

ARTIGOS CIENTÍFICOS

Artigo científico original

Artigo científico de revisão

PESQUISA BIBLIOGRÁFICA NA PUB MED

<http://www.ncbi.nlm.nih.gov/>

Pesquisa por assunto

Ferramentas de restrição da pesquisa

Pesquisa por autor

Pesquisa de artigos científicos de revisão e originais

Objectivos desta aula

- . Familiarização com artigos científicos: tipos de artigos e a estrutura mais comum
 - . Identificação das diferentes secções que constituem um artigo científico
 - . O processo de publicação de um artigo científico – a importância de “peer review” (revisão por pares)
 - . Criação de uma lista de referências bibliográficas
 - . Modo de elaboração da lista de referências – formatação
-
- . Pesquisa de artigos científicos na PubMed
 - . Pesquisa por tema/palavras chave
 - . Pesquisa por autor
-
- . Realização de uma ficha de consolidação de conhecimentos

O QUE É UM ARTIGO CIENTÍFICO E DE QUE FORMA ESTÁ ORGANIZADO?

General Research Article Organization:

Title

Authors (Affiliations; Contact Information)

Summary or Abstract

Key Words

Introduction

Experimental Procedures or Material and Methods

Results

Discussion

Acknowledgements

References

Figures and Tables (inserted in the text)

Figure and Table Legends (same page as figure or table)

Supplemental Data.

<http://www.cell.com/misc/page?page=authors#SubmissionRA>

O QUE CONSTITUÍ CADA UMA DAS SECÇÕES DE UM ARTIGO CIENTÍFICO?

Preparation of Specific Sections

Title

The title should convey the conceptual significance of the paper to a broad readership.



Authors/Affiliations

Author names should be spelled out rather than set in initials. Affiliations should contain the following core information: department(s)/subunit(s); institution; city, state/region, postal code; country.

Contact

The contact line should include the email address and phone/fax numbers of the **corresponding author**. The published corresponding author is responsible for ensuring adherence to all editorial and submission policies and for any communications that may result post-publication. One corresponding author is preferred, but two are allowed.

Additional Footnotes

Footnotes are only allowed on page 1 of the text (and in tables). They may include a present address or statement of equal contribution to the manuscript.

Summary/Abstract

The Summary consists of a single paragraph of fewer than 150 words. It should clearly convey the conceptual advance and significance of the work to a broad readership. In particular, the abstract should contain a brief background of the question, a description of the results without extensive experimental detail, and a summary of the significance of the findings. References should not be cited in the Summary.

O QUE CONSTITUÍ CADA UMA DAS SECÇÕES DE UM ARTIGO CIENTÍFICO (CONT)?

Preparation of Specific Sections (cont)

Introduction

The Introduction should be succinct (with or without subheadings) and should present the background information necessary to provide a biological context for the results.

Results

This section should be divided with subheadings. Description of the results presented.

Discussion

The Discussion should explain the significance of the results and place them into a broader context. It should not be redundant with the Results section. This section may contain subheadings and can in some cases be combined with the Results section.

Materials and Methods / Experimental Procedures

The Experimental Procedures section needs to include sufficient detail so that readers can understand how the experiments were done, and so that all procedures can be repeated, in conjunction with cited references. This section should also include a description of any statistical methods employed in the study.

Acknowledgments

This section may acknowledge contributions from non-authors, list funding sources, and should include a statement of any conflict of interests. This section may be used to list the contributions of individual authors.

O QUE CONSTITUÍ CADA UMA DAS SECÇÕES DE UM ARTIGO CIENTÍFICO?

Preparation of Specific Sections (cont)

References

References should include only articles that are published or in press. Unpublished data, submitted manuscripts, abstracts, and personal communications should be cited within the text only. Personal communication should be documented by a letter of permission. Submitted articles should be cited as unpublished data, data not shown, or personal communication. Style for references:

Article in a periodical: Sondheimer, N., and Lindquist, S. (2000). Rnq1: an epigenetic modifier of protein function in yeast. *Mol. Cell* 5, 163-172.

Article in a book: King, S.M. (2003). Dynein motors: Structure, mechanochemistry and regulation. In *Molecular Motors*, M. Schliwa, ed. (Weinheim, Germany: Wiley-VCH Verlag GmbH), pp. 45–78.

An entire book: Cowan, W.M., Jessell, T.M., and Zipursky, S.L. (1997). *Molecular and Cellular Approaches to Neural Development* (New York: Oxford University Press).

