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LOKALNI PERIFERNI ANALGETIČKI EFEKAT ESLIKARBAZEPIN ACETATA U MODELU TRIGEMINALNOG BOLA: ULOGA SEROTONINSKIH 5-$HT_{1B/1D}$ I KANABINOIDNIH CB_1/CB_2 RECEPTORA

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UTICAJ FORMULACIJE MIKOFENOLNE KISELINE NA NEŽELJENE EFEKTE KOD PACIJENATA NAKON TRANSPLANTACIJE BUBREGA

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Upotrebu imunosupresivnih lekova kod pacijenata sa transplantiranim bubregom prate mnogobrojni neželjeni efekti. Oni mogu značajno da smanje adherencu pacijenata i utiču na preživljavanje grafta. Mikofenolna kiselina (MPA) često je korišćen imunosupresivni lek koji je na tržištu dostupan u obliku estra (mikofenolat mofetil, MMF) ili u obliku soli (mikofenolat natrijum, EC-MPS). Cilj istraživanja bio je da procenimo učestalost i razlike u ispoljenim neželjenim efektima tokom terapije MMF/EC-MPS kod pacijenata sa transplantiranim bubregom.

Istraživanje je obuhvatilo 77 pacijenata sa transplantiranim bubregom (53 muškarca i 24 žene) koji su bili praćeni na Klinici za nefrologiju (Klinički centar NIš, Srbija). Pacijenti su oralno koristili takrolimus, kortikosteroide (prednizolon) i MMF ili EC-MPS. Za procenu neželjenih efekata terapije korišćen je upitnik koju su razvili nefrolozi sa Univerziteta u Bafalu, SAD. Upitnik je obuhvatao osamnaest negativnih efekata koji su podeljeni u gastrointestinalne, estetske i efekte na centralni nervni sistem (CNS). Za statističku analizu podataka korišćen je SPSS 20 softverski paket (Studentov t-test). Najčešći neželjeni efekti bili su gastrointestinalni (80,9%), zatim CNS (71,16%) i estetski (62,66%). Pacijenti koji su primali MMF imali su značajno izraženije gastrointestinalne neželjene efekte (0,25 ± 0.19) u poređenju sa onima na terapiji EC-MPS (0,16 ± 0.13). Dijareja je bila najučestalija gastronitestinalna tegoba (43,8%). Nije bilo razlike u CNS, estetskim i kumulativnim neželjenim efektima među pacijentima lečenim EC-MPS i MMF.

Kod pacijenata sa transplantiranim bubregom najčešće su bili prisutni gastrointestinalni neželjeni efekti. Oni su bili značajno izraženiji kod pacijenata koji su primali MMF u odnosu na EC-MPS, za razliku od ostalih tipova neželjenih efekata koji se nisu razlikovali u odnosu na formulaciju. Prospektivno praćenje neželjenih efekata MPA terapije može da poboljša bezbednost pacijenata i adherencu pacijenata nakon transplantacije.

THE INFLUENCE OF MICOPHENOLIC ACID FORMULATION ON THE ADVERSE EFFECTS IN RENAL TRANSPLANT RECIPIENTS

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After renal transplantation, many patients experience adverse effects from immunosuppressive drugs. When these adverse effects occur, patient adherence with immunosuppression may be reduced, impacting allograft survival. Mycophenolic acid (MPA) is a widely used immunosuppressive drug and it is available either as an ester prodrug (mycophenolate mofetil, MMF) or as a sodium salt (mycophenolate sodium, EC-MPS). The purpose of this study was to determine the frequency and differences in adverse effects with MMF/EC-MPS in renal transplant recipients.

This prospective study included 77 stable renal transplant recipients (53 men and 24 women) who were treated in the Clinic of Nephrology (University Clinical Centre of Nis, Serbia). Patients received oral MMF or EC-MPS as part of a triple immunosuppressive regimen, which also included corticosteroids (prednisolone) and tacrolimus. To determine the adverse effects of therapy we used a survey developed by nephrologists at the University of Buffalo, USA. Nephrologists evaluated 18 adverse effects which were organized into gastrointestinal, central nervous system (CNS) and aesthetic domains. Statistical analysis was performed using SPSS software version 20 (Student t test). The most common adverse effects were gastrointestinal (80.9%), followed by CNS (71.16%) and aesthetic adverse effects (62.66%). Patients treated with MMF experienced a significantly pronounced gastrointestinal adverse effect ratio (0.25 ± 0.19) compared to EC-MPS (0.16 ± 0.13). The most frequent gastrointestinal event was diarrhea (43.8%). There was no difference between patients treated with EC-MPS or MMF for the aesthetic, CNS and cumulative adverse effect ratios.

Gastrointestinal adverse effects were the most common in renal transplant recipients. The numbers and types of adverse effects were not different between the two treatments, except gastrointestinal adverse effects which were significantly more pronounced in patients treated with MMF. Prospective clinical monitoring of MPA adverse effects may improve patient safety and post-transplant immunosuppressive adherence.

EFEKAT ODABRANIH PREPARATA L-KARNITINA U MODULACIJI EKSPRESIJE GENA ZA HIPOKSIJSKI INDUCIBILNI FAKTOR 1A U KULTURI LIMFOCITA

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Postoje tvrdnje da brojni dodaci prehrani zbog svojih antioksidativnih i antiinflamatornih efekata imaju sveukupno pozitivne učinke na zdravlje pojedinca. L-karnitin kao suplement koristi se u različite svrhe: od dodatka u prehrani, u različitim medicinskim tretmanima do reguliranja tjelesne težine. Cilj ovog istraživanja je bio da se procjeni dejstvo L-karnitina i L-karnitina s dodatkom vitamina B6 u oksidativnom stresu in vitro praćenjem ekspresije gena uključenog u ove procese.

