NCBES Galway Neuroscience Centre's Annual Research Day 2013

Time	Speaker	Title
9.10		Arrival
9.20	Dr. David Finn, GNC Leader	Meeting opening
9.30	Prof. Artur Swiergiel University of Gdansk, Poland.	"Functions of Neuropeptides – Corticotrophin Releasing Factor (CRF)"
10.30	Tea/coffee Poster judging	
11.30	Ms. Karen Bannerton Pharmacology & Therapeutics	"Characterisation of desipramine-induced responses in the rat forced swim test: influence of bedding and age"
11.45	Joanne Kenny Psychiatry & Anatomy	"The course of cognitive deficits in a 4-year follow-up study of first episode psychosis patients and clinical correlates"
12.00	Mr. Dara Bree Pharmacology & Therapeutics	"Characterisation of the affective component of pain processing associated with a novel model of acute postoperative pain"
12.15	Dr. Honorata Kraskiewicz NFB & Anatomy	"The Development of a Growth Factor Delivery Platform Technology for Nerve Tissue Regeneration"
12.30	Ms. Nikita Burke Physiology	"Microglia: the glue that link depression and chronic pain"
12.45	Ms. Ruth Concannon Pharmacology & Therapeutics	"Upregulation of the Cannabinoid Type-2 Receptor (CB2) Endocannabinoid System Following Intra-Striatal Administration Of The Inflammagen, Lipopolysaccharide"
13.00	Lunch Poster viewing	
14.00	Ms. Elaine Jennings Pharmacology & Therapeutics	Enhanced formalin-evoked nociceptive behaviour in Wistar-Kyoto rats is associated with alterations in the endocannabinoid system in the lateral periaqueductal grey"
14.15	Ms. Sinead Lydon Psychology	"A Systematic Review of Physiological Reactivity in Autism: Implications for our Understanding of Associated Atypical Behaviours"
14.30	Ms. Kate McDonnell-Dowling Pharmacology & Therapeutics	"Methamphetamine exposure during pregnancy at pharmacological doses produces neurodevelopmental effects in rat offspring"
14.45	Ms. Michelle Naughton NCBES	"Increased Endoplasmic Reticulum Stress Signalling in White Matter Development in the Rat Cerebellum"
15.00	Ms. Catalina Vallejo NFB	"Biofunctionalization of Electrically Conducting Polymers"
15:15	Tea/coffee Poster viewing	
15:45	Dr. Derek Morris TCIN, TCD/NUI Galway	"High-throughput genomic approaches reveal the complexity of schizophrenia genetics"
16.45	Dr. David Finn, GNC Leader	Prize-giving
17.00	Prof. Gary Donohoe Psychology	Inaugural Professorial Lecture: "From Descartes to Darwin: The social brain and mental health" in Fottrell Lecture Theatre, Arts Millennium Building
18.00	Reception with refreshments - hosted by the School of Psychology in the Arts Millennium Foyer	

Talks: Room G065 in Arts Millennium Extension

Posters: Foyer of Arts Millennium Building

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Poster	Presenter	Title
1	Ms. Orla Brady *Occupational Therapy*	Evaluating and comparing the effectiveness of Sonas and Cognitive Stimulation Therapy (CST) on Cognition, Quality of life, Activities of Daily Living (ADL's), Communication, Neuropsychiatric symptoms and Occupational Performance within a group session in older adults with Dementia.
2	Ms. Aileen Cronin *Pharmacology & Therapeutics*	6-Hydroxydopamine Treatment Models Parkinson's Disease in Zebrafish
3	Ms. Marie Fitzgibbon *Physiology*	The effects of repeated interferon-alpha administration on depressive-like and nociceptive behaviour in two different mouse strains
4	Ms. Sinead Healy NCBES	Iron Loading in Brain Slices: development of a novel *in vitro* platform to assess the impact of an iron-loaded environment in Multiple Sclerosis (MS)
5	Ms. Rebecca Henry *Physiology*	Central inhibition of fatty acid amide hydrolase attenuates TLR-3 induced expression of interferon-gamma and related genes in the rat hippocampus
6	Ms. Deirdre Hoban *Pharmacology & Therapeutics*	Assessment of a Fibrin Scaffold for Delivery of GDNF-Overexpressing Mesenchymal Stem Cells to the Rat Brain
7	Mr. Alan Hoban *NCBES*	Endoplasmic reticulum Stress molecules: XBP1 and pIRE1 as Potential Novel Markers of Cerebellar Striping
8	Mr. Daniel Kerr *Physiology*	Enhanced neuroinflammatory response to TLR4 activation in the valproic acid rat model of autism
9	Dr. Michelle Roche *Physiology*	Cortical expression of microtubular and synaptic proteins is reduced in the olfactory bulbectomised mouse model of depression
10	Martin Madill *REMEDI*	Induction of neural stem cells directly from control and amyotrophic lateral sclerosis (ALS) patient fibroblasts.
11	Mr. Manish Madusa Pharmacology & Therapeutics	TRPV1 mRNA expression within the brain of two rat strains differing in nociceptive - responsivity.
12	Ms. Ann-Marie Morrissey *Occupational Therapy*	Benefitting Client, Family and Care Staff: Implementation of an Individualised Therapeutic Programme for a Long-Term Disorder of Consciousness Patient
13	Mr. Omar Mothersill Psychology	Increased medial prefrontal activity during dynamic face processing in schizophrenia
14	Ms. Carol Naughton *Pharmacology & Therapeutics*	Comparative assessment of the motor dysfunction induced by neurotoxic, inflammatory and environmental Parkinson's disease-related neurotoxins in rats
15	Ms. Stefani O'Donoghue *Psychiatry*	An Investigation of Global and Local Brain Network Structure in Bipolar Disorder
16	Dr. Bright Okine *Pharmacology & Therapeutics*	Administration of N-palmitoylethanolamide directly into the medial prefrontal cortex reduces formalin-evoked nociceptive behaviour in rats

Talks: Room G065 in Arts Millennium Extension

Posters: Foyer of Arts Millennium Building

NCBES Galway Neuroscience Centre's Annual Research Day 2013

Title

Characterisation of desipramine-induced responses in the rat forced swim test: influence of bedding and age

Authors

Bannerton, K.[(1)(2)], Cronin, A. [(1)(2)], Kleefeld, S. [(1)(2)],, J.P. Kelly[(1)(2)]

Affiliations

[1]Discipline of Pharmacology and Therapeutics, NUI, Galway
[2]Galway Neuroscience Centre, NCBES, NUI, Galway

Abstract

Background: The forced swim test (FST) is the most widely used test for evaluating antidepressant efficacy in rodents [1]. However, the FST experimental parameters differ markedly between laboratories; two potential sources of variation are the age of animals [2] and the animals' experimental bedding [3].

Aim: To examine the influence of bedding and age using the antidepressant desipramine (DMI) in the FST.

Methods: Ten week old (young) male Sprague-Dawley rats were used, and singly housed prior to testing, either in wood shaving or corn cob bedding; in addition there were seven month old (middle aged) and 16 month (old) groups of animals (housed in wood shavings). Immobility, climbing and swimming time were assessed in the FST following subacute DMI (10 mg/kg,sc, 24, 5 and 1 hour prior to a 5 min FST exposure). A Two-Way ANOVA was performed, followed where appropriate by a Student-Newman Keuls *post hoc* test ($p<0.05$, n=5-6).

Results: Corn cob bedding altered baseline immobility and climbing, but not significantly. There was a significant reduction in immobility and concomitant increase in climbing following DMI treatment in young animals, regardless of bedding type. The DMI-induced effects were not observed in the middle aged rats, but were seen in the old group.

Conclusions: These results emphasise the need for standardization of important parameters used in the FST, such as age at time of testing, in order for valid comparisons to be made between laboratories in the search for novel antidepressant compounds.

*Acknowledgments :*This work was funded by a Pharmacology postgraduate fellowship

References:

[1] Porsolt, R.D., Anton, G., Blavet, N., Jalfre, M. 1978. Behavioural despair in rats: a new model sensitive to antidepressant treatments. Eur J Pharmacol. 47 (4): 379-391.

[2]Karanges, E., Li, K.M., Motbey, C., Callaghan, P.D., Katsifis, A., McGregor, I.S. 2011. Differential behavioural and neurochemical outcomes from chronic paroxetine treatment in adolescent and adult rats: a model of adverse antidepressant effects in human adolescents? Int J Neurospychopharmacol. 14 (4): 491-504.

[3]Sakhai, S.A., Preslik, J., Francis, D.D. 2013. Influence of housing variables on the development of stress-sensitive behaviors in the rat. Physiol Behav. 120, 156-163.

