

Designação do Projeto	EPIRaft - Contribution of neuronal membrane and lipid raft remodeling to the pathophysiology of mesial temporal lobe epilepsy (MTLE): insight into the beneficial effects of the ketogenic diet therapy. FCT 02/SAICT/2017; LISBOA-01-0145-FEDER-028311.
Código do Projeto	
Objetivo Principal	Study the contribution of changes synaptic lipid domains to the pathophysiological changes in synaptic plasticity and cognition in mesial temporal lobe epilepsy.
Região de Intervenção	Lisboa e Norte
Entidade Beneficiária	FCiências.ID – Associação para a Investigação e Desenvolvimento de Ciências
Data de Aprovação	2 de maio de 2018
Data de Início	1 de julho de 2018
Data de Conclusão	30 de junho de 2021
Custo Total Elegível	236 512,18€
Apoio Financeiro da União Europeia	FEDER – 107 733,16€
Apoio Financeiro Público Nacional/ Regional	OE – 128 778,56€

Objetivos

Estudar a contribuição das alterações nos domínios lipídicos sinápticos para as alterações na plasticidade sináptica na epilepsia do lobo temporal mesial (*do inglês*, MTLE). Avaliar os efeitos da dieta cetogénica nestas alterações.

Atividades

Utilização de animais modelo de MTLE para avaliar as alterações lipídicas e alterações nos domínios lipídicos em terminais nervosos isolados.

Determinar o grau de peroxidação lipídica nestas preparações.

Estender estes estudos a membranas/sinaptossomas obtidas de tecido obtido das cirurgias de ressecção de doentes com MTLE.



Resultados Esperados / Atingidos

Alterações na composição lipídica causadas por neurogénese e peroxidação lipídica em modelos de epilepsia in vivo e in vitro.

Alterações na presença e dinâmica de jangadas planares e caveolas em modelos de epilepsia in vivo e in vitro.

Recuperação dos danos lipídicos (peroxidação, alteração na composição e dinâmica de jangadas) com a dieta cetogénica.

Publicações:

Published full papers:

1. ***Cunha-Reis D**, Vaz SH and Correia-de-Sá P (2023) Editorial: Cellular and molecular targets in epileptogenesis focusing on disease prevention *Front Cell Neurosci.*, 17: 1251038. doi: 10.3389/fncel.2023.1251038. (IF: 5,3; **Q1**, Times cited**: 0)
2. Carvalho-Rosa JD, Rodrigues NC, Silva-Cruz A, Vaz SH and ***Cunha-Reis D** (2023) Epileptiform activity influences theta-burst induced LTP in the adult hippocampus: a role for synaptic lipid raft disruption in early metaplasticity? *Front Cell Neurosci.*, 17:1117697. doi: 10.3389/fncel.2023.1117697. (IF: 5,3; **Q1**, Times cited**: 0)
3. Serpa, A.; Bento, M.; Pawlak, S.; Caulino-Rocha, A.; and ***Cunha-Reis, D.** (2022) Opposing reduced VPAC₁ and enhanced VPAC₂ VIP receptors in the hippocampus of the Li²⁺-pilocarpine rat model of temporal lobe epilepsy, *Neurochemistry International*, 158 (9), 105383 doi: 10.1016/j.neuint.2022.105383. PMID: 35787395 (IF: 4,297; **Q2**, Times cited**: 1).
4. Caulino-Rocha, A.; Rodrigues, N.C.; Ribeiro, J.A. and ***Cunha-Reis, D.** (2022) Endogenous VIP VPAC₁ receptor activation modulates theta burst induced LTP in the hippocampus: transduction pathways and GABAergic mechanisms, *Biology*, 11(5):627, doi: 10.3390/biology11050627. PMID: 35625355 (IF: 5,168; **Q1**, Times cited**: 2).
5. Rodrigues, N.C.; Silva-Cruz, A.; Caulino-Rocha, A.; Bento-Oliveira, A.; Ribeiro, J.A. and ***Cunha-Reis, D.** (2021) Hippocampal CA1 theta burst-induced LTP from weaning to adulthood: Cellular and molecular mechanisms in young male rats revisited, *Eur. J. Neurosci.* 54(4):5272-5292, doi: 10.1111/ejn.15390. PMID: 34251729 (IF: 3,39; **Q3**, Times cited**: 4).
6. ***Cunha-Reis, D.** and Caulino-Rocha, A. (2021) Corrigendum: VIP Modulation of Hippocampal Synaptic Plasticity: A Role for VIP Receptors as Therapeutic Targets in Cognitive Decline and Mesial Temporal Lobe Epilepsy. *Front Cell Neurosci.*, 15:691978. doi: 10.3389/fncel.2021.691978. PMID: 34054434 (IF: 6,147; **Q1**, Times cited**: 0).
7. ***Cunha-Reis, D.**; Caulino-Rocha, A. and Correia-de-Sá P (2021) VIPergic neuroprotection in epileptogenesis: challenges and opportunities, *Pharmacol. Res.*, 164:105356. (review) doi: 10.1016/j.phrs.2020.105356. PMID: 33338622 (IF: 10,334; **Q1**, Times cited**: 8).
8. ***Cunha-Reis, D.** and Caulino-Rocha, A. (2020) VIP modulation of hippocampal synaptic plasticity: a role for VIP receptors as therapeutic targets in cognitive decline and mesial temporal lobe epilepsy, *Front. Cell. Neurosci.*, 14:153. (review) doi: 10.3389/fncel.2020.00153. PMID: 32595454 (IF: 5,51; **Q1**, Times cited**: 10).