U ovoj studiji smo testirali dva komercijalno dostupna preparata: jedan koji sadrži L-karnitin u obliku kapsula u dozi od 500 mg i drugi, tečni preparat L- karnitin sa dodatkom vitamina B6 (2,8 mg – 200% RDA). Kulture limfocita su uspostavljene standardnim postupkom i tretirane tokom 72 sata odabranim koncentracijama L-karnitina/L-karnitina sa vitaminom B6. Kao negativna kontrola korišteni su netretirani limfociti. Ukupna mRNA je izolovana iz tretiranih i netretiranih ćelija. Real Time- PCR metoda je bila korištena za procjenu ekspresije HIF1A (eng. hypoxia inducible factor) gena, a kao konstitutivni gen je korišten GAPDH. L-karnitin je smanjio transkripciju HIF1α gena u koncentracijama od 50 μmol/l, 250 μmol/l, 500 μmol/l i 1000 μmol/l (p=0,001; p=0,017; p=0,001 i p=0,0015, redom). L-karnitin sa vitaminom B6 značajno je redukovao transkripciju HIF1α gena u koncentracijama od 50 μmol/l i 1000 μmol/l (p=0,007 i p=0,015, redom), dok u koncentracijama od 250 μmol/l i 500 μmol/l nije značajno povećao transkripciju HIF1α gena (p=0,0915 i p=0,807, redom).

L-karnitin je u rasponu koncentracija od 50 μmol/l do 1000 μmol/l smanjio ekspresiju gena koji kodira HIF1α gen, što ukazuje na moguću inhibiciju proinflamatornih procesa. Međutim, u kombinaciji sa vitaminom B6, L-karnitin je smanjio tranksripciju gena za HIF1α samo u koncentracijama od 50 μmol/l i 1000 μmol/l, dok je u koncentraciji od 250 μmol/l imao tendenciju povećanja njegove transkripcije; smisao ovog nalaza zahtjeva dalje razjašnjenje.

EFFECT OF SELECTED L-CARNITINE PREPARATIONS ON EXPRESSION OF A GENE FOR HYPOXIA INDUCIBLE FACTOR 1A IN THE LYMPHOCYTE CULTURE

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It is claimed that many nutritional supplements, because of their antioxidant and anti-inflammatory effects, have an overall positive influence on human health. L-carnitine as a supplement is used for various purposes: as food supplement, in medical treatment, or for body weight regulation. The aim of this study was to assess the effect of L-carnitine and L- carnitine supplemented with vitamin B6 in oxidative stress in vitro by analysis of expression of a gene involved in these processes.

In this study we tested two commercially available preparations: capsules of L-carnitine at a dosage of 500 mg, and a liquid L-carnitine supplemented with vitamin B6 (2.8 mg - 200% RDA). Lymphocyte cultures were established by standard procedure and treated with selected concentrations of L-carnitin/L-carnitine with vitamin B6 from the start of cultivation. Cultivation lasted for 72 hours. Total mRNA was isolated from treated and non-treated cells. Real-Time PCR was used to assess relative gene expression of hypoxia-inducible factor-1α (HIF-1α) and GAPDH as the housekeeping gene for normalization.

L-carnitine reduced the transcription of the HIF1α gene at concentrations of 50 μmol/l, 250 μmol/l, 500 μmol/l and 1000 μmol/l ($p=0.001$; $p=0.017$; $p=0.001$ and $p=0.0015$, respectively). L-carnitine with vitamin B6 significantly reduced the transcription of the HIF1α gene, at concentrations of 50 μmol/l and 1000 μmol/l ($p=0.007$ and $p=0.015$, respectively), while at concentrations of 250 μmol/l and 500 μmol/l insignificantly increased the transcription of the HIF1α gene ($p=0.0915$ and $p=0.807$, respectively). L-carnitine in the concentration range 50 μmol/l to 1000 μmol/l reduced the expression of the gene encoding HIF1α, which indicates possible inhibition of proinflammatory processes. However, when combined with vitamin B6, L-carnitine reduced the transcription of the HIF1α gene only at concentrations of 50 μmol/l and 1000 μmol/l, while at concentration of 250 μmol/l tended to increase its transcription; the meaning of this finding needs further clarification.

GL-II-73, POZITIVNI ALOSTERNI MODULATOR α5 GABAA RECEPTORA, REDUKUJE LIPOPOLISAHARIDOM-IZAZVANO PONAŠANJE SLIČNO DEPRESIVNOM KOD C57BL/6 MIŠEVA

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Izmenjena GABA-ergička (γ-aminobuterna kiselina) neurotransmisija se dovodi u vezu sa poremećajima raspoloženja. U ovom radu je ispitan uticaj GL-II-73, pozitivnog alosternog modulatora na α5 GABAA receptorima, u lipopolisaharidom (LPS)-izazvanom mišjem modelu ponašanja koje se povezuje sa depresijom.

GL-II-73 ili ketamin (pozitivna kontrola modela) u dozi od 10 ili 6 mg/kg, redom, primenjeni su mužjacima C57BL/6 miševa (ukupan broj=75) neposredno pre primene 0.5 mg/kg LPS-a. Prisustvo bolesnog ponašanja (eng*. sickness behavior*) je praćeno merenjem telesne mase (TM), unosa hrane (UH) i broja ulazaka u kvadrante tokom 5 minuta testa spontane lokomotorne aktivnosti (UK). TM i UH su mereni 2, 6, 24 i 28 sati, a UK2 i 24 sata nakon primene tretmana. Preferencija ka saharozi (SP) u SP testu (SPT), kao indikator anhedonije, i vreme provedeno u imobilnosti (VI) u testu forsiranog plivanja (FPT), kao indikator bihejvioralnog očaja, mereni su 24-28 sata i 28 sati nakon primene tretmana, redom. Životinje koje se nisu razbolele nakon primene LPS-a ili koje nisu konzumirale više od 0,1 ml tečnosti za vreme SPT-a su bile isključene iz analize.

U ovom radu pokazano je da je tretman LPS-om indukovao bolesno ponašanje kao i ponašanje nalik depresivnom kod miševa tako što je snizio TM, UH, UK, SP i nastojao da poveća VI. Pretretman sa ketaminom je povratio vrednosti UH u intervalu 24-28 sata, UK posle 24 h, kao i SP, dok je pretretman sa GL-II-73 normalizovao SP i imao tendenciju da smanji VI. Ovi rezultati pokazuju da je ketamin ublažio bolesno ponašanje i anhedoniju kod miševa bez efekta na bihejvioralni očaj, dok je GL-II-73, iako bez efekta na bolesno ponašanje, redukovao anhedoniju i imao tendenciju da smanji bihejvioralni očaj.