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NCBES Galway Neuroscience Centre's Annual Research Day 2013

Title

THE COURSE OF COGNITIVE DEFICITS IN A 4-YEAR FOLLOW-UP STUDY OF FIRST EPISODE PSYCHOSIS PATIENTS AND CLINICAL CORRELATES

Authors

Joanne Kenney[1,2], Heike Anderson Schmidt[1,3], Sophia Arndt[1], John McFarland[1], Cathy Scanlon[1], Colm McDonald[1], Dara M Cannon[2]

Affiliations

[1]Clinical Neuroimaging Laboratory, Departments of [1]Psychiatry & [2]Anatomy, School of Medicine, College of Medicine, Nursing and Health Sciences, National University of Ireland Galway, Galway, Ireland. [3] Department of Psychiatry and Psychotherapy, Section of Psychiatric Genetics, University Medical Centre Goettingen, Georg-August-University, Germany.

Abstract

Background:

Deficits of neurocognition in first-episode psychosis (FEP) are a dominant feature of the disorder (1). However, the course of cognitive deficits in FEP individuals over time is unclear.

Aim:

We aimed to examine the course of cognitive deficits in FEP individuals compared to healthy controls (HCs) over 4 years and the relationship with clinical variables.

Methods:

Twenty two FEP patients and 21 HCs underwent testing in seven areas of cognition at first presentation and on average four years later (mean duration±SD, 4±0.8 yrs) using the MATRICS cognitive consensus battery. Variation in cognitive scores was examined using ANCOVA and relationship with clinical variables using correlation analysis.

Results:

The cognitive domain *Speed of processing* did not significantly improve as much over time ($F=6.9$, $p<0.05$) in FEP patients (mean±SD = 0.27±9.6) compared to controls (mean±SD = 3.5±7.3). The change in other cognitive metrics in the FEP group did not differ statistically from the HCs. Duration of untreated psychosis (DUP), and positive or negative symptoms were not associated with speed of processing among patient group alone.

Conclusions:

The course of cognitive deficits in FEP appears to remain largely stable with the exception of speed of processing. It has been suggested that processing speed could be a core cognitive deficit in schizophrenia (2). Our findings that clinical variables were not related to cognitive change over time supports other research which states that clinical and cognitive features of psychosis may be independent manifestations (3).

Acknowledgments:

We would like to thanks the participants, the radiographers and Radiology Department at UCHG. This work was supported by a Health Research Award from the Health Research Board.

References:

1. Green at al. 2004
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Talks: Room G065 in Arts Millennium Extension

Posters: Foyer of Arts Millennium Building

NCBES Galway Neuroscience Centre's Annual Research Day 2013

Title

Characterisation of the affective component of pain processing associated with a novel model of acute postoperative pain

Authors

Dara Bree[1,2,3], Orla Moriarty[1,3 4], Daniel C. Broom[4], John P. Kelly[1,3], Michelle Roche[2,3], David P. Finn[1,3].

Affiliations

[1]Pharmacology and Therapeutics, [2]Physiology, School of Medicine, [3]Galway Neuroscience Centre and Centre for Pain Research, NCBES, National University of Ireland, Galway, Ireland, [4]Research and Development, Covidien, USA.

Abstract

Background:

Acute postoperative pain remains a significant healthcare issue. Traditional behavioural assays of nociception in rodents have focused on the sensory component of pain processing. The place escape avoidance paradigm (PEAP) is a method devised to study the multidimensional pain experience in rodents (LaBuda *et al.*, 2000).

Aim:

We aimed to investigate the affective/motivational component of postoperative pain associated with inguinal hernia repair in rats.

Methods:

Under isoflurane anaesthesia (5% induction, 2.5% maintenance), adult male Lister-Hooded rats underwent surgery to model Lichtenstein inguinal hernia repair, or a sham procedure (n=7-10 per group). Post-surgical behavioural characterisation involved monitoring of home cage and open field activity as well as PEAP testing. Rats received a single subcutaneous injection of carprofen (5mg/kg) 60 min prior to surgery, morphine (3mg/kg) 150 min post-surgery or vehicle. PEAP testing was carried out for 30 min at 3h post-surgery.

Results:

Rats that underwent surgery spent a significantly longer proportion of the trial duration in the light compartment in avoidance of the noxious stimulus compared with sham animals. Surgery animals also displayed fewer entries into the light as well as an increased percentage response to noxious stimulation compared with sham animals. Morphine and carprofen treatment in surgery animals resulted in significantly less time spent in the light compartment compared with vehicle-treated controls. Surgery-induced reductions in locomotor activity in both the home cage and the open field were evident in surgery animals compared with sham controls.

Conclusions:

These data support characterisation of the affective/motivational component of pain processing associated with a novel, anatomically relevant model of acute postoperative pain.

Acknowledgments:

Supported by the IDA and Covidien

LaBuda CJ, Fuchs PN (2000). A behavioral test paradigm to measure the aversive quality of inflammatory and neuropathic pain in rats. *Experimental neurology* **163**(2)**:** 490-494.

Talks: Room G065 in Arts Millennium Extension

Posters: Foyer of Arts Millennium Building

NCBES Galway Neuroscience Centre's Annual Research Day 2013

Title

The Development of a Growth Factor Delivery Platform Technology for Nerve Tissue Regeneration

Authors

Honorata Kraskiewicz[1], Bridget Breen[1], Timothy Sargeant[2], , Siobhan McMahon[1,3] and Abhay Pandit[1]

Affiliations

[1] Network of Excellence for Functional Biomaterials (NFB), [3] Anatomy, National University of Ireland, Galway, Ireland, [2] Covidien, 60 Middletown Avenue, North Haven, CT 06473, USA

Abstract

Background:

The ability of neurotrophins to promote neuronal survival, development, synaptic plasticity and neurotransmission have inspired researchers to use these molecules as possible therapeutic agents for damaged neurons in a variety of diseases including SCI. However, a controlled delivery of therapeutic molecules to injured tissue remains one of the greatest challenges facing the translation of novel drug therapeutics field.

Aim:

The overall goal of this project is to develop an innovative protein-protein delivery technology of nerve growth factor (NGF) by an electrostatically assembled protein-based (collagen) reservoir system that can be directly injected into the injury site and provide long term release of the therapeutic.

Methods:

Scanning Electron Microscopy: morphological characterisation of collagen hollow-spheres
Fluorescent Microscopy: loading of microspheres with growth factor
Enzyme-Linked Immunosorbent Assay: characterisation of loading and release profile
Live/Death Assay; AlamarBlue Assay: cytotoxicity of spheres
Neuronal Outgrowth Assay: bioactivity of released growth factor

Results:

A protein-based biomimetic hollow reservoir system was fabricated using a template method. The capability of neurotrophins to localise in these reservoir systems was confirmed by confocal images of fluorescently labelled collagen and NGF. Highly cross-linked collagen spheres showed the slowest release rate. Biological activity of released NGF was assessed using rat pheochromocytoma (PC12) cell line and primary rat dorsal root ganglion (DRG) cell bioassay where cell treatment with NGF-loaded reservoirs induced significant neuronal outgrowth, similar to that seen in NGF treated controls.

Conclusions:

The collagen hollow microspheres developed have a potential for use as a reservoir for neurotrophic factors for multiple neurotherapeutic applications.

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Posters: Foyer of Arts Millennium Building

NCBES Galway Neuroscience Centre's Annual Research Day 2013

Title
Microglia: the glue that link depression and chronic pain

Authors
NN Burke [a], E Geoghegan [a], S Chen [b], O Moriarty [b], D Kerr [b], DP Finn [b], M Roche [a]

Affiliations [a] Physiology, [b] Pharmacology and Therapeutics, School of Medicine, NCBES Centre for Pain Research and Galway Neuroscience Centre, National University of Ireland Galway, Ireland.

Abstract

Background: Neuropathic pain is a chronic, intractable condition which is highly comorbid with, and exacerbated by, the presence of depression[1]. Increasing evidence indicates that central immune activation may underlie the pathological relationship between these conditions[2].

Aim: The present study investigated nociceptive and neuropathic pain responding in an animal model of depression, the olfactory bulbectomised (OB) rat. The role of microglia and cytokines in depression-pain interactions were determined by gene expression analysis and pharmacological studies.