Book chapters:

Cunha-Reis, D. (2020) Zinco: Senhor zinco, proteja essas sinapses! In 'Os Elementos em Ciências - Uma viagem pela Tabela Periódica'. Ciências ULisboa. Eds. A. Mourato, AP Carvalho, F. Martins, T. Pamplona. ISBN: 978-972-9348-22-8.

Published abstracts of communications in proceedings of scientific meetings with referees:

1. (P) Bento M, Caulino-Rocha A, Gil M, and ***Cunha-Reis D** (2022) 'Postweaning development influences synaptic VPAC₁ and VPAC₂ receptor expression and the expression and phosphorylation of AMPA GluA1 and GluA2 subunits', *Proceedings of the 2nd International Meeting of the Portuguese Society of Physiology, Frontiers in Physiology, in the press.*
2. (C) ***Cunha-Reis D** (2022) 'Exploring the role of metaplasticity in synaptic function under physiological conditions and in animal models of aging and epilepsy using integrative approaches', *Proceedings of the 2nd International Meeting of the Portuguese Society of Physiology, Frontiers in Physiology, in the press.*
3. (C) Bento M, Serpa A, Caulino-Rocha, A, Pawlak S, and ***Cunha-Reis, D.** (2022) 'VPAC₁ and VPAC₂ receptors are oppositely altered in the Li²⁺-pilocarpine model of temporal lobe epilepsy', *Proceedings of the 2nd International Meeting of the Portuguese Society of Physiology, Frontiers in Physiology, in the press.*
4. (P) Gil M, Caulino-Rocha A, Vila-Verde B, Reis-Borges D, Nascimento C, and ***Cunha-Reis D** (2022) 'Altered synaptic physiology and impaired cognition, response to novelty and motor behavior in a rodent model of accelerated aging', *Proceedings of the Neuronus 2022 Meeting, Acta Neurobiologiae Experimentalis*, 82(Supp1): XCVI (IF: 1,269, Q4).
5. (P) Amat-Garcia L, Rodrigues NC, Carvalho-Rosa J, Silva I, and ***Cunha-Reis D** (2022) 'Profound alterations in hippocampal lipid rafts follow in vitro epileptiform activity, hypoxia and oxygen-glucose deprivation', *Proceedings of the Neuronus 2022 Meeting, Acta Neurobiologiae Experimentalis*, 82(Supp1):LII (IF: 1,269, Q4).
6. (P) Gil M, Bento M, Rodrigues NC, Silva-Cruz A and **Cunha-Reis D** (2022). Postweaning development shifts endogenous VPAC₁ modulation of LTP induced by theta-burst stimulation. *Proceedings of the meeting Europhysiology 2022 (Meeting of the Federation of the European Physiological Societies, 16-18th September 2022), Acta Physiologica*, 236 (S725), e13877, 795. doi: 10.1111/apha.13877 (IF: 7,523, Q1).
7. (C) Carvalho-Rosa J, Rodrigues NC, Silva-Cruz A and **Cunha-Reis D** (2021). Metaplasticity following brain hyperactivity and brief hypoxia: significance for endogenous neuroprotection *Simpósio Brasileiro-Ibérico de Fisiologia – 'Cellular and molecular pathways controlling homeostasis by the brain'*, *Proceedings of the 56th Annual Congress of SBFis (Sociedade Brasileira de Fisiologia, 14th October 2021). Biomed Biopharm Res.*, 18(2)265. doi: 10.19277/bbr.18.2.265. (No IF).
8. (C) **Cunha-Reis D** (2020) Mismatch Novelty Exploration Training Shaping of Hippocampal Synaptic Plasticity and Cognition and The Role of Disinhibition and VIP Expressing Interneurons. Invited plenary lecture at the 1^o Encontro Luso-Brasileiro de Fisiologia, *Proceedings of the 55th Annual Congress of SBFis (Sociedade Brasileira de Fisiologia, 3rd October 2020). Biomed Biopharm Res.*, 17(2):3. doi: 10.19277/bbr.17.2.243. (No IF).
9. (P) Caulino-Rocha A, Aidil-Carvalho F, Ribeiro JA, and **Cunha-Reis D** (2020) Influence of novelty exploration training on modulation of hippocampal synaptic plasticity by endogenous VIP acting on VPAC1 receptors. Communication to the 55th Annual Congress of SBFis (Sociedade Brasileira de Fisiologia). *Proceedings of the 55th Annual Congress of SBFis (Sociedade Brasileira de Fisiologia, 3rd October 2020). Biomed Biopharm Res.*, 17(2):198. doi: 10.19277/bbr.17.2.243. (No IF).
10. (P) Carvalho-Rosa J, **Cunha-Reis D** (2019). Endogenous VIP VPAC1 receptor activation during ictal and interictal-like activity induced *in vitro* by bicuculine and 0-Mg²⁺ modulates subsequent LTP expression in the rat hippocampus. *Front Cell Neurosci Conference Abstract: XVI Meeting of the Portuguese Society for Neuroscience (SPN2019)*. doi: 10.3389/conf.fncel.2019.01.00028. (IF: 3,92;