GL-II-73, pozitivni modulator α5 GABAA receptora, redukovao je anhedoniju i bihejvioralni očaj u LPS-om izazvanom mišjem modelu ponašanja nalik na depresivnom, što pruža potencijalno novi pristupu tretmanu depresivnih poremećaja.

α5 GABAA RECEPTOR POSITIVE ALLOSTERIC MODULATION BY GL-II-73 REDUCED LIPOPOLYSACCHARIDE-INDUCED DEPRESSIVE–LIKE BEHAVIOR IN C57BL/6 MICE

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γ-Aminobutyric acid (GABA) signaling is likely disrupted in mood disorders. We investigated the influence of GL-II-73, an α5 GABAA receptor positive allosteric modulator, in the lipopolysaccharide (LPS)-induced murine model of depressive-like behavior.

GL-II-73 or ketamine (a positive control of the model) dosed at 10 and 6 mg/kg, respectively, were administered to male C57BL/6 mice (total N=75) immediately before the application of 0.5 mg/kg of LPS. Sickness behavior was assessed by measuring body weight (BW), food intake (FI) and number of quadrant entries during 5 min of spontaneous locomotor activity assay (QE). BW and FI were measured 2, 6, 24 and 28 h, and QE 2 and 24 h after the treatment administration. Sucrose preference (SP) in SP test (SPT), as an indicator of anhedonia, and time immobile (TI) in forced swim test (FST), as an indicator of behavioral despair, were measured 24-28 h and 28 h after treatment administration, respectively. Animals which did not exhibit sickness behavior or consumed less than 0.1 ml of liquid during SPT were excluded from analysis.

We demonstrated that treatment with LPS induced sickness and depressive-like behavior in mice by ultimately decreasing BW, FI, QE, SP and tending to increase the TI. Pretreatment with ketamine restored FI at 24-28 h, QE at 24 h and SP, and GL-II-73 restored SP and tended to restore TI. We showed that ketamine reduced sickness behavior and anhedonia with no effect on behavioral despair, while GL-II-73, although with no effect on sickness behavior, reduced anhedonia and tended to reduce behavioral despair.

GL-II-73, an α5 GABAA receptor positive allosteric modulator, reduced anhedonia and behavioral despair in LPS-induced murine model of depressive-like behavior, suggesting a novel approach in the treatment of depression.

NOVI POZITIVNI MODULATOR α4-GABAA RECEPTORA, XHE-III-74, SMANJUJE UNOS ALKOHOLA U MIŠIJEM MODELU „PIJENJA U MRAKU"

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Cilj ove studije bio je da se ispita da li akutni tretman ligandom XHe-III-74, novim pozitivnim modulatorom α4-$GABA_A$ receptora, može smanjiti unos alkohola u mišijem modelu „pijenja u mraku" (eng. *drinking in the dark – DID*).

Eksperimenti su sprovedeni na odraslim miševima soja C57BL/6. Moguće sedativno dejstvo XHe-III-74 (0,5; 2 ili 5 mg/kg, i.p.) ispitano je u testu spontane lokomotorne aktivnosti (SLA). Prvog dana jednog ciklusa DID eksperimenta svaka životinja imala je dvočasovni pristup alkoholu (etanol 20%, v/v). Drugog dana tretman je primenjivan 20 minuta pre pristupa alkoholu, a trećeg dana pacovi nisu tretirani ničim. U svim DID eksperimentima svaka životinja je prošla kroz četiri ciklusa tako da je u svakom primila jednu od tri doze tretmana ili placebo. U prvom DID eksperimentu testirali smo efekat XHe-III-74 (0,8; 2 ili 5 mg/kg) na unos vode (n=12, po dozi), dok smo u drugom testirali efekat istih doza na unos alkohola (n=14). Ekekat referetnog leka, naltreksona (1; 4 ili 16 mg/kg) testiran je u trećem eksperimentu. U SLA testu, nijedna od odabranih doza XHe-III-74 nije smanjila pređeni put životinje ($F_{3,20}$=0,48; p=0,703). U prvom DID eksperiementu, tretman XHe-III-74 nije uticao na unos vode ($F_{3,33}$=0,39; p=0,763). Unos alkohola, meren u drugom DID eksperimentu, izmenjen je pod dejstvom XHe-III-74 tretmana ($F_{3,39}$=7,41; p<0,001), gde je doza XHe-III-74 od 5 mg/kg značajno smanjila unos u poređenju sa kontrolom (p<0,001). U trećem eksperimentu, naltrekson je značajno smanjio unos alkohola (F60,3=22.18; p<0,001), i to u sve tri doze: 1 mg/kg (p<0,001); 4 mg/kg (p<0,001) i 16 mg/kg (p<0,001).

Uz očekivani izostanak sedativnog dejstva, XHe-III-74, pozitivni modulator α4-$GABA_A$ receptora, ispoljio je evidentan potencijal za smanjenje unosa alkohola u mišijem DID modelu, koji se može porediti sa onim postignutim primenom naltreksona, referentnog leka u terapiji poremećaja unosa alkohola.

A NOVEL POSITIVE MODULATOR OF α4-GABAA RECEPTORS, XHE-III-74, REDUCES ETHANOL INTAKE IN MOUSE „DRINKING IN THE DARK" MODEL

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The present study aimed to investigate whether acute treatment with XHe-III-74, a novel positive modulator of α4-$GABA_A$ receptors, may reduce alcohol intake in mouse model of „drinking in the dark" (DID).