Methods: Mechanical and cold nociceptive responding was examined in the OB rat prior to and following L5-L6 spinal nerve ligation (SNL), a model of neuropathic pain. The expression of CD11b (microglial marker), and the cytokines IL-1beta and IL-10 were assessed in the prefrontal cortex (PFC) by qRT-PCR. Microglial activation was inhibited acutely (80mg/kg i.p.) and chronically (75mg/kg/day p.o.) by systemic minocycline administration and the effect on depressive-like and nociceptive behaviour was examined.

Results: OB rats exhibited mechanical and cold allodynia prior to nerve injury. SNL resulted in mechanical and cold allodynia of the ipsilateral hind-paw of both sham and OB animals. However, OB animals exhibited exacerbated cold allodynia following SNL when compared to sham-operated counterparts. OB-SNL animals exhibited increased IL-1beta and IL-10 mRNA in the PFC when compared to sham-operated counterparts. Chronic, but not acute, treatment with minocycline elicited an antidepressant-like effect in OB rats without altering mechanical or cold nociceptive responding. Chronic minocycline attenuated SNL-induced mechanical allodynia over time in both sham and OB rats, although the onset and magnitude of this effect was more pronounced in OB animals. In comparison, acute minocycline completely prevented the development of SNL-induced mechanical allodynia in both sham and OB rats. SNL-induced cold allodynia in both sham and OB animals was attenuated by chronic minocycline administration.

Conclusion: These data further support a role for microglia and cytokines in depression, neuropathic pain and their interaction.

Acknowledgments: The authors would like to gratefully acknowledge funding received from the Discipline of Physiology, the Millennium Fund, and the College of Medicine, Nursing and Health Sciences, National University of Ireland Galway.

References

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2. Norman, G.J., et al., *Stress and IL-1beta contribute to the development of depressive-like behavior following peripheral nerve injury.* Mol Psychiatry, 2010. **15**(4): p. 404-14.

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NCBES Galway Neuroscience Centre's Annual Research Day 2013

Title

Upregulation of the Cannabinoid Type-2 Receptor (CB_2) Endocannabinoid System Following Intra-Striatal Administration Of The Inflammagen, Lipopolysaccharide

Authors

R.M. Concannon[1,2], B.N. Okine[1,2], D.P. Finn[1,2], E Dowd[1,2]

Affiliations

[1]Department of Pharmacology & Therapeutics, [2]NCBES Galway Neuroscience Centre, National University of Ireland Galway, Galway, Ireland.

Abstract

Background:

In recent years, it has become evident that Parkinson's disease is associated with a self-sustaining cycle of neuroinflammation and neurodegeneration with dying neurons activating microglia, which, once activated, can release several factors which kill further neurons (1). One emerging pharmacological target that has the potential to break this cycle is the microglial CB_2 receptor which, when activated, can suppress pro-inflammatory and enhance anti-inflammatory cytokine release from these cells, and reduce their neurotoxicity (2). However, little is known about CB_2 receptor expression in inflammation-driven animal models of Parkinson's disease which is essential for preclinical assessment of the anti-Parkinsonian efficacy of drugs targeting the CB_2 receptor.

Aim:

The aim of this study was to determine if CB_2 receptor expression is altered following intra-striatal lipopolysaccharide (LPS) administration.

Methods:

Vehicle or LPS was injected unilaterally into the adult rat striatum. LPS-induced motor dysfunction was assessed using a battery of lateralised motor tasks on Days 7, 14 and 28 post surgery, and changes in CD11b (a microglial marker) and CB_2, FAAH, MAGL gene expression were assessed using qRT-PCR at Days 1, 4, 14 and 28 after surgery (n=7 rats per treatment, per time-point). LPS-induced striatal microgliosis was also confirmed using OX-42 immunohistochemistry.

Results:

Unilateral LPS administration induced significant striatal inflammation on the ipsilateral side which was associated with contralateral motor deficits in all behavioural tasks. Moreover, LPS administration was also associated with upregulation of CB_2 gene expression and induced alterations in levels of endocannabinoid degrading enzymes.

Conclusions:

This study has revealed that striatal CB_2 receptor mRNA is significantly increased in the inflammation-driven LPS model of Parkinson's disease. These data indicate that this model may be useful for further investigation of the CB_2 receptor as a target for anti-inflammatory disease modification in Parkinson's disease

Acknowledgments:

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2.Ashton JC, Glass M. The cannabinoid CB2 receptor as a target for inflammation-dependent neurodegeneration. Current neuropharmacology. 2007;5(2):73.

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Title

Enhanced formalin-evoked nociceptive behaviour in Wistar-Kyoto rats is associated with alterations in the endocannabinoid system in the lateral periaqueductal grey

Authors

Elaine M. Jennings* [1,3], Weredeselam M. Olango* [1,3] , Kieran Rea* [1,3] , Bright Okine* [1,3], Tracy Lynskey, Fiona McGowan*[1,3], Michelle Roche* [2,3], David P. Finn *[1,3]

Affiliations

[1] Pharmacology and Therapeutics, [2] Physiology, School of Medicine, [3] NCBES Centre for Pain Research and Galway Neuroscience Centre, National University of Ireland, Galway, Ireland.

Abstract

Background: Wistar-Kyoto (WKY) rats display stress hyper-responsivity and enhanced nociceptive responding compared with Sprague-Dawley (SD) rats (Burke et al., 2010). The endocannabinoid system has been implicated in stress-induced hyperalgesia (Shen et al., 2010) .

Aim: Investigate whether altered expression and/or functionality of CB_1 receptors in the periaqueductal grey (PAG) and neuronal activity in components of the descending pain pathway, underlie hyperalgesia to formalin injection in WKY versus SD rats.

Methods: Adult male SD and WKY rats were used. Tissue levels of endocannabinoids and CB_1 receptor mRNA in the PAG were measured by LC-MS-MS and qRT-PCR, respectively. Another cohort of male SD and WKY rats received bilateral microinjection of vehicle or the CB_1 receptor agonist, arachidonyl-2-chloroethylamide (ACEA; 0.05 pmol), into the lateral PAG (lPAG) and formalin-evoked nociceptive behaviour and quantitative immunohistochemical analysis of c-Fos staining in the rostral ventromedial medulla (RVM) and dorsal horn of the spinal cord (DHSC) were assessed.

Results: WKY rats exhibited greater formalin-evoked nociceptive behaviour than SD rats. WKY rats had lower CB_1 receptor mRNA and increased levels of the endocannabinoid 2-arachidonoyl glycerol (2-AG) in the lPAG, compared with SD rats. Intra-lPAG administration of ACEA reduced formalin-evoked nociceptive behaviour and increased c-Fos in the RVM and reduced c-Fos expression in the superficial DHSC SD rats only.

Conclusions: Enhanced formalin-evoked nociceptive behaviour in WKY rats is associated with increased 2-AG levels and down-regulation of CB_1 receptor mRNA expression in the lPAG. In contrast to SD rats, CB_1 receptor activation in the lPAG of WKY rats did not modulate formalin-evoked nociceptive behaviour or neuronal activation in the RVM or DHSC. Thus, dysfunction of the endocannabinoid system within the descending inhibitory pathway may contribute to the WKY hyperagelsic phenotype.

Acknowledgments: Science Foundation Ireland (10/IN.1/B2976) and IRCSET

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Title

A Systematic Review of Physiological Reactivity in Autism: Implications for our Understanding of Associated Atypical Behaviours

Authors

Lydon, S[1]., Healy, O.[1], Reed, P[2]., Hughes, B.M[1]., & Goodwin, M.S.[3]

Affiliations

[1] National University of Ireland, Galway
[2] Swansea University, Swansea, UK
[3] Northeastern University, MA, USA

Abstract

Background:
The prevalence of abnormal behavioral reactivity to a variety of stimuli among individuals with autism spectrum disorder (ASD) has led researchers to examine whether physiological reactivity is atypical in this population.

Aim:
The current review sought to examine the literature describing physiological reactivity in response to sensory, social/emotional, and stressor stimuli among individuals with ASD.

Methods:
A systematic review of the literature on physiological reactivity in ASD was conducted. Studies were reviewed if they (1) included at least one participant diagnosed with ASD, and (2) recorded physiological activity through the measurement of either (a) HR or HRV, (b) blood pressure, (c) EDA, or (d) cortisol, and (3) exposed participant(s) to at least one stimulus condition that constituted a difference from baseline conditions.

Results:
Abnormalities in reactivity to sensory, social and emotional, and stressor stimuli were identified in 76.9%, 66.7%, and 75% of controlled studies respectively. However, the extant literature is characterized by variable and inconsistent findings.