OUTRAS FORMAS DE LISTAR AS REFERÊNCIAS:

EMBO J: Akhmedkhanov A, Toniolo P, Zeleniuch-Jacquotte A, Koenig KL, Shore RE (2002) Aspirin and lung cancer in women. *Br J Cancer* **87**: 49-53

JBC: MacDonald, G. M., Steenhuis, J. J., and Barry, B. A. (1995) *J. Biol. Chem.* **270**, 8420-8428

Obrigatório constar: Nome dos Autores; nome da revista, volume e nº das págs, e ano de publicação; opcional (de acordo com as regras da publicação): título do artigo

DIFERENTES FORMAS DE INSERIR AS REFERÊNCIAS NO TEXTO

Alexandra Isabel Rosa and Sara Duarte-Silva are joint first authors.

Electronic supplementary material The online version of this article (<https://doi.org/10.1007/s12035-018-1062-4>) contains supplementary material, which is available to authorized users.

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Introduction

The cellular mechanisms underlying dopaminergic cell death in Parkinson's disease (PD) are still not fully understood, but neuroinflammation, mitochondrial dysfunction and oxidative stress are thought to contribute to dopaminergic cell loss in both familial and sporadic cases [1, 2].

Glia play a key role in the antioxidant defense, as well as in supplying molecules to support and monitor the neuronal micro-environment [3]. When activated by dying neurons, these cells are known to phagocytose cellular debris and to secrete a number of pro-inflammatory mediators [1, 4, 5], further contributing to neuronal degeneration, hence creating a vicious cycle of inflammation and cell death, which exacerbates and propagates the neurodegenerative process [6]. Indeed, glial activation plays an important role in the progression of neuronal dysfunction in PD, as reactive microglia and astrocytes, and increased levels of cytokines have been reported in PD patient's brains [7–13].



Todas as referências inseridas no texto têm de ser listadas no final do documento em secção própria, e vice-versa

Specialty section:

*This article was submitted to
Neurodegeneration,
a section of the journal
Frontiers in Neuroscience*

Received: 28 February 2018

Accepted: 18 May 2018

Published: 07 June 2018

Citation:

Videira PAQ and Castro-Caldas M
(2018) Linking Glycation
and Glycosylation With Inflammation
in Parkinson's Disease.
Front. Neurosci. 12:381.
doi: 10.3389/fnins.2018.00381

knowledge of the pathogenic mechanisms, or as biomarkers of the disease.

Keywords: Parkinson's disease, mitochondrial dysfunction, inflammation, glycation, glycosylation, aging

PARKINSON'S DISEASE

Parkinson's disease (PD) is the second most common age-related neurodegenerative disease, clinically characterized by typical motor symptoms such as resting tremor, rigidity, bradykinesia, gait, and balance dysfunction that result in near total immobility and strongly impair patients' quality of life (Chaudhuri et al., 2006; Thomas and Beal, 2007; Jankovic, 2008). Currently, it is well accepted that several non-motor symptoms are also a key component of PD. These symptoms include hyposmia, constipation, hallucinations, depression, anxiety, sleep dysfunction, apathy, and dementia, and some of them may even arise in the pre-motor phase of the disease (Zis et al., 2015; Poewe et al., 2017).

O QUE CONSTITUÍ CADA UMA DAS SECÇÕES DE UM ARTIGO CIENTÍFICO?

Preparation of Specific Sections (cont)

Figure Legends

Each figure legend should have a brief title that describes the entire figure without citing specific panels, followed by a description of each panel. For any figures presenting pooled data, the measures should be defined in the figure legends (for example, data are represented as mean \pm SEM).

Tables

Tables should include a title, and footnotes and/or legend should be concise. Include tables in the submitted manuscript as a separate section.

Supplemental Data

Supplemental data are restricted to items that are directly pertinent to the conclusions of the paper. All figures and tables should have titles and legends.

Supplemental Movies and Excel Spreadsheets

DIFERENTES TIPOS DE ARTIGOS CIENTÍFICOS

Research articles (Artigos científicos originais)

Manuscripts should be divided into the following sections: Title page, Summary, Introduction, Results, Discussion, Materials and Methods, Acknowledgements, References, Figure legends.

Short reports or Letters (Pequenos artigos científicos originais)

These are short (maximum 3000 words), high-impact papers that can be accompanied by up to four display items (figures or tables). The style of a Short Report follows that of a Research Article in JCS, the only difference being that Results and Discussion should be combined into a single Results and Discussion section.