All experiments were conducted on adult C57BL/6 mice. Potential sedative properties of XHe-III-74, (0.5, 2 or 5 mg/kg, i.p.) were assessed using spontaneous locomotor activity (SLA) test. On the 1st day of one DID cycle each animal had 2-h access to ethanol (20%, v/v), on the 2nd day treatment was given 20 min before the access to ethanol, while on the 3rd day the animal was not treated in any way. In all DID experiments each animal passed through four cycles and respectively receive one of three treatment doses or solvent in each cycle. In Experiment 1 we tested whether XHe-III-74 (0.8, 2 or 5 mg/kg) had any effects on water intake (n=12 per treatment dose), while in Experiment 2, the same doses were used to test potential decrease of ethanol intake (n=14). Effects of the reference drug, naltrexone (1; 4 and 16 mg/kg) were tested in Experiment 3 (n=21). In the SLA test, none of the selected XHe-III-74 doses decreased the distance traveled ($F_{3,20}$=0.48; p=0.703). In DID Experiment 1, XHe-III-74 treatment didn't affect water intake ($F_{33,3}$=0.39; p=0.763). Ethanol intake, measured in Experiment 2, was affected by XHe-III-74 treatment ($F_{39,3}$=7.41; p<0.001), with 5 mg/kg XHe-III-74 significantly reducing the intake relative to control (p<0.001). In Experiment 3, naltrexone significantly affected the intake of ethanol ($F_{60,3}$=22.18; p<0.001), with all three doses reducing the intake: 1 mg/kg (p<0.001); 4 mg/kg (p<0.001) and 16 mg/kg (p<0.001).

With expected lack of sedative actions, XHe-III-74, a positive modulator of α4-$GABA_A$Rs, exhibited a clear potential for decreasing ethanol intake in mouse DID model, comparable to that of naltrexone, a reference drug in alcohol use disorder.

BIHEJVIORALNA KARAKTERIZACIJA SOCIJABILNOSTII SOCIJALNE MEMORIJE 5XFAD TRANSGENIH MIŠEVA KAO MODELA ALCHAJMEROVE BOLESTI

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Kod pacijenata koji boluju od Alchajmerove bolesti dolazi do poremećaja u socijalizaciji i socijalnoj memoriji. 5xFAD miševi predstavljaju široko korišćen progresivni model u ispitivanju ove bolesti, u kome socijalna interakcija i socijalno prepoznavanje nisu detaljno istraženi. Cilj rada bio je da se bihejvioralno okarakterišu socijabilnost i socijalna memorija oba pola 5xFAD životinja u periodu samog početka stvaranja plaka.

U eksperimentu su korišćeni transgeni (11 mužjaka, 11 ženki) i netransgeni (kontrolna grupa; 13 mužjaka, 12 ženki) 5xFAD miševi starosti 2 meseca koji su podvrgnute testu tri komore. Protokol obuhvata tri uzastopne faze: habituaciju, socijalnu interakciju i socijalno prepoznavanje.

Na lokomotornu aktivnost životinja, procenjenu u fazi habituacije, ne utiču ni pol ni genotip. U testu socijalne interakcije, kontrolni mužjaci su proveli statistički značajno više vremena u komori sa mišem i češće su ulazili u ovu, u odnosu na praznu komoru, što nije bio slučaj kod kontrolnih ženki. Ni transgeni mužjaci ni transgene ženke nisu razlikovali praznu i komoru sa mišem, što ukazuje da 5xFAD genotip može da ima nepovoljan uticaj na socijabilnost. U testu socijalnog prepoznavanja, samo su netransgeni mužjaci, ali ne i netransgene ženke, niti transgene životinje diskriminisali poznatog i novog miša, što je pokazano statistički značajno dužim vremenom provedenim sa novim mišem, kao i većim brojem ulazaka u zonu sa novim u odnosu na zonu sa poznatim mišem.

Rano odraslo doba predstavlja period u kome postoji izmenjena socijabilnost kod 5xFAD mužjaka. Netransgene ženke nisu pokazale očekivanu socijalnu interakciju i prepoznavanje, što onemogućava izvođenje zaključaka o transgenim ženkama. Potrebno je nastaviti karakterizaciju socijalnog ponašanja ovih miševa tokom progresije stvaranja plaka i razvoja ostalih simptoma bolesti.

BEHAVIORAL CHARACTERIZATION OF SOCIABILITY AND SOCIAL MEMORY IN THE 5XFAD TRANSGENIC MICE AS A MODEL OF ALZHEIMER DISEASE

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Patients suffering from Alzheimer disease experience desocialization and social memory impairment. Transgenic 5xFAD mice represent a widely used progressive model of this disease, in which social interaction and social recognition have not been thoroughly explored yet. Our aim was to characterize the sociability and social memory of both genders of 5xFAD animals at the very onset of plaque deposition.

Two months old transgenic mice (11 males, 11 females) and their non-transgenic litter mates (control groups; 13 males, 12 females) were assessed in the three-chamber test. The protocol consisted of successive phases of habituation, social interaction and social recognition.

The general locomotor activity, as assessed in the habituation phase, was not significantly affected by genotype or gender. In the social interaction phase, as expected, control males spent more time and entered more frequently the chamber with the con-specific than the empty one; however, this was not the case with female controls. Both, transgenic males and females did not distinguish between these two chambers, which indicates that the 5xFAD genotype might have an adverse impact on sociability. In the social recognition phase, only non-transgenic male, but not non-transgenic female or transgenic mice, discriminated between familiar and novel mouse, as demonstrated by the increased time the animal spent in, and a greater number of entries into the zone with a novel versus the familiar mouse.

The early adulthood represents a period in which sociability in 5xFAD male mice is altered. Female non-transgenic animals did not show expected social interaction and recognition, which precludes any conclusions about the behavior of transgenic females. It is necessary to continue characterizing the social behavior of these mice during the progression of plaque generation and development of other symptoms.

FARMAKOTERAPIJA NEUROENDOKRINIH TUMORA PANKREASA

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Neuroendokrini tumori pankreasa (pNET), na osnovu funkcionalne aktivnosti (vrste hormona koje tumor sekretuje) obuhvataju insulinom, VIP-om, glukagonom, somatostatinom, kao i tumore koji sekretuju hormone koji se ne produkuju u pankreasu - gastrinom, kortikotropinom, gonadotropinom i dr. Najbolji vid lečenja je hirurško odstranjivanje tumora, koje je često neprimenljivo zbog nepristupačnih lokalizacija, kasnog postavljanja dijagnoze i metastatskog širenja. Medikamentozna terapija uključuje primenu analoga somatostatina (SSA-oktreotid, lanreotid, vapreotid, pasireotid), alkilirajućih agenasa (streptozocin, temozolomid, dakarbazin), platine, radioobeleženih peptida, kao i savremenih terapeutika-sunitiniba, everolimusa i bevacizumaba. Rad ima za cilj da prikaže razlike između konvencionalnih i savremenih lekova u terapiji pNET-a. Urađena je komparativna analiza efikasnosti različitih grupa lekova u terapiji pNET-a.

U terapiji metastatskih i neoperabilnih pNET-a u novije vreme su indikovani sunitinib, everolimus, bevacizumab, u vidu mono- ili kombinovane terapije.

Za razliku od tradicionalnih, ovi lekovi imaju ciljna dejstva, inhibirajući angiogenezu tumorskih ćelija. Inhibicijom angiogeneze sprečavaju rast tumora pankreasa i proliferaciju endotelnih ćelija, fibroblasta i glatkih mišićnih ćelija. Everolimus je selektivan inhibitor mTOR, smanjuje nivo VEGF (vaskularnog endotelnog faktora rasta koji potencira angiogenezu tumora). Bevacizumab, anti-VEGF antitelo prepoznaje i blokira specifične proteine prisutne u tumorskim ćelijama. Sunitinib deluje dvostruko na maligne ćelije: sprečava njihovo umnožavanje i rast krvnih sudova inhibicijom receptorskih tirozin-kinaza: c-kit, RET, CSF-1R, Flt3, PDGFR i VEGFR. Budući da ovi lekovi selektivno inhibiraju stvaranje novih krvnih sudova, oni manje oštećuju normalne ćelije od tradicionalnih citostatika, jer postojeći krvni sudovi ostaju očuvani za snabdevanje normalnih ćelija. Pored toga, mnogobrojne studije pokazuju njihovu izrazito povoljniju farmakovigilancu i duže preživljavanje pacijenata. Multidisciplinarni pristup, razvoj i primena selektivnijih lekova u terapiji pNET-a, koji poboljšavaju kvalitet života pacijenata, od suštinskog je značaja, naročito kada se ima u vidu činjenica da se radi o retkim i nedovoljno proučenim entitetima.

PHARMACOTHERAPY OF PANCREATIC NEUROENDOCRINE TUMORS

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Pancreatic neuroendocrine tumors (pNETs), based on the type of hormone that is secreted are divided into: insulinoma, VIPoma, glucagonoma, somatostatinoma and nonpancreatic hormone tumors (gastrinoma, gonadotroph, corticotroph adenomas). The most effective treatment is surgical removal of tumors, which is often not applicable due to inaccessible localization, late diagnosis and metastatic spread. Pharmacotherapy includes administration of somatostatin analogues (SSA-octreotide, lanreotide, vapreotide, pasireotide), alkylating agents (streptozocin, temozolomide, dacarbazine), platinum, a peptide receptor radionuclide therapy, as well as the modern therapeutics-sunitinib, everolimus, bevacizumab. The paper aims to show the differences between conventional and modern drugs in the pNETs treatment.

Comparative analysis of the efficiency of different pharmacological groups in the treatment of pNETs was performed.

In recent years, sunitinib, everolimus, and bevacizumab, as mono- or polytherapy,are indicated for the treatment of metastatic and inoperable pNETs. Unlike traditional therapy, these drugs have a target of action, inhibition of angiogenesis of tumor cells, tumor growth and proliferation of endothelial cells, fibroblasts, and smooth muscle cells. Everolimus is a selective mTOR inhibitor that reduces the level of VEGF (vascular endothelial growth factor). Bevacizumab, an anti-VEGF antibody, recognizes and blocks specific proteins present in tumor cells. Sunitinib acts doubly on malignant cells: prevents their multiplication, and the angiogenesis by inhibition of receptor tyrosine kinases: c-kit, RET, CSF-1R, Flt3, PDGFR, and VEGFR. Since these drugs selectively inhibit angiogenesis, they less damage normal cells than traditional cytostatics, as existing blood vessels remain preserved for normal cell supply. In addition, numerous studies have shown their far more suitable pharmacovigilance and longer patient survival. Multidisciplinary approach, development and application of selective drugs in the treatment of pNET swhich improve the quality of life of patients is essential considering the fact that pNETs are rare and insufficiently investigated entities.

DOZIRANJE APIKSABANA I RIVAROKSABANA KOD PACIJENATA SA PLUĆNOM EMBOLIJOM: DA LI JEDNA DOZA ODGOVARA SVIMA?

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Apiksaban i rivaroksaban su direktni oralni antikoagulansi (DOAK) koji inhibiraju faktor koagulacije Xa i često se propisuju pacijentima sa plućnom embolijom (PE). U fiziološkim uslovima, kada je očuvana bubrežna funkcija i ukoliko ekstremne osobine pacijenata nisu udružene, svaki od ova dva leka ima jedinstveno doziranje bez obzira na telesnu masu, godine života ili pol. Ipak, mnoge studije nisu uključivale starije ili ekstremno gojazne pacijente, tako da podaci o efikasnosti i bezbednosti ovih lekova za ovu populaciju nedostaju. Cilj ove studije bio je da se uporedi anti-Xa aktivnost kod pacijenata sa PE u zavisnosti od njihovog indeksa telesne mase, godina života i pola.

U ovoj retrospektivnoj, opservacionoj studiji preseka jedne zdravstvene ustanove, konsekutivni pacijenti sa PE su svrstani u grupu koja je dobijala apiksaban ili rivaroksaban nakon otpusta. Nakon jednomesečne stabilne terapije, u uzorku krvi dobijenoj venepunkcijom određivana je anti-Xa aktivnost. U svakoj od grupa vrednosti anti-Xa su poređene između pacijenata sa normalnom telesnom masom i gojaznih, zatim između mlađih i starijih od 75 godina života i između muškaraca i žena.

U studiju je bilo uključeno 167 pacijenata, 56 (33,5%) na apiksabanu i 111 (66,5%) na rivaroksabanu. U grupi pacijenata lečenih apiksabanom nije postojala značajna razlika u anti-Xa aktivnosti između pacijenata sa normalnom telesnom masom i gojaznih (p=0,285), mlađih i starijih od 75 godina (p=0,663) ili između muškaraca i žena (p=0,092). Takođe, ni u grupi pacijenata lečenih rivaroksabanom nije postojala značajna razlika u anti-Xa aktivnosti za iste kriterijume (p=0,938, p=0,885 i p=0,102, redom). Kod pacijenata sa PE, nakon jednomesečne terapije bilo apiksabanom ili rivaroksabanom, telesna masa, godine života ili pol ne utiču značajno na anti-Xa aktivnost.

APIXABAN AND RIVAROXABAN DOSING IN PULMONARY EMBOLISM PATIENTS: DOES ONE DOSE FITS ALL?

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Apixaban and rivaroxaban are direct oral anticoagulants (DOACs) which block coagulation factor Xa and are commonly prescribed to the patients diagnosed with pulmonary embolism (PE). In normal conditions, with preserved kidney function and if extreme patients' characteristics are not combined, each drug has the same dosage regardless of age, body mass or sex. However, many trials did not include elderly patients or those with extreme obesity, so data of drug efficacy and safety with single and predefined dosage in such population is still lacking. The objective of this study was to compare an anti-Xa activity in PE patients considering their different body mass index, age and sex.

In this single-center retrospective, observational cross-sectional study, consecutive PE patients were allocated to either apixaban or rivaroxaban group regarding the DOAC they received after hospital discharge. After one month on stable therapy, anti-Xa activity was measured in the blood collected by vene puncture during the trough drug concentration. In each of apixaban and rivaroxaban group anti-Xa activity values were compared between normal weighted and obese, younger and older than 75 years of age, males and females.

Overall 167 patients were involved in this study, 56 (33.5%) in the apixaban group and 111 (66.5%) in the rivaroxaban group. In the apixaban group, the difference in anti-Xa activity was not significant between normal weighted and obese, younger and older than 75 years of age, and males and females ($p=0.285$, $p=0.663$ and $p=0.092$, respectively). In the rivaroxaban group, no significant difference was found either for the same criteria ($p=0.938$, $p=0.885$, and $p=0.102$, respectively). In PE patients, after one month of treatment with a single recommended dosage of apixaban or rivaroxaban, anti-Xa activity is not significantly influenced by patient's body mass, age or sex.

UČEŠĆE HOLINERGIČKIH RECEPTORA U ANALGETIČKOM DEJSTVU VORTIOKSETINA

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Vortioksetin je noviji antidepresiv sa multimodalnim mehanizmom dejstva. Za razliku od većine antidepresiva poseduje prokognitivna svojstva, čemu verovatno doprinosi potenciranje holinergičke neurotransmisije. Poznato je da se antidepresivi koriste u lečenju različitih bolnih stanja, uključujući i ona trigeminalnog porekla. Nedavno smo pokazali da vortioksetin ostvaruje efikasnost u orofacijalnom formalinskom testu u miševa, modelu trigeminalnog bola. Kako bismo razjasnili mehanizam analgetičkog dejstva vortioksetina u ovom modelu bola, cilj našeg rada je bio da se ispita potencijalno učešće holinergičkih (muskarinskih i α_7-nikotinskih) receptora, imajući u vidu njihov značaj u modulaciji bola.

Bolna preosetljivost orofacijalnog regiona miševa izazivana je supkutanom injekcijom rastvora formalina (2 %, 20 µl). Merni parametar je ukupno vreme provedeno u bolnom ponašanju (trljanje njuške) tokom prve (0-9 min nakon formalina) i druge (9-45 min nakon formalina) faze testa. Najpre smo potvrdili efikasnost vortioksetina u ovom testu, a potom smo pratili uticaj atropina (neselektivnog antagoniste muskarinskih receptora) i metillikakonitina (selektivnog antagoniste α_7-nikotinskih receptora) na analgetičko dejstvo fiksne, efektivne doze vortioksetina. Vortioksetin je primenjivan peroralno (p.o.), a antagonisti intraperitonealno (i.p.) 60 min pre rastvora formalina.

Vortioksetin (5-20 mg/kg; p.o.) je značajno i dozno-zavisno smanjio vreme provedeno u nociceptivnom ponašanju u drugoj fazi testa sa maksimalnim efektom od 75%. Atropin (2,5 i 5 mg/kg; i.p.) i metilikakonitin (1 i 6 mg/kg; i.p.) su značajno inhibirali analgetičko dejstvo vortioksetina (15 mg/kg; p.o.) na dozno-zavisan način u drugoj fazi testa. Maksimalna inhibicija iznosila je 92% i 100% za atropin i metillikakonitin, redom.

Prikazani rezultati ukazuju da je analgetičko dejstvo vortioksetina u modelu trigeminalnog bola u miševa posredovano, barem delimično, muskarinskim i α_7-nikotinskim holinergičkim receptorima.

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THE INVOLVEMENT OF CHOLINERGIC RECEPTORS IN THE ANALGESIC EFFECT OF VORTIOXETINE

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Vortioxetine is a novel antidepressant with multimodal activity. Unlike most other antidepressants, it possesses procognitive properties and the enhancement of cholinergic neurotransmission probably contributes to this effect. Antidepressants have been used to treat various pain conditions, including those of trigeminal origin. We have recently demonstrated that vortioxetine exerts the analgesic effect in the orofacial formalin test in mice (model of trigeminal pain). To elucidate the mechanism of vortioxetine's analgesic effect in this pain model, the aim of our study was to examine the involvement of cholinergic (muscarinic and α_7-nicotinic) receptors in vortioxetine-induced antinociception, given their important role in pain modulation.