Conclusions:
This body of literature is characterized by inconsistent findings, regardless of the type of stimulus which is examined. These inconsistencies make it difficult to specify what the specific abnormalities in PR are, and what differentiates individuals with ASD who present with atypical PR to stimuli from individuals with ASD who present with typical PR. However, the discrepancies in findings, the complex relationship between PR and behavior, the association between PR and important health outcomes, and the potential physiological dysregulations suggested by findings, highlight the importance of research in this area and avenues for further study.

Acknowledgments: This research was supported by the Irish Research Council's EMBARK Postgraduate Scholarship Scheme [RS/2012/134]

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Title

Methamphetamine exposure during pregnancy at pharmacological doses produces neurodevelopmental effects in rat offspring.

Authors

K. McDonnell Dowling[1], M. Donlon[1], J.P. Kelly[1]

Affiliations

[1]Discipline of Pharmacology and Therapeutics, National University of Ireland, Galway, Ireland.

Abstract

Background:

In recent years methamphetamine (MA) has become a popular drug of abuse among women of childbearing age and hence MA abuse in pregnant women is becoming an increasingly prevalent issue[1]. Despite its widespread use, studies examining MA effects on the developing offspring are limited.

Aim:

Thus, the aim of this study was to determine if *in utero* MA exposure in rats at pharmacological doses can have a negative impact on neonatal neurodevelopment and behaviour.

Methods:

Pregnant Sprague-Dawley dams (n=6-10dams/group) received MA (0.625, 1.25, 2.5, 5 or 10mg/kg) or control (distilled water) once daily via oral gavage from gestational day 7-21. A range of standard neurodevelopment parameters were examined in the neonatal period. Data was analysed using Repeated-Measures ANOVA and Two-way ANOVA or Friedman's ANOVA and Kruskal-Wallis, with relevant *post-hoc* tests.

Results:

MA exposure *in utero* significantly decreased the total body weight gain during the dosing period in the 5 and 10mg/kg MA-exposed, compared to controls. The incidences of stillborns, filial death or cannibalism increased with increasing dose of MA. There were no neurodevelopmental deficits observed with offspring exposed to the 0.625 or 1.25mg/kg MA doses. However, exposure to the 2.5mg/kg MA dose resulted in a significant reduction in ano-genital distance in males, and in both sexes resulted in delayed fur appearance and eye opening, impairments in surface righting reflex and a reduction in body length.

Conclusions:

By using pharmacologically relevant doses, this study demonstrates that MA can have a profound dose-related effect on maternal and neonatal outcome. If extrapolated to the clinical scenario this will give cause for concern regarding the risks associated with this drug of abuse at relatively low doses.

Acknowledgments:

This project was supported by a PhD fellowship awarded by the College of Medicine, NUI, Galway.

1. National Advisory Committee on Drugs (NACD) & Public Health Information and Research Branch (PHIRB) 2008, Ballsbridge, Dublin 4 & Stormont, Belfast.

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NCBES Galway Neuroscience Centre's Annual Research Day 2013

Title
Increased Endoplasmic Reticulum Stress Signalling in White Matter Development in the Rat Cerebellum

Authors

M. Naughton; J. McMahon; U. Fitzgerald

Affiliations
Multiple Sclerosis & Stroke Research Group, Galway Neuroscience Centre, NCBES, National University of Ireland, Galway.

Abstract

Background:
Myelinating oligodendrocytes dramatically expand their cell membrane to ensheath multiple axons simultaneously. Membranous proteins and lipids are primarily synthesised in the endoplasmic reticulum which, when placed under stress, may trigger the Unfolded Protein Response (UPR) in order to increase its capacity.

Aim:
To assess the activation status of the UPR in developing white matter tracts.

Methods:
FFPE cerebella from Sprague-Dawley rats at postnatal days 7, 10, 14, 17 and adult (n
Chromogenic immunohistochemistry was used to characterise myelin development and ER stress. Numbers of positive cells per mm^2 for activated ER stress sensors (pIRE1, ATF6, pPERK) and their associated targets were calculated from randomised and blinded images of developing tracts in lobules III and IV.

Results:
Although expression of pPERK and associated molecules (peIF2alpha, CHOP) were negligible, nuclear ATF6 (active) increased at P10 (vs P17 and adult, $p<0.01$), and pIRE1 expression peaked at P14 (vs P7 and adult, $p<0.01$). Targets of the UPR including the potent transcription factor XBP1, ER chaperone GRP94 and folding enzyme PDI, were also significantly upregulated in this active period of myelination.

Conclusions:
ATF6 and pIRE1-mediated signalling is upregulated in a time-course that corresponds with early stages of myelination. In agreement with Lin et al[1], PERK signalling is not activated. For the first time we show the UPR during developmental myelination. This data may be relevant to understand mechanisms underlying remyelination in disorders such as multiple sclerosis.

Acknowledgments:
Grant support from the Health Research Board and MS Ireland (MRCG/2011/21) is gratefully acknowledged. Dr. McMahon is supported by the NUIG Foundation Office.

References:

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Title Biofunctionalization of Electrically Conducting Polymers

Authors
Catalina Vallejo-Giraldo[1], Abhay Pandit[1] Manus Jonathan Paul Biggs[1]

Affiliations
Network of Excellence for Functional Biomaterials (NFB), National University of Ireland, Galway

Abstract

Background:
During the last decade, evidence has emerged that following implantation of a recording or stimulating neural electrode, glial scar formation at the electrode–tissue interface accelerates neural loss and increases electrical signal impedance, compromising the efficiency of the stimulating system. Studies with conducting polymers as electrode coatings have shown enhanced tissue integration and electrode performance **in situ** through biochemical and physicomechanical functionalization

Aim:
We have developed a method for depositing a conducting polymeric Poly(3,4ethylenedioxythiophene):poly(styrenesulfonate) (PEDOT:PSS) coating onto the electrode surface which can be topographical modified to regulate cellular adhesion in vitro

Methods:
PEDOT:PSS polymeric films were electrodeposited via a three-electrode electrocell system and characterized by four point probe analysis and EIS (conductivity), AFM (roughness), SEM (morphology), and profilometry (thickness). Finally the cytocompatibility of the PEDOT:PSS films was evaluated by culturing SH-5YSY cells on electrodeposited PEDOT:PSS films.

Results:
PEDOT:PSS polymeric films demonstrated altered roughness and conducting profiles by altering the current density of film deposition. Furthermore, preliminary cellular studies show that SH-SY5Y cells, are associated with a greater viability and proliferation rate on smooth PEDOT:PSS polymeric films relative to rough.

Conclusions:
Topographical and morphological characterization showed that different levels of roughness can be obtained by varying the currents used for electrochemical deposition. Live/Dead assessment of SH-SY5Y cells demonstrated that cell adhesion and viability is higher on smoother surface PEDOT:PSS films.

Acknowledgments:
This work was funded through SFI. Thanks to Dr. Donal Leech and the Biomolecular Electronics Research Laboratory, Ms. Sarah Burke for aiding with the experimental set-up and Dr. Leo Quinlan

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Evaluating and comparing the effectiveness of Sonas and Cognitive Stimulation Therapy (CST) on Cognition, Quality of life, Activities of Daily Living (ADL's), Communication, Neuropsychiatric symptoms and Occupational Performance within a group session in older adults with Dementia.

Brady. Orla[1,4], O Halloran. Joanne[2], Rafiq. Atiqa[3], O Cuill. Micheal[5], Shiel. Agnes[4]

1 Senior Occupational Therapist, HSE, Psychiatry of Later Life, St. Loman's Hospital, Mullingar, Co Westmeath, Ireland.
2 Clinical Psychologist, Department of Psychology, National University of Ireland, Co Galway, Ireland.
3 Senior Registrar, HSE, Our lady of Lourdes Hospital, Navan, Co Meath, Ireland.
4 Discipline of Occupational Therapy, National University of Ireland, Galway, Ireland.
5 Consultant Psychiatrist in Old Age Psychiatry, HSE, Psychiatry of Later Life, St. Loman's Hospital, Mullingar, Co Westmeath, Ireland.

Abstract

Background
This study describes a comparison of two interventions used with people with dementia. Sonas is a therapeutic communication activity where group sessions involve cognitive, sensory and social stimulation (Sonas aPc 2011). Cognitive Stimulation Therapy (CST) is a is a non-invasive psychological intervention also for dementia; group sessions focuses on the improvement and strengthening of spare cognitive resources as well as the maintenance of social and interaction skills (Spector et al, 2003).

Aim:
To evaluate and compare the use of Sonas and CST in a Psychiatry of Later Life setting in patients' with moderate level of cognitive impairment secondary to Dementia.