Reviews (Artigos de revisão)

Personal viewpoints are valuable, but they should not take precedence over dispassionate reportage, and they should always be clearly presented within the relevant section as viewpoint rather than masquerade as firm deduction. Published material that goes against the author's viewpoint must be cited appropriately and not disregarded. Viewpoint can be used creatively at the end of a review to inform a section on future directions, and this is the preferable place for it.

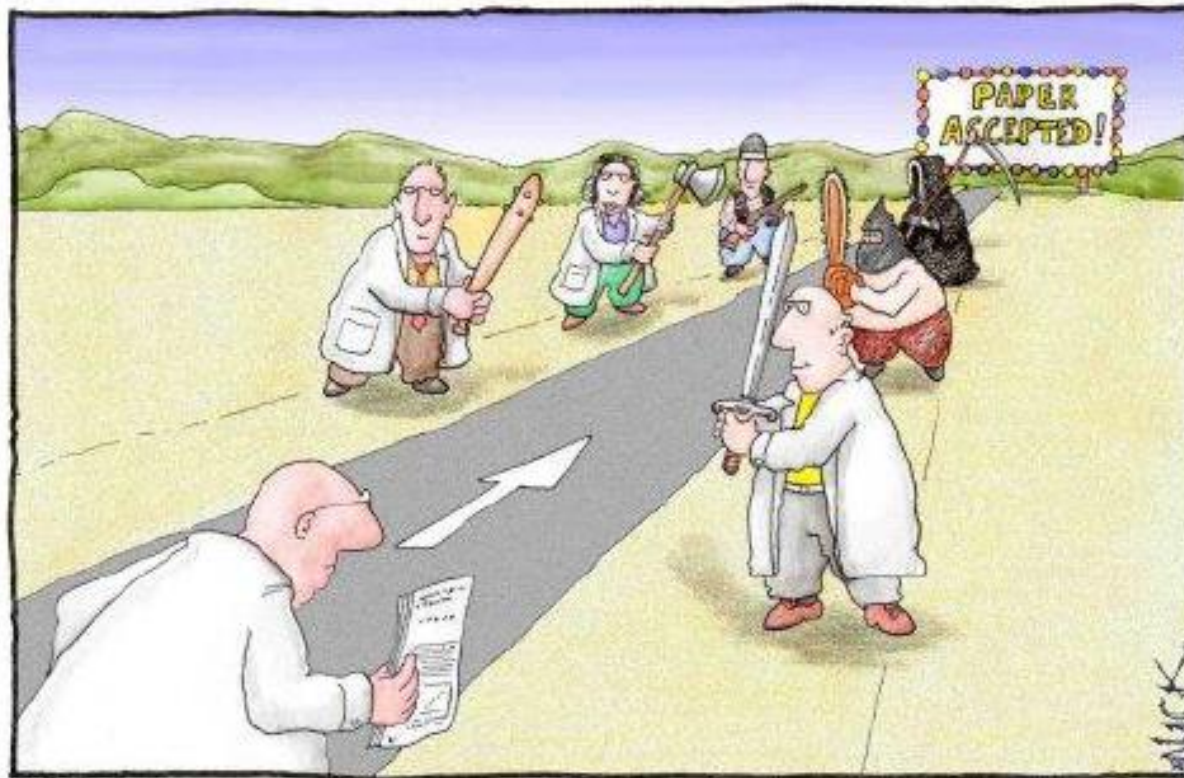
Manuscripts should be divided into the following sections: Title page, Summary, Text, Acknowledgements, References, Figure legends.

J Cell Science: http://www.biologists.com/web/submissions/jcs_information.html#anchor_art_type

British Journal of Pharmacology: http://www.nature.com/bjp/bjp_reviews_instructions.pdf

Os artigos científicos indexados à PubMed ou outra base dados similar são referências de confiança e robustas, pois as revistas lá representadas obrigam a que os seus artigos sejam sujeitos a escrutínio/avaliação por especialista conceituados do assunto (normalmente 2 ou 3 e o editor da revista). Só depois desta “prova” é que o artigo, normalmente depois de ser melhorado tendo em conta as sugestões/“ordens” dos avaliadores (referees), é publicado (noutros casos é rejeitado e nunca mais se houve falar dele...).

É desta forma que os autores encaram o processo de revisão do seu artigo:

