour, emotion and locomo-

tor activity. Their location in the periaqueductal grey matter and dorsal spinal cord may explain their involvement in pain sensation and modulation. Colocallization of the CB_1 receptors with the oroxinergic projection system in the lateral hypothalamus is responsible for their implication in feeding behaviour. CB_2 receptors were found in the cells of immune system (spleen, macrophages). It should be noted that ECS may also play a role in the regulation of fertility and pre-and postnatal development. The stimulation of ECS receptors is associated with the activation of MAPK, PI/PKB and MEK/ERK signalling pathways with increased activity of different transcription factors. CB_1 receptors are involved in neuronal exitability by decreasing synaptic input, implying retrograde transmission and presynaptic inhibition resulting in reduction of neurotransmitter release. In the article it is also described an ionic mechanisms of release of ECS and the steps of their synthesis as well as participation of a transporter in ECS uptaken process in neurons and astrocytes. Aside from this it is proposed the mechanisms of analgesic action of ECS especially concerning reduction in neuropathic pain in comparison to opioids and possible involvement of α_2-adrenoceptors in antinociceptive activity of ECS. Some analgesic properties of ECS is due to their inhibitory action on cyclooxygenase-2 (COX-2). Recent evidences showed that regarding antinociceptive action of ECS along with CB_1 receptors most significant receptors are PPAR-alpha and TRPV receptors. There are controversial data concerning the influence of ECS on cognitive function. Knockout mices with the absence of CB_1 receptors have showed improved memory and long-term potentiation proofing the significant role of ECS in the disorders of "old memories". Some data suggests that genetic or pharmacological inhibition of COX-2 activity may reduce disorders in hippocampal long-term synaptic plasticity and fear memory, as well as supports improving effects of tetrahydrocannabinoids (THC) on neurodegenerative processes such as Alzheimer's disease, because THC facilitates to marked expression of an important endopeptidase neprilysin for degradation of AB proteins. A number of evidence indicates the possible involvement of ECS in schizophrenia and major depressive disorders. Assumingly such beneficial effect of ECS is associated with M1/M2 microglial polarization process.

In conclusion it is suggested that ECS as natural ligand for their corresponding receptors provide wide spectrum of pharmacological effects may become an interesting targets for future therapeutic intervention.

Keywords: endocannabinoids, CB_1, CB_2-receptors, anandamide, arachidonoylglycerol, adenylylcyclase, neurotransmitter, mitogen-activated protein kinase, cyclooxygenase-2, pain, nociception, microglia

РЕЗЮМЕ

ЦЕНТРАЛЬНЫЕ И ПЕРИФЕРИЧЕСКИЕ ЭФФЕКТЫ, ОПОСРЕДОВАННЫЕ ЭНДОКАННАБИНОИДНЫМИ РЕЦЕПТОРАМИ (ОБЗОР)

Гонгадзе М.В., Пачкориа К.З., Окуджава М.В., Антелава Н.А., Гонгадзе Н.В.

Тбилисский государственный медицинский университет, департамент медицинской фармакологии, Грузия