Methods:
A single blind randomised controlled trial was carried out to compare the effectiveness of Sonas and CST. Subjects were recruited from an inpatient psychiatric facility, a nursing home and the community. Groups within these categories were randomly allocated to one of two conditions: CST and Sonas. Outcome measures assess QOL, Cognition, Mood, Activities of Daily Living (ADL), Communication, Neuropsychiatric symptoms and Occupational Performance within a group.

Results:
The preliminary results indicate that there is a positive statistically significant difference change in both groups on the SMMSE, the OTTOS and the QOL-AD. The CST group only showed improvements on the Holden Communication Scale. No changes in ADL's.

Conclusions:
Preliminary analysis suggests that change was demonstrated in both groups in the areas of Cognition, Occupational performance within a group and QOL demonstrating their effectiveness. In terms of communication the CST group only demonstrated improvements; suggesting that CST may be a more effective intervention for this client group.

Acknowledgments:
HSE Staff, Psychiatry of Later Life, Midlands

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Title

6-Hydroxydopamine Treatment Models Parkinson's Disease in Zebrafish.

Authors
Aileen Cronin, Miriam Moriarty, Elke Rink, Maura Grealy

Affiliations

Abstract

Background:
Parkinson's disease is a debilitating disease caused by degeneration of dopaminergic neurons. The disease is linked to both environmental insults and genetic mutations. The introduction of L-DOPA in the 1960's has revolutionised the treatment of Parkinson's disease and is currently the most effective symptomatic therapy available. Recently, effects on both canonical and non-canonical Wnt pathways have been demonstrated.

Aim:
To develop a 6-hydroxdopamine (6-OHDA) model of Parkinson's disease in Zebrafish and to assess the effects on locomotor activity, dopaminergic neuronal expression and Wnt signalling. Further investigation will aim to assess the neuroprotective effects of Levodopa (L-DOPA).

Methods:
Zebrafish embryos were exposed to 250 µM of the toxin 6-hydroxydopamine (6-OHDA) from 2 to 5 days post fertilization (dpf). Effects on dopaminergic neurons were assessed by immunohistochemistry, locomotor activity was assessed by Daniovision®, and effects on gene expression by quantitative RTPCR (qRTPCR) at 5 dpf. The effect of L-DOPA on locomotor activity, dopaminergic neurons and gene expression are currently being assessed.

Results:
Treatment with 6-OHDA caused a major loss of dopaminergic neurons by 5 dpf. Locomotor activity was decreased in the treated larvae ($P<0.001$). Expression of both Wnt 1 and Wnt 5b were reduced following treatment with 6-OHDA. Results of the effects of L-DOPA will be discussed.

Conclusions:
These findings confirm the zebrafish as a useful model for the study of Parkinson's disease.

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Title

THE EFFECTS OF REPEATED INTERFERON-ALPHA ADMINISTRATION ON DEPRESSIVE-LIKE AND NOCICEPTIVE BEHAVIOUR IN TWO DIFFERENT MOUSE STRAINS

Authors

Fitzgibbon M[1, 3], Burke N.N.[1, 3], Finn D.P.[2, 3], Roche M.[1, 3]

Affiliations

[1]Physiology, [2]Pharmacology and Therapeutics, School of Medicine, [2]NCBES Galway Neuroscience Cluster and Centre for Pain Research, National University of Ireland, Galway, Ireland.

Abstract

Background:

Interferon-alpha (IFN-α) is a pro-inflammatory cytokine commonly used to treat various cancers and infections. However, use of this treatment strategy is associated with depression in up to 60% of patients (1) and a higher incidence of painful symptoms such as headache and joint pain (2).

Aim:

This study investigated the effect of repeated IFN-α administration on depressive-like behaviour and nociceptive responding in two genetically different mouse strains.

Methods:

Male C57BL/6J (C57) and CD1 mice were administered hIFN-α (Roferon-A: 400 or 800 IU/g s.c.) or saline vehicle once daily for 23 days. Body weight and locomotor activity were assessed throughout the study. Depressive-like behaviour was assessed in the tail suspension and forced swim tests. Thermal and inflammatory nociceptive responding was assessed using the hot plate and formalin tests respectively. Data were analysed by one-way or repeated measures ANOVA followed by Dunnetts post-hoc test. $P<0.05$ was deemed significant.

Results:

Repeated IFN-α administration did not alter body weight or locomotor activity of C57 or CD1 mice. Immobility in the tail suspension test was slightly increased in IFN-α-treated C57 mice after 7 days, although this failed to reach statistical significance. IFN-α administration did not alter immobility time in the forced swim test of either strain of mice. Latency to respond in the hot plate test was reduced in a dose-dependent manner in IFN-α-treated C57 mice, an effect not observed in CD1 mice. Formalin-induced inflammatory pain behaviour was not altered by repeated IFN-α treatment in either strain of mice.

Conclusions:

In summary, repeated IFN-α administration did not induce depressive-like behaviour but enhanced nociceptive responding to a thermal stimulus in C57 mice. Thus, depending on genetic background, repeated IFN-α treatment may alter nociceptive processing prior to, or in the absence of, alterations in emotional behaviour.

Acknowledgments:

Funding from Molecular Medicine Ireland Clinical & Translational Research Scholars Programme is acknowledged.

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Iron Loading in Brain Slices: development of a novel *in vitro* platform to assess the impact of an iron-loaded environment in Multiple Sclerosis (MS)

Authors
Sinead Healy, Michelle Naughton, Jill McMahon, Una FitzGerald

Affiliations
Galway Neuroscience Centre, NCBES, NUI Galway

Abstract

Background:
Iron is known to accumulate in the brain of MS patients, but its role in disease remains unclear. Clarification of how brain iron is regulated could reveal a role for iron in MS progression[1-3].

Aim:
To develop an organotypic hippocampal slice model of iron loading in the brain.

Methods:
Organotypic hippocampal slices derived from postnatal P10/P11 rats were cultured for 10 days before being exposed to iron[4]. Endogenous iron content was also assessed in non-cultured postnatal hippocampus (P8-45; n=3-5.) Iron levels were quantified using a ferrozine colorimetric assay[5] and viability of cells assessed using a LDH assay.

Results:
For the first time in organotypic brain slices, we demonstrate that treatment with 10 μM ferrous ammonium sulfate (12 hr) produces a 1.7-fold increase in iron content when compared with vehicle (8.4±0.2 versus 4.9±0.7 nmol/mg; $p<0.05$) without affecting viability. Similarly, 10 μM ferrocene exposure under serum free conditions produced a 1.7-fold increase without affecting toxicity ($p<0.05$). Encouragingly, levels of iron detected in cultured hippocampal slices were similar to those in the equivalent non-cultured hippocampus
The amount of iron detected was highest at P08 (13.6±1.3 nmol/mg), declined sharply at P10/P11 (5.5±0.8 nmol/mg) before a transient peak at P14 (12.5±2.8 nmol/mg) and a final levelling off during the third postnatal week (6.0±1.0 nmol/mg). There was no difference in iron content from the fourth postnatal week onwards (6.0±0.9 nmol/mg at P21). There were also regional variations in iron content in P10/11 brain.

Conclusions:
This slice model of iron loading appears to be a promising platform for the study of iron regulation in MS.

Acknowledgments:
This work is kindly supported by a College of Science Fellowship and the Foundation Office of NUIG.

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Central inhibition of fatty acid amide hydrolase attenuates TLR-3 induced expression of interferon-gamma and related genes in the rat hippocampus

R. Henry[1,3], D. Kerr[1,2,3*], D. P. Finn[2,3], M. Roche[1,3]

[1]Physiology and [2]Pharmacology and Therapeutics, School of Medicine, [3]NCBES Centre for Pain Research and Galway Neuroscience Centre, National University of Ireland, Galway, Ireland.

Background: Interferon gamma (IFNγ) is considered to play a major role in the pathogenesis of several neurological disorders (1). Exogenous and endogenous cannabinoids (endocannabinoids) regulate IFNγ expression and/or signalling (2). However, the extent to which the brain's endocannabinoid system modulates expression of IFNγ and related genes under conditions of acute neuroinflammation remains unknown.

Aim: This study examined the effects of enhancing brain endocannabinoid tone using a selective inhibitor of fatty acid amide hydrolase (FAAH), on expression of IFNγ and related genes in the rat hippocampus following toll-like receptor (TLR)-3 stimulation.

Methods: Male Sprague Dawley rats (n=6-9 per group) received the FAAH inhibitor, URB597 (50µg, in 100% DMSO), or vehicle, i.c.v. at an infusion rate of 5µl/minute, 30 minutes prior to systemic administration of the TLR-3 agonist polyinosinic:polycytidylic acid (polyI:C:. 3mg/kg, i.p.) or sterile saline. Animals were sacrificed at 4 or 8 hours post polyI:C challenge, the hippocampus dissected out and snap-frozen. The expression of IL-12, IFNγ, iNOS, IFNγ-inducible protein 10 (IP-10), and IL-10 were determined using qRT-PCR. Concentrations of the endocannabinoids, anandamide and 2-AG, and related fatty acid ethanolamines, OEA and PEA were determined using LC-MS-MS. Data were analyzed using a 2-way ANOVA followed by Fisher's LSD post-hoc test. $P < 0.05$ was deemed significant.

Results: URB597 did not alter anandamide or 2-AG levels but significantly increased OEA and PEA concentrations at both 4 and 8 hours post polyI:C administration. PolyI:C increased expression of IFNγ, iNOS, IP-10 and IL-10 at 4 hours and iNOS, IP-10 and IL-10 at 8 hours. URB597 attenuated the polyI:C-induced expression of IFN-γ and IP-10 at 4 hours but did not alter the expression of IL-12, iNOS or IL-10 at either of the time points examined.

Conclusions: This study demonstrates that enhancing levels of FAAH substrates, namely OEA and PEA directly within the brain attenuates the expression of IFNγ and related genes in the hippocampus following TLR-3 activation.

Acknowledgments: Funding provided by Science Foundation Ireland Research Frontiers Project (Grant no. 11/RFP/NES/3175).

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Title

Assessment of a Fibrin Scaffold for Delivery of GDNF-Overexpressing Mesenchymal Stem Cells to the Rat Brain

Authors

C. Ryan[1], D.B. Hoban[1], M. Ni Fhlathartaigh[1], A. Pandit[2], E. Dowd[1]

Affiliations

[1]Department of Pharmacology & Therapeutics, NUI Galway.
[2]Network of Excellence for Functional Biomaterials, NUI Galway

Abstract

Background: The most effective experimental neuroprotectant for Parkinson's disease identified to date from extensive preclinical studies is the neurotrophin, glial cell line-derived neurotrophic factor (GDNF). However, its efficacy in clinical trials has been hampered by issues related to its delivery. A possible alternative approach for GDNF delivery is through *ex vivo* gene therapy, in which suitable cells, such as bone marrow-derived mesenchymal stem cells (MSCs), are genetically engineered to overexpress the neurotrophin prior to transplantation. However, MSCs delivered to the CNS typically exhibit poor survival post transplantation, accompanied by microglial activation and astrocyte recruitment at the graft site(1, 2).

Aim: In this study, the suitability of a fibrin scaffold was evaluated as a support matrix for the delivery of GDNF-overexpressing MSCs (GDNF-MSCs) to the rat brain.

Methods: 32 adult male Sprague Dawley rats were separated into 4 groups and received 30,000 GDNF-MSCs in transplantation medium, or in a fibrin matrix composed of 15, 30, or 60 mg/ml of fibrinogen (all with 4 I.U. of thrombin). Rats were sacrificed (for immunohistochemical analysis for graft survival, GDNF release, microglia, astrocytes and fibrin) at days 1, 4, 7 or 14 post-transplantation.

Results: This study demonstrated that the fibrin matrix did not affect GDNF-MSC survival or impede the release of GDNF into surrounding striatal tissue. This study also showed that encapsulation of GDNF-MSCs in a fibrin matrix did not trigger a significant immune response by the host brain.

Conclusions: In conclusion, fibrin was shown to be a well-tolerated cell delivery scaffold, however further investigation is necessary for the optimisation of scaffold composition and/or its functionalization, in order to increase cell survival, and hence enhance GDNF release in the brain in the long-term.

Acknowledgments: This work was funded by Science Foundation Ireland.

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NCBES Galway Neuroscience Centre's Annual Research Day 2013

Title: Endoplasmic reticulum Stress molecules: XBP1 and pIRE1 as Potential Novel Markers of Cerebellar Striping.

Authors: A. Hoban[1,2], M. Naughton[1], J. McMahon[1], U. FitzGerald[1]
[1]Galway Neuroscience Centre, NCBES, NUIG, Galway, Ireland
[2]Galway Neuroscience Centre, Pharmacology and Therapeutics, NUIG, Galway, Ireland

Affiliations : NCBES Galway Neuroscience Centre, Galway

Abstract

Background:
Many components of the adult cerebellum are organised into parasagittal stripes, exemplified by alternating zebrin II expression in the Purkinje cell population. The endoplasmic reticulum (ER) is an organelle that is the site of synthesis for secretory and membrane proteins. When the ER's capacity becomes overwhelmed, a signalling cascade known as ER stress or the unfolded protein response (UPR) is activated. ER stress/UPR can occur under both physiological and pathological conditions.

Aim:
The aim of this study is to map the distribution of ER stress proteins in the normal rat cerebellum and to uncover any particular pattern of expression.

Methods:
Immunohistochemisrey was carried out on 7 adult rat cerebelli which were sectioned transversely and 220 sections stained for zebrin II and 11 different ER-stress proteins. These included chaperones (BiP, ORP150, GRP94, calreticulin), folding enzymes (PDI), transcription factors (XBP1, ATF6, CHOP) and proteins that became activated upon phosphorylation (p-PERK, p-eif2α, p-IRE1). Following this whole-mount immunohiostochemistry was carried out in order to examine three-dimensional patterns of expression. Serial sections were stained with XBP1 and pIRE1 and examined for symmetry within the Purkinje cell population.

Results:
We have demonstrated that pIRE1 and XBP1 show heterogeneous immunoreactivity, possibly in a striping configuration, suggesting these markers are normally expressed in subsets of Purkinje cells.

Conclusions:
The mapping of expression of markers of ER stress has not previously been reported in normal adult rat cerebellum. Our data suggests that pIRE1 and XBP1 could have a role in normal cerebellar function.

Acknowledgments:

The Foundation Office of NUIG.

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Title

ENHANCED NEUROINFLAMMATORY RESPONSE TO TLR4 ACTIVATION IN THE VALPROIC ACID RAT MODEL OF AUTISM

Authors

Kerr D.M.[1,2,3], Finn D.P.[2,3] and Roche M.[1,3]

Affiliations

[1]Physiology and [2]Pharmacology and Therapeutics, School of Medicine, [3]NCBES Centre for Pain Research and Galway Neuroscience Centre, National University of Ireland, Galway, Ireland.

Abstract

Background:

Autism is a neurodevelopmental disorder characterised by impairment in social interaction, deficits in communications and stereotyped patterns of behaviour. Neuoinflammatory processes have been proposed to may be involved in the pathophysiology of this disorder and autistic patients have altered response to immune stimulation[1,2] This study investigated the expression of neuroinflammatory mediators in the absence and present of TLR-4 activation, in discrete brain regions in the valproic acid (VPA) rat model of autism[3].

Methods:

Pregnant female Sprague Dawley rats received VPA (600mg/kg s.c.) or saline on gestational day G12.5. On postnatal day 46, animals were administered LPS (100µg/kg i.p.) or saline and 2hrs later animals were sacrificed, the cortex, hippocampus and cerebellum dissected out, snap frozen and stored at -80^{o}C. Quantitative RT-PCR was used to assess the mRNA expression of immune mediators in the different brain regions. Data were analysed using unpaired t-test or Mann-Whitney U test. $P<0.05$ was deemed significant

Results:

The expression of CCL5 in the cortex and GFAP in the hippocampus was increased and decreased respectively in VPA-exposed rats when compared to controls. LPS increased the expression of the inflammatory cytokines IL-1β, TNFα, IL-6, IL-10 and CCL2 in the cortex, hippocampus and cerebellum of saline- and VPA-exposed animals. LPS-induced IL-1β and CCL2 expression in the cortex, TNF-α expression in the hippocampus and GFAP and IL-1β expression in the cerebellum were significantly augmented in VPA-exposed animals when compared with controls

Conclusion:

The data demonstrates that prenatal VPA exposure results in a heightened neuroinflammatory response to TLR-4 activation during adolescence, mimicking inflammatory responses reported in autistic children.

Acknowledgments:

Funding received from discipline of Physiology and Pharmacology and Therapeutics NUI Galway.

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NCBES Galway Neuroscience Centre's Annual Research Day 2013

Title

CORTICAL EXPRESSION OF MICROTUBULAR AND SYNAPTIC PROTEINS IS REDUCED IN THE OLFACTORY BULBECTOMISED MOUSE MODEL OF DEPRESSION

Authors

N. Ladurelle[1], M. Bianchi[2], M. Roche[3]

Affiliations

[1]INSERM U788, Le Kremlin-Bicêtre, France, [2]MAPREG, Le Kremlin-Bicêtre, France, [3]Physiology, NCBES Galway Neuroscience Centre and Centre for Pain Research, National University of Ireland Galway, Ireland

Abstract

Background:

Microtubules are fundamental in the maintenance and remodeling of axons, dendrites and dentritic spines and changes in neuronal microtubule dynamics play a role in the pathogenesis and treatment of depression[1]. This study examined the expression of markers of microtubule dynamics in the olfactory bulbectomised (OB) rodent model of depression.

Methods:

Bilateral OB or sham surgery was carried out on male C57Bl6J mice. Behaviour was assessed in the open field (OF), elevated plus maze (EPM), forced swim test (FST) and tail suspension test (TST) following a 2-week recovery period. Twenty-four hours following behavioural assessment animals were sacrificed, the frontal cortex dissected and stored at -80°C until analysis. Alpha-tubulin isoforms [Tyr-Tub; Glu-Tub; Δ2-Tub and Acet-Tub], total tubulin (TOT-Tub), total MAP2 and phosphorylated MAP2 (p-MAP2) and the synaptic proteins, synaptophysin, postsynaptic density-95 (PSD-95) and spinophilin were determined using infrared western blotting. Data were analysed using unpaired t-test, $P<0.05$ was deemed significant

Results:

OB mice exhibited increased distance moved in the OF and EPM and more time on the open arms of the EPM compared to sham-counterparts. The duration of immobility in the FST and TST did not differ between groups. Protein levels of the neuronal specific tubulin Δ2-Tub, total MAP2 and p-MAP2 in the frontal cortex were reduced in OB mice compared to sham-counterparts. There was no effect of OB on other alpha-tubulin isoforms. Finally, the expression of synaptophysin and spinophilin, but not PSD-95, was reduced in the frontal cortex of OB mice compared to sham counterparts.

Conclusion:

OB mice exhibit alterations in neuronal microtubule dynamics accompanied by reduced expression of synaptic proteins within the frontal cortex, effects which may underlie the behavioural changes observed.

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NCBES Galway Neuroscience Centre's Annual Research Day 2013

Title: Induction of neural stem cells directly from control and amyotrophic lateral sclerosis (ALS) patient fibroblasts.

Authors: Martin Madill, Sanbing Shen.

Affiliations: REMEDI

Abstract

Background: Somatic cellular reprogramming is one of the most important developments in stem cell biology in recent years. Induced pluripotent stem cells (iPSCs) enable the generation of any cell type, allowing investigations into many disorders and offer a potential source of cells for cellular therapies. More recent advances have focused on the direct induction of specific cell types, including neurons and neural stem cells (1,2). Herein we aim to reprogram healthy and amyotrophic lateral sclerosis (ALS) patient fibroblasts directly into neural stem cells (NSCs).

Aim: To directly induce a neural stem cell fate from control and ALS patient fibroblasts.

Methods: pMXs-vector based retroviruses encoding the following transcription factors were generated in Phoenix cells; OCT4, KLF4, SOX2, C-MYC, LIN28A, IGF2, RARB Δ384, BRN2, FOXG1 and GFP. p53shRNA and NESTIN-GFP lentiviruses were generated in HEK293T cells. Human dermal fibroblasts were transduced with various cocktails of transcription factors and maintained in NSC promoting culture conditions. Neural stem cell phenotype was assessed by immunocytochemistry, RT-PCR and Western blotting.

Results: Cells transduced with OCT4, KLF4, SOX2 and C-MYC underwent sphere formation and subsequently developed NSC-like morphology in monolayer culture. Immunocytochemistry showed these cells to be Nestin positive, indicative of a neural stem cell phenotype. RT-PCR showed upregulation of NSC specific markers, in addition to the down regulation of COL1A1, a fibroblast specific marker. Expression of NANOG, a marker of pluripotency, was not detected by immunocytochemistry or RT-PCR.

Conclusions: These methodologies allow the generation of neural stem cells from fibroblasts more rapidly and simply than via iPSCs. Further analyses will be needed to assess their capabilities for tri-lineage differentiation.

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Title

TRPV1 mRNA expression within the brain of two rat strains differing in nociceptive -responsivity.

Authors

Manish K. Madasu [1,3]; Bright Okine [1, 3]; Weredeselam M. Olango [1, 3]; Michelle Roche [2, 3]; David P. Finn[1, 3.]

Affiliations

1. Pharmacology and Therapeutics; 2. Physiology, School of Medicine; 3. Galway Neuroscience Centre and Centre for Pain Research, NCBES, National University of Ireland, University Road, Galway, Ireland.

Abstract

Background:

The Wistar-Kyoto (WKY) rat is a stress-hyperresponsive strain that exhibits a hyperalgesic phenotype, compared with the Sprague-Dawley (SD) strain[1]. The role of the transient receptor potential vanilloid receptor 1 (TRPV1) in peripheral and central pain processing is well established[2].

Aim:

The aim of the present study was to complete a comparative analysis of TRPV1 mRNA expression within the brain of WKY and SD rats that had received intra-plantar injection of either saline or formalin.

Methods:

Adult male WKY or SD rats received intra-plantar injection of either saline (SAL) or formalin (FORM) under brief anaesthesia and nociceptive behaviour assessed for 30 minutes to generate composite pain scores (CPS). Rats were killed at the end of the formalin trial period and total RNA was extracted from frozen punches of periaqueductal grey (PAG), rostroventromedial medulla (RVM), hippocampus (HIPP), amygdala (BLA) and prefrontal cortex (PFC). qRT-PCR was used to determine the expression of mRNA coding for TRPV1. Data were analysed by two-way ANOVA followed by Fisher's LSD post-hoc test.

Results:

WKY rats exhibited significantly higher formalin-evoked nociceptive behaviour than SD counterparts, indicating a hyperalgesic phenotype. TRPV1 mRNA levels were significantly higher in the dorsal PAG, lower in the lateral PAG and no significant differences in the ventrolateral PAG of saline-treated SD rats compared with WKY counterparts. Formalin treatment was associated with reduced TRPV1 mRNA expression in the dorsal PAG and increased TRPV1 mRNA expression in the ventral PAG of SD rats only. Formalin administration was associated with significant reductions in TRPV1 mRNA expression in the PFC and ventral hippocampus of SD rats only and in the BLA of both WKY and SD rats.

Conclusions:

These data provide evidence for rapid, dynamic formalin-evoked alterations in TRPV1 gene expression in pain-related brain regions of SD and WKY rats.

Acknowledgments:

This work was funded by grants from Science Foundation Ireland (10/IN.1/B2976) and College of Science, National University of Ireland, Galway.

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NCBES Galway Neuroscience Centre's Annual Research Day 2013

Title
Benefitting Client, Family and Care Staff: Implementation of an Individualised Therapeutic Programme for a Long-Term Disorder of Consciousness Patient

Authors
Ann-Marie Morrissey and Prof. Agnes Shiel

Affiliations
Occupational Therapy, NUI Galway

Abstract

Background: More people are surviving severe brain injury with a disorder of consciousness (DoC) and long-term these clients are being cared for in residential community settings. These settings can lack specialist intervention, skills and resources to care for a client with DoC. This study explored the benefit of implementing a comprehensive therapeutic programme for a 55 year old women, diagnosed as being in a persistent vegetative state, nine years after her initial anoxic injury

Aims: 1). To evaluate the benefit of providing an intensive therapeutic programme on the (a) client, (b) client's family and (c) care staff in a residential community setting.
2). To evaluate the benefits and difficulties in providing such a programme in a non-specialist setting.

Method: A single subject approach was chosen due to the heterogeneity of this client population. A therapeutic programme was then administered over a six month period.

Results: Benefits to client, family and care staff were recorded. It was identified that the client was able to communicate yes/no responses reliably via a switch. This was nine years after her accident. Her care plan and daily treatment were altered as a result of this finding.

Conclusion: DoC clients may benefit from a specialist assessment and intervention long-term. This pilot study has highlighted the benefits to participant, family and care staff from the provision of an individualised therapeutic programme.

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Title Increased medial prefrontal activity during dynamic face processing in schizophrenia

Authors: Omar Mothersill[a, b], Derek W. Morris[a, b], Sinead Kelly[a, b], Emma Jane Rose[a, b, c], Ciara Fahey[a, b], Carol O'Brien[a, b], Ronan Lyne[a, b], Richard Reilly[b], Michael Gill[a, b], Aiden P. Corvin[a, b], Gary Donohoe[a, b, d]

Affiliations: a. Neuropsychiatric Genetics Group, Department of Psychiatry, Trinity College Dublin, Ireland.
b. Trinity College Institute for Neuroscience, Trinity College Dublin, Ireland.
c. Transdisciplinary Science and Translational Prevention Program (TSTPP), Research Triangle Institute International, Baltimore, Maryland, United States
d. School of Psychology, National University of Ireland, Galway, Ireland.

Abstract

Background: Processing the emotional content of faces is recognised as a key deficit of schizophrenia [1], associated with poorer functional outcomes [2] and possibly contributing to severity of clinical symptoms such as paranoia [3]. At a neural level, fMRI studies have reported altered limbic activation in response to faces [1, 4]. However, many studies may be limited by the use of cognitively demanding tasks and static facial stimuli [5, 6].

Aim: The current study used a face processing task that involved implicit face processing and dynamic stimuli to further characterise activation differences in emotional brain regions in schizophrenia patients compared to healthy controls.

Methods: We used fMRI to examine neural activity in 26 patients with a DSM-IV diagnosis of schizophrenia and 21 age- and gender-matched healthy controls, while they participated in a face-processing task designed by Grosbras and Paus [7], which involved viewing video clips of angry and neutral facial expressions.

Results: While viewing angry faces, schizophrenia patients showed significantly increased activation of the medial prefrontal cortex, an important brain region in emotion processing and regulation, compared to healthy controls ($p<0.05$, whole brain FWE-corrected at the cluster level).

Conclusions: Increased detection of threat may contribute to the development of paranoia. Further examination of the neurobiology of social cognition in schizophrenia using fMRI may help establish targets to probe effects of emerging treatments or help identify risk factors for illness, which may help in the development of prevention strategies.

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Title

Comparative assessment of the motor dysfunction induced by neurotoxic, inflammatory and environmental Parkinson's disease-related neurotoxins in rats

Authors

Carol Naughton, Deirdre Hoban, Ruth Concannon, Jennifer Feehan, Aoife McNulty, Niamh Moriarty, Deirdre Rooney and Eilís Dowd

Affiliations

Pharmacology & Therapeutics, Galway Neuroscience Centre, National Centre for Biomedical Engineering Science, NUI Galway.

Abstract

Background:

For almost 50 years, Parkinson's disease has been modelled in preclinical animals using selective catecholaminergic neurotoxins such as 6-hydroxydopamine and MPTP. However, because these models bear little etiological resemblance to the human condition, more recently, there has been a considerable drive to develop and characterise models with improved validity for the human condition. Two such models are those induced by the bacterial inflammagen, LPS, and the organic pesticide, rotenone. However, these models have been poorly characterised with respect to the more established models.

Aim:

Thus, the aim of this project was to characterise the motor impairments induced by LPS and rotenone with those induced by the classic neurotoxin, 6-hydroxydopamine.

Methods:

Twenty four male Sprague Dawley rats were used in this study. These underwent baseline testing on a variety of tests of lateralised motor function (the Stepping Test, the Whisker Test, the Corridor Test and the Cylinder Test). The rats were then divided into three performance-matched groups for unilateral intrastriatal infusion of 6-hydroxydopamine (28 □g, n=8), LPS (20 □
weeks. Rats were also tested for amphetamine-induced rotational asymmetry three weeks after lesion surgery.

Results:

Unilateral intra-striatal infusion of all three neurotoxins induced a significant impairment in contralateral motor function which was evident from the first day after lesion surgery. However, the impairment induced by 6-hydroxydopamine was significantly more pronounced and stable than that induced by the other neurotoxins. When the rats were tested for amphetamine-induced rotation (which is the classic test for dopaminergic asymmetry), it was found that the 6-hydroxydopamine and rotenone-lesioned rats rotated significantly in the ipsilateral direction, while LPS-lesioned rats did not rotate at all.

Conclusions:

This study demonstrates that there are key differences in the patterns of motor dysfunction induced by different Parkinsonian neurotoxins. These differences should be taken into consideration when selecting the most appropriate model for Parkinson's disease preclinical studies.

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Title

An Investigation of Global and Local Brain Network Structure in Bipolar Disorder

Authors

Stefani O'Donoghue[1,3,4], Natalie Forde, Louise Emsell, Camilla Langan, Cathy Scanlon[1,3], Dara Cannon[2,3] and Colm McDonald[1,3]

Affiliations

[1]Clinical Neuroimaging Laboratory, Departments of Psychiatry and [2]Anatomy, College of Medicine, Nursing and Health Sciences, Ireland and [3]Department of Electrical/Electronic Engineering, National University of Ireland Galway, Galway, Ireland, [3]NCBES Galway Neuroscience Center, National University of Ireland Galway, Galway Ireland. [4]Hardiman Research Scholarship

Abstract

Background: Symptoms of bipolar disorder suggest a disconnection in emotional regulation. Therefore, investigating the whole brain and fronto-limbic circuitry is of interest in this study. Network analysis is a novel technique used to identify global and local brain connection patterns[1].

Aim: This study aims to identify global and local brain network differences between patients with bipolar disorder and healthy controls using graph theory-based network analysis. This study will also examine more closely fronto- limbic sub-network structure based on previous research of white matter microstructure in this circuit[2].

Methods: Participants were recruited as part of the Galway Bipolar Study (44 Healthy Controls & 28 subjects with Bipolar Disorder). Diffusion MRI data was acquired on a 1.5 Tesla Scanner. Connectivity matrices were produced using ExploreDTI. Network metrics of integration (characteristic path length, degree, global efficiency) and segregation (clustering coefficient) were generated using the Brain Connectivity Toolbox (BCT) through MATLAB.

Results: Properties of integration and segregation revealed no between group differences at the global level. At the local level, subjects with bipolar disorder exhibited lower clustering coefficient relative to controls in the left anterior portion of the cingulum [F= 6.6, p= 0.012].

Conclusions: Clustering coefficient measures the density of connections between a brain region and its nearest neighbours[1]. While no global differences were found, reduced clustering coefficient of the cingulum may indicate disrupted network structure at the local level[3]. White matter disorganization of the cingulum has been reported in previous tractography findings[2]. Measures of integration and segregation provide a novel method of interpreting brain architecture.

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Title

ADMINISTRATION OF *N*-PALMITOYLETHANOLAMIDE DIRECTLY INTO THE MEDIAL PREFRONTAL CORTEX REDUCES FORMALIN-EVOKED NOCICEPTIVE BEHAVIOR IN RATS

Authors

Bright N Okine[1, 3], Kieran Rea [1.3] Brendan Harhen[3], Michelle Roche[2, 3] and David P. Finn[1, 3]

Affiliations

[1]Pharmacology and Therapeutics, [2]Physiology, School of Medicine, [3]Galway Neuroscience Centre and Centre for Pain Research, NCBES, National University of Ireland, University Road, Galway, Ireland

Abstract

Background: PEA is an endogenous agonist of the peroxisome proliferator-activated receptor (PPAR)-α and is widely distributed in the brain, including the medial prefrontal cortex (mPFC)[1], an area associated with affective and cognitive components of pain[2]. Numerous studies have reported antinociceptive effects of PEA in animal models of inflammatory and neuropathic pain[3-5], however the specific role of PEA within the mPFC in pain processing is unknown.

Aim: To determine the effects of intra-mPFC administration of PEA on formalin-evoked nociceptive behaviour and hindpaw oedema in rats.

Methods: Adult male Sprague-Dawley rats received intra-mPFC injections of PEA, PEA + GW6471 (PPAR-α antagonist), GW6471 alone, or vehicle via bilaterally implanted stainless steel guide cannulae, 10 minutes prior to intraplantar formalin (2.5%) injection. Nociceptive behaviour was assessed for 60 minutes and analysed using Ethovision XT software. Post-mortem brain tissues were harvested for histological verification of injection sites and measurement of levels of endogenous PPAR ligands by liquid chromatography-tandem mass spectrometry.

Results: Intra-mPFC administration of PEA significantly reduced formalin-evoked nociceptive behaviour in rats. The antinociceptive effects of PEA were not blocked by co-administration with the selective PPAR-α antagonist GW6471 which, alone, reduced nociceptive behaviour. Intra-mPFC PEA did not alter formalin-induced hindpaw oedema but did result in increased levels of PEA, and a trend for higher levels of AEA, in the mPFC

Conclusion: Exogeneous administration of PEA into mPFC reduces formalin-evoked nociceptive behaviour in rats, an effect which may not be mediated by PPAR-α. Further studies are required to characterise the receptor mechanisms involved.

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