Trigeminal nociception was induced by a subcutaneous injection of formalin solution (2%, 20 μL) into the perinasal area of mice. Time spent in nociceptive behavior (face rubbing) in the first phase (0-9 min post-formalin) and second phase (9-45 min post-formalin) of the test was measured. Firstly, we confirmed the efficacy of vortioxetine in this test, and then the influence of atropine (nonselective muscarinic receptor antagonist) and methyllicaconitine (selective α_7-nicotinic receptor antagonist) on the analgesic effect of a fixed, effective dose of vortioxetine was monitored. Vortioxetine was administered perorally (p.o.), and antagonists were applied intraperitoneally (i.p.), 60 min before formalin injection.

Vortioxetine (5-20 mg/kg; p.o.) significantly and dose-dependently reduced time spent in nociceptive behavior in the second phase of the test with maximum effect of 75%. In antagonist study, atropine (2.5 and 5 mg/kg; i.p.) and methyllycaconitine (1 and 6 mg/kg; i.p.) significantly decreased the analgesic effect of vortioxetine (15 mg/kg, p.o.) in a dose-related manner in the second phase of the test. The values of maximal inhibition were 92% and 100% for atropine and methyllycaconitine, respectively. Presented results suggest that the analgesic effect of vortioxetine in a trigeminal pain model is mediated, at least in part, by muscarinic and α_7-nicotinic cholinergic receptors.

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VORTIOKSETIN UBLAŽAVA TRIGEMINALNI BOL: UČEŠĆE ADRENERGIČKIH RECEPTORA

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U trigeminalnoj regiji se javljaju neka od najčešćih i onesposobljavajućih bolnih stanja. U lečenju bolova trigeminalnog porekla neretko se poseže za alternativnim analgeticima, kao što su antidepresivi. Vortioksetin je antidepresiv novijeg datuma sa jedinstvenim farmakološkim profilom. Prethodno smo pokazali da vortioksetin ostvaruje efikasnost u orofacijalnom formalinskom testu u miševa (model trigeminalnog bola), ali mehanizam njegovog analgetičkog dejstva nije razjašnjen. Poznato je da vortioksetin povećava nivo ekstracelularnog noradrenalina u određenim regijama mozga, uključujući i one koje su od značaja za trigeminalnu nocicepciju. Stoga je cilj našeg rada bio da ispitamo učešće adrenergičkih (α_2 i β_1) receptora u analgetičkom dejstvu vortioksetina u modelu trigeminalnog bola.

Trigeminalna nocicepcija je izazivana supkutanom injekcijom rastvora formalina (2%, 20 μl) u perinazalnu regiju miševa. Merni parametar je ukupno vreme provedeno u bolnom ponašanju (trljanje njuške) tokom prve (0-9 min nakon formalina) i druge (9-45 min nakon formalina) faze testa. Najpre smo potvrdili efikasnost vortioksetina u ovom testu, a potom smo pratili uticaj johimbina (selektivnog antagoniste α_2–adrenergičkih receptora) i metoprolola (selektivnog antagoniste β_1–adrenergičkih receptora) na analgetičko dejstvo fiksne, efektivne doze vortioksetina. Vortioksetin je primenjivan peroralno (p.o.), a antagonisti intraperitonealno (i.p.) 60 min pre rastvora formalina.

Vortioksetin (5-20 mg/kg; p.o.) je statistički značajno i dozno-zavisno smanjio vreme provedeno u bolnom ponašanju u drugoj fazi testa. Analgetički efekat izražen u procentima iznosio je 35-75%. Adrenergički antagonisti, johimbin (1 i 2 mg/kg; i.p.) i metoprolol (1 i 2 mg/kg; i.p.), značajno su i dozno-zavisno inhibirali analgetičko dejstvo vortioksetina (15 mg/kg; p.o.) u drugoj fazi testa. Maksimalna inhibicija analgetičkog dejstva vortioksetina iznosila je 79% za johimbin i 90% za metoprolol. Rezultati ukazuju da su u analgetičko dejstvo vortioksetina u modelu trigeminalnog bola uključeni, barem delimično, α_2- i β_1-adrenergički receptori.

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VORTIOXETINE ALLEVIATES TRIGEMINAL PAIN: THE INVOLVEMENT OF ADRENERGIC RECEPTORS

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Some of the most prevalent and debilitating pain conditions arise from the trigeminal region. In the treatment of trigeminal pain alternative analgesics, such as antidepressants, are commonly used. Vortioxetine is a novel antidepressant with a unique pharmacological profile. We have recently shown that vortioxetine exerts the analgesic effect in the orofacial formalin test in mice (model of trigeminal pain), but the mechanism of its antinociception is not elucidated. Vortioxetine increases the level of extracellular noradrenaline in certain brain regions, including those relevant for trigeminal nociception. Therefore, the aim of our study was to examine the involvement of adrenergic (α_2 i β_1) receptors in vortioxetine-induced analgesia in a trigeminal pain model.

Trigeminal nociception was induced by a subcutaneous injection of formalin (2%, 20 μL) into the perinasal area of mice. Time spent in nociceptive behavior (face rubbing) in the first phase (0-9 min post-formalin) and second phase (9-45 min post-formalin) of the test was measured. Firstly, we confirmed the efficacy of vortioxetine in this test, then the influence of yohimbine (selective α_2–adrenoceptor antagonist) and metoprolol (selective β_1-adrenoceptor antagonist) on the analgesic effect of a fixed, effective dose of vortioxetine was monitored. Vortioxetine was administered by oral (p.o.) gavage, and antagonists were applied intraperitoneally (i.p.) 60 min before formalin injection.

Vortioxetine (5-20 mg/kg; p.o.) significantly and dose-dependently reduced time spent in nociceptive behavior in the second phase of the test. The analgesic effects of vortioxetine ranged from 35% to 75%. Adrenergic antagonists, yohimbine (1 and 2 mg/kg; i.p.) and metoprolol (1 and 2 mg/kg; i.p.) significantly decreased the analgesic effect of vortioxetine (15 mg/kg, p.o.) in a dose-related manner in the second phase of the test. The maximum inhibition of the analgesic effect of vortioxetine was 79% for yohimbine and 90% for metoprolol. The results of the present study show that α_2- and β_1-adrenergic receptors are involved, at least partially, in the analgesic effect of vortioxetine in a trigeminal pain model.