Статья посвящается эффектам воспроизводимых эндоканнабиноидами путем стимуляции их одноименных рецепторов. В настоящее время идентифицировано наличие трех типов эндоканнабиноидов (ЭК), таких как: анандамид (АА), 2-арахидоно глицерол (АГ) и пальмитоилэнатоламид (РЕ), реализирующих свои эффекты путем активации CB_1 и CB_2 ЭК рецепторов. АА проявляет более выраженную аффинность к CB_1 рецепторам, в то время как 2-АГ обладает равной аффиностью к обеим - CB_1 и CB_2 рецепторам, в отличие от РЕ, который в основном связывается с унидентальными CB_2 «похожими» рецепторами. CB_1 рецепторы локализованы в центральной и периферической нервной системах будучи идентифицированы в большом количестве в коре головного мозга, в базальных ганглиях, в спинном мозге, в можечке, в гиппокампе и в ольфакторном тракте, являясь ответственными в модуляции ЭК когнитивной функции, памяти, поведения, эмоции и локомоторной активности. Их локализацией в периакедуктальном сером веществе и в дорзальном спинном мозге может быть обьяснено вовлечение ЭК в модуляции и перцепции болевых ощущении. Ко-локализация CB_1 рецепторов с ороксинергической системой латерального гипоталамуса свидетельствует об их возможном участии в пищевом поведении. CB_2 рецепторы идентифицированы в клетках иммунной системы (селезенка, макрофаги). Следует отметить, что ЭК могут играть определенную роль в фертилности и пре- и постнатальном развитии. Стимуляция ЭК рецепторов ассоцируется с активации МАРК, РИ/РКВ и МЕК/ЕРК сигнальных путей с увеличением активности различных транкрипторных факторов. CB_1 рецепторы также вовлечены в неирональное возбуждение путем изменения синаптического входа, подразумевающего ретроградную трансмиссию и пресинаптическую ингибицию с уменьшением выделения нейротрансмиттера. В статье также акцентировано внимание на ионные механизмы выделения ЭК и стадии их синтеза, также как и на участие транспортера в процессе захвата ЭК нейронами и астроцитами. Помимо этого, предлагаются механизмы антиноцицептивного действия ЭК, особенно при нейропатической боли, при которой они порой проявляют более выраженную эффективность в сравнении с опиоидами при возможном участии альфа-2 адренорецепторов. Часть антиноцицептивной активности ЭК обусловлена их ингибирующим влиянием на циклооксигеназу-2. Недавние исследования свидетельствуют что в болеутоляющем действии ЭК вместе CB_1 рецепторами участвуют TRPV и PPAR рецепторы. В отношении влияния ЭК на когнитивную функцию имеются противоположные данные. У «нокаутированных» мышей с отсутствием CB_1 рецепторов улучшалась память и длительная потенциация свидетельствующая о значимой роли ЭК в расстройстве «старой» памяти. Некоторые данные указывают, что генетическая или фармакологическая ингибиция активности циклоогсигеназы-2 сопряжена с уменьшением расстройств в гипокампальной длительной синаптической пластичности и памяти, также как и способствует поддержке положительных, улучшающих эффектов тетрагидроканнабиноидов на нейродегенеративные процессы, например болезни Альцгеймера, вследствии увеличения экспрессии эндопептидазы деградирующей АВ протеины. Часть исследовании указывает на возможное участие ЭК в шизофрении и депрессивных расстройств путем улучшения симптомов этих заболеваний. Предположительно эти благоприятные эффкты ЭК ассоцированы с процессами поляризации М1/М2 микроглий.

В заключении можно отметить,что ЭК являющиеся природными лигандами соответствующих ЭК рецепторов обладают широким спектром фармакологических эффектов, которые могут стать в будущем интересными мишенями для терапевтической интервенции.

რეზიუმე

ენდოკანაბინოიდების რეცეპტორებით განპირობებული ცენტრალური და პერიფერიული ეფექტები (მიმოხილვა)

მ. ღონღაძე, ქ.პაჭკორია, მ.ოკუჯავა, ნ.ანთელავა, ნ.გონგაძე

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტის სამედიცინო ფარმაკოლოგიის დეპარტამენტი, საქართველო

სტატია ეხება ენდოკანაბინოიდების მოქმედებას მათი თანამოსახელე რეცეპტორების სტიმულაციის შედეგად. ამჟამად კარგად არის დადგენილი სამი ტიპის ენდოკანაბინოიდების (ეკ) არსებობა, როგორიცაა: ანანდამიდი (აა), არაქიდინოგლიცეროლი(2-აგ) და პალმიტოილეთანოლამიდი (პე), რომელთა ეფექტებიც რეალიზდება CB_1 და CB_2 ეკ რეცეპტორების აქტივაციით. ანანდამიდი პარციული აგონისტია ორივე რეცეპტორის მიმართ, უფრო მაღალი აფინურობით CB_1 რეცეპტორებისადმი, მაშინ როდესაც 2-აგ ავლენს თანაბარ აგონისტურ თვისებებს ორივე რეცეპტორის მიმართ პე-თან შედარებით, რომელიც უერთდება "CB_2-ის მაგვარ" უნიდენტალურ რეცეპტორებს. CB_1 რეცეპტორები ჩართულია ნეირონულ აგზნებაში სინაპსური შესავლის შემცირებით, რაც გულისხმობს რეტროგრადულ ტრანსმისიას და პრესინაპსურ ინჰიბიციას ნეიროტრანსმიტერის გამოთავისუფლების დაქვეითებით. სტატიაში ასევე აღწერილი ეკ პროდუქციის იონური მექანიზმები და მათი სინთეზის საფეხურები, ისევე როგორც ტრანსპორტერის მონაწილეობა ეკ მიტაცების პროცესში ნეირონებისა და ასტროციტების მიერ. ამასთან ერთად წარმოდგენილია ეკ ანალგეზიური მოქმედების მექანიზმები განსაკუთრებით ნეიროპათიური ტკივილის მიმართ ოპიოიდებთან შედარებით და ალფა-2 ადრენორეცეპტორების შესაძლო მონაწილეობა ეკ-ის ანტინოციცეპტურ მოქმედებაში. ეკ-ის ანალგეზიური თვისებები ნაწილობრივ განპირობებულია ციკლოოქსიგენაზა-2-ზე (ცოგ-2) მათი მაინჰიბირებელი ეფექტით. არსებული მონაცემების მიხედვით ეკ-ის ანტინოციცეპტური მოქმედების რეალიზაციაში CB_1 რეცეპტორებთან ერთად მონაწილეობს PPAR-ალფა და TRPV რეცეპტორები. ეკ-ის კოგნიტურ ფუნქციაზე ზეგავლენის მხრივ მონაცემები წინააღმდეგობრივია. კერძოდ, ე.წ. "ნოკაუტირებულ" თაგვებში CB_1 რეცეპტორების არ არსებობით ადგილი ჰქონდა მეხსიერების და ხანგრძლივი პოტენციალის გაუმჯობესებას, რითაც დასტურდება ეკ მნიშვნელოვანი მონაწილეობა "ძველი მეხსიერების" დარღვევების პროცესში. ზოგიერთი მონაცემი მიუთითებს, რომ ცოგ-2-ის აქტივობის ფარმაკოლოგიური და გენეტიკური ინჰიბიციით შესაძლებელია შემცირდეს დარღვევები ჰიპოკამპის ხანგრძლივი სინაპსური პლასტიურობისა და მეხსიერების მხრივ, ისევე როგორც გაუმჯობესდეს ტეტრაჰიდროკანაბინოიდების პოზიტიური ეფექტები, კერძოდ, მათი ზეგავლენა ნეიროდეგენერაციულ პროცესებთან მიმართებაში, მაგ. ალცჰაიმერის დაავადების დროს, როდესაც ეკ ზრდიან ენდოპეპტიდაზა ნეპრილიზინის ექსპრესიას, რომელიც ხელს უწყობს AB პროტეინების დეგრადაციას. ზოგიერთი მონაცემებით მტკიცდება ეკ-ის მონაწილეობის საკითხი დეპრესიული ხასიათის დარღვევებისა და შიზოფრენიის დროს. სავარაუდოდ, ეკ-ის აღნიშნული სასარგებლო ეფექტები ასოცირდება M1/M2 მიკროგლიურ პოლარიზაციის პროცესებთან.

დასკვნის სახით შეიძლება ითქვას, რომ ეკ-ბი როგორც ბუნებრივი ენდოგენური ლიგანდები თავისი თანამოსახელე რეცეპტორების მიმართ ხასიათდება ფარმაკოლოგიური აქტივობის ფართო სპექტრით, რომელიც შესაძლოა მომავალში საინტერესო სამიზნედ მოგვევლინოს თერაპიული ინტერვენციის თვალსაზრისით.