Q2).

11. (P) Vila-Verde B, Reis-Borges D, Nascimento C, **Cunha-Reis D** (2019). Impaired response to novelty and motor behavior in the D-Gal rat model of accelerated aging. *Front Cell Neurosci Conference Abstract: XVI Meeting of the Portuguese Society for Neuroscience (SPN2019)*. doi: 10.3389/conf.fncel.2019.01.00002. (IF: 3,92; Q2).

Teses:

December 2021 – José Diogo Carvalho Rosa, - 'Changes in synaptic plasticity, lipid raft composition in the hippocampus in different ages and gender, induced *in vitro* by epileptiform activity and neuroprotective role of VPAC₁ VIP receptor antagonists', MSc in Human Biology and Environment, DBA CIÊNCIAS, ULISBOA, <http://hdl.handle.net/10451/51710>. Co-supervisor Teresa Rebelo, DBA, CIÊNCIAS, ULISBOA.

November 2020 (internal supervision at Ciências, ULisboa) – Margarida Nóbrega Campos de Freitas Araújo, - 'Investigating the mechanisms of synaptic dysfunction in late-onset Alzheimer's disease', Mestrado em Biologia Molecular e Genética, DBV, CIÊNCIAS, ULISBOA (<http://hdl.handle.net/10451/48747>). Main supervisor Cláudia Guimas Almeida, CEDOC, UNL.

January 2019 – Andreia Bento de Oliveira - 'Changes in synaptic plasticity and lipid raft composition in a rat model of temporal lobe epilepsy'. MSc in Biochemistry, DQB CIÊNCIAS, ULISBOA (<http://hdl.handle.net/10451/37090>). Co-supervisor Rodrigo Almeida, DQB, CIÊNCIAS, ULISBOA.

Comunicações em congressos/encontros científicos:

Other communications to scientific societies:**- Viva voce communications:**

1. (C) Caulino-Rocha A, Gil M, Rodrigues NC, Ribeiro JA and **Cunha-Reis D** (2022) 'Postweaning development influences endogenous VPAC₁ modulation of LTP induced by theta-burst stimulation' Communication to the 52nd Reunion of The Portuguese Pharmacological Society, Porto, Portugal, 9th -11th February 2022.
2. (C) Carvalho-Rosa J, Rodrigues NC, Silva-Cruz A and **Cunha-Reis D** (2021) 'Metaplasticity following brain hyperactivity and brief hypoxia: significance for endogenous neuroprotection' - Invited lecture at Simpósio Brasileiro-Ibérico de Fisiologia – 'Cellular and molecular pathways controlling homeostasis by the brain', representing the Portuguese Society of Physiology held at the 56^o Congresso Annual da SBFis (Sociedade Brasileira de Fisiologia. 11th -14th October 2021. Online.

- Poster communications:

1. (P) Caulino-Rocha A, Aidil-Carvalho F, Ribeiro JA, and **Cunha-Reis D** (2020) Influence of novelty exploration training on modulation of hippocampal synaptic plasticity by endogenous VIP acting on VPAC₁ receptors. Communication to the 55th Annual Congress of SBFis (Sociedade Brasileira de Fisiologia). Proceedings of the 55th Annual Congress of SBFis (Sociedade Brasileira de Fisiologia, 3rd October 2020). *Biomed Biopharm Res.*, 17(2):198. doi: 10.19277/bbr.17.2.243. (No IF).
2. (P) Carvalho-Rosa J, Rodrigues NC, **Cunha-Reis D** (2020) VPAC₁ receptor activation by endogenous VIP during interictal-like activity induced *in vitro* by 0-Mg²⁺ influences subsequent LTP expression in the rat hippocampus. Communication to the 12th FENS Forum of European Neuroscience – Fens 2020, Glasgow, UK, 11th -15th July 2020. Online.
3. (P) Caulino-Rocha A, Rodrigues NC, Bento Oliveira A, Ribeiro JA, **Cunha-Reis D** (2020) Molecular pathways involved in VIP inhibition of LTP in the CA1 area of the hippocampus. Communication to the 12th FENS Forum of European Neuroscience – Fens 2020, Glasgow, UK, 11th -15th July 2020. Online.

4. (P) Carvalho-Rosa J, **Cunha-Reis D** (2019). Endogenous VIP VPAC1 receptor activation during ictal and interictal-like activity induced in vitro by bicuculine and 0-Mg²⁺ modulates subsequent LTP expression in the rat hippocampus. Communication to the XVI Meeting of the Portuguese Society for Neuroscience (SPN2019), May 30th – June 1st, Lisboa, Portugal.
5. (P) Vila-Verde B, Reis-Borges D, Nascimento C, **Cunha-Reis D** (2019). Impaired response to novelty and motor behaviour in the D-Gal rat model of accelerated aging. Communication to the XVI Meeting of the Portuguese Society for Neuroscience (SPN2019), May 30th – June 1st, Lisboa, Portugal.
6. (P) Bento-Oliveira A, Pereira P, Amaro Leal A, **Cunha Reis D** (2019) Evidence for altered lipid raft composition and synaptic plasticity in a rat model of MTLE. Communication to the *1st International Meeting of The Portuguese Society of Physiology - Physioma 2019*, Lisbon, Portugal, 10th -11th October 2019.

Outreach:

- 30th September 2022** – ‘*Epilepsia e pontos de encontro na membrana dos neurónios*’ – outreach activity for all ages at **Noite Europeia dos Investigadores 2022, MNHNAC, ULisboa**, presenting the Epilepsy and Aging Lab, diversity in research activities and CIÊNCIAS, ULISBOA’s Neuroscience Research.
- 4th May 2022** – ‘*Pontos de encontro na membrana dos neurónios*’ – outreach activity for high-school student visits at **CIÊNCIAS, ULISBOA Open Day**, presenting the department’s diversity in research activities and CIÊNCIAS, ULISBOA’s offer in BSc, MSc and PhD training.
- 30th March 2022** - Representing **Departamento de Química e Bioquímica**, Ciências, ULisboa in the **FUTURALIA** event, presenting the department’s offer in BSc, MSc and PhD training.
- February 2022 – March 2022** – **Organizer** and **participant** of the **Brain Awareness Week 2022** activities that have taken place from 14-20th March 2022 at **BioISI** – Biosystems and Integrative Sciences Institute, Ciências, ULisboa. Lectures and practical activities involved 6 BioISI researchers and collaborators in the fields of Biology, Biochemistry, Biomedical Engineering and Informatics. (<http://bioisi.pt/bioisi-hosted-a-high-school-students-visit-within-the-brain-awareness-week/>).
- 27th May 2019** - Representing **Departamento de Química e Bioquímica**, Ciências, ULisboa in the **1st Science Speed Dating** event, presenting her research interests to the department’s biochemistry students.
- 4th April 2019** - Representing **Departamento de Química e Bioquímica**, Ciências, ULisboa in the **FUTURALIA** event, presenting the department’s offer in BSc, MSc and PhD training.
- February 2019 – March 2019**– **Organizer** and **participant** of the **Brain Awareness Week 2019** activities that have taken place from 11-17th March 2019 at **BioISI** – Biosystems and Integrative Sciences Institute, Ciências, ULisboa. Lectures and practical activities involved over 15 BioISI researchers and collaborators in the fields of Biology, Biochemistry, Biomedical Engineering and Informatics. (<http://bioisi.pt/newsletter-april/>).