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LOKALNI PERIFERNI ANALGETIČKI EFEKAT ESLIKARBAZEPIN ACETATA U MODELU TRIGEMINALNOG BOLA: ULOGA SEROTONINSKIH 5-$HT_{1B/1D}$ I KANABINOIDNIH CB_1/CB_2 RECEPTORA

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Eslikarbazepin acetat (ESL) je nov predstavnik dibenzazepinskih antiepileptika, koji je pokazao efikasnost u ublažavanju trigeminalnog bola u prekliničkim i kliničkim studijama. Međutim, tačno mesto i mehanizam analgetičkog dejstva ESL nisu u potpunosti razjašnjeni. Prethodno smo pokazali da se analgetički efekat peroralno primenjenog ESL, u modelu trigeminalnog bola, može inhibirati sistemskom primenom antagonista serotoninskih 5-$HT_{1B/1D}$ i kanabinoidnih CB_1/CB_2 receptora. U ovom radu smo hteli da proširimo postojeće rezultate i ispitamo efikasnost ESL u modelu trigeminalnog bola (orofacijalni formalinski test) nakon lokalne periferne primene, i ulogu perifernih serotoninskih 5-$HT_{1B/1D}$ i kanabinoidnih CB_1/CB_2 receptora u nastanku lokalnog efekta ESL.

Trigeminalni bol je izazivan supkutanom injekcijom rastvora formalina u perinazalnu regiju miševa. Nakon injekcije formalina merili smo vreme provedeno u nociceptivnom ponašanju u prvoj i drugoj fazi testa. ESL je primenjivan supkutano u perinazalnu regiju, 20 min pre formalina. Dodatno, ispitali smo efekte najveće testirane doze ESL nakon kontralateralne primene (u odnosu na stranu formalinske injekcije), u cilju potvrde lokalne prirode efekta. Ulogu perifernih receptora smo ispitali tako što smo pratili uticaj antagonista serotoninskih 5-$HT_{1B/1D}$ (GR127935), kanabinoidnih CB_1 (AM251) ili CB_2 receptora (AM630) na analgetički efekat fiksne, efikasne doze ESL (antagonisti su primenjeni supkutano, zajedno sa ESL).

Lokalna primena ESL (7,5-30 μg/mišu)je proizvela značajan, dozno-zavisan analgetički efekat od 35-60% u drugoj fazi testa. Kontralateralna primena najveće testirane doze ESL (30 μg/mišu) nije imala značajan efekat u orofacijalnom formalinskomtestu. Antagonisti GR127935 (2,5 i 5 μg/mišu), AM251 (3 i 7,5 μg/mišu) i AM630 (1 i 2,5 μg/mišu) doveli su do značajne, dozno-zavisne inhibicije analgetičkog efekta ESL (15 μg/mišu). Stepeni inhibicije analgetičkog efekta ESL za veće doze antagonista su bili 69% za GR127935, 99% za AM251 i 89% za AM630. ESL ispoljava analgetički efekat nakon lokalne periferne primene u modelu trigeminalnog bola koji je posredovan, bar delom, perifernim serotoninskim 5-$HT_{1B/1D}$ i kanabinoidnim CB_1/CB_2 receptorima.

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THE LOCALPERIPHERAL ANALGESIC EFFECTOF ESLICARBAZEPINE ACETATE IN A TRIGEMINAL PAIN MODEL: THE ROLE OFSEROTONIN 5-$HT_{1B/1D}$ AND CANNABINOID CB_1/CB_2 RECEPTORS

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Eslicarbazepine acetate (ESL) is a novel dibenzazepine antiepileptic drug, which has demonstrated efficacy against trigeminal pain in preclinical and clinical studies. However, the exact site andmechanism of ESL's analgesic action are not completely understood. We have previously demonstrated that the analgesic effects of perorally administered ESL, in a trigeminal pain model, can be inhibited by systemicapplication of serotonin 5-$HT_{1B/1D}$ and cannabinoid CB_1/CB_2 receptor antagonists. In this study, we aimed to expand the existing data and examine the efficacy of locally peripherally administered ESL in a trigeminal pain model (the orofacial formalin test) and the role of peripheral serotonin 5-$HT_{1B/1D}$ and cannabinoid CB_1/CB_2receptors in mediating the localeffects of ESL.

Trigeminal pain was induced with a subcutaneous injection of formalin solution into the perinasal region of mice. After the formalin injection we measured the time spent in nociceptive behavior in the first and second phase of the test. ESL was administered subcutaneously into the perinasal region, 20 min before the formalin injection. Additionally, we examined the effects of the highest tested ESL dose after contralateral application (with respect to the side of formalin injection) in order to confirm the local nature of its effect. The role of peripheral receptors was examined by evaluating the influence of a serotonin 5-$HT_{1B/1D}$ (GR127935), cannabinoid CB_1 (AM251) or CB_2receptor antagonist (AM630) on the analgesic effect of a fixed, effective dose of ESL (the antagonists were subcutaneously coadministered with ESL).

Local application of ESL (7.5-30 μg/mouse) produced a significant and dose-dependent analgesic effect of 35-60% in the second phase of the test. Contralateral application of the highest tested dose of ESL (30 μg/mouse) had no significant effect in the orofacial formalin test. The antagonists GR127935 (2.5 and 5 μg/mouse), AM251 (3 and 7.5 μg/mouse) and AM630 (1 and 2.5 μg/mouse) produced a significant and dose-dependent inhibition of the analgesic effect of ESL (15 μg/mouse). The levels of inhibition of ESL's analgesic effect achieved with the higher antagonist doses were 69% for GR127935, 99% for AM251 and 89% for AM630. ESL produces an analgesic effect in a trigeminal pain model after local peripheral application that is mediated, in part, by peripheral serotonin 5-$HT_{1B/1D}$ and cannabinoid CB_1/CB_2 receptors.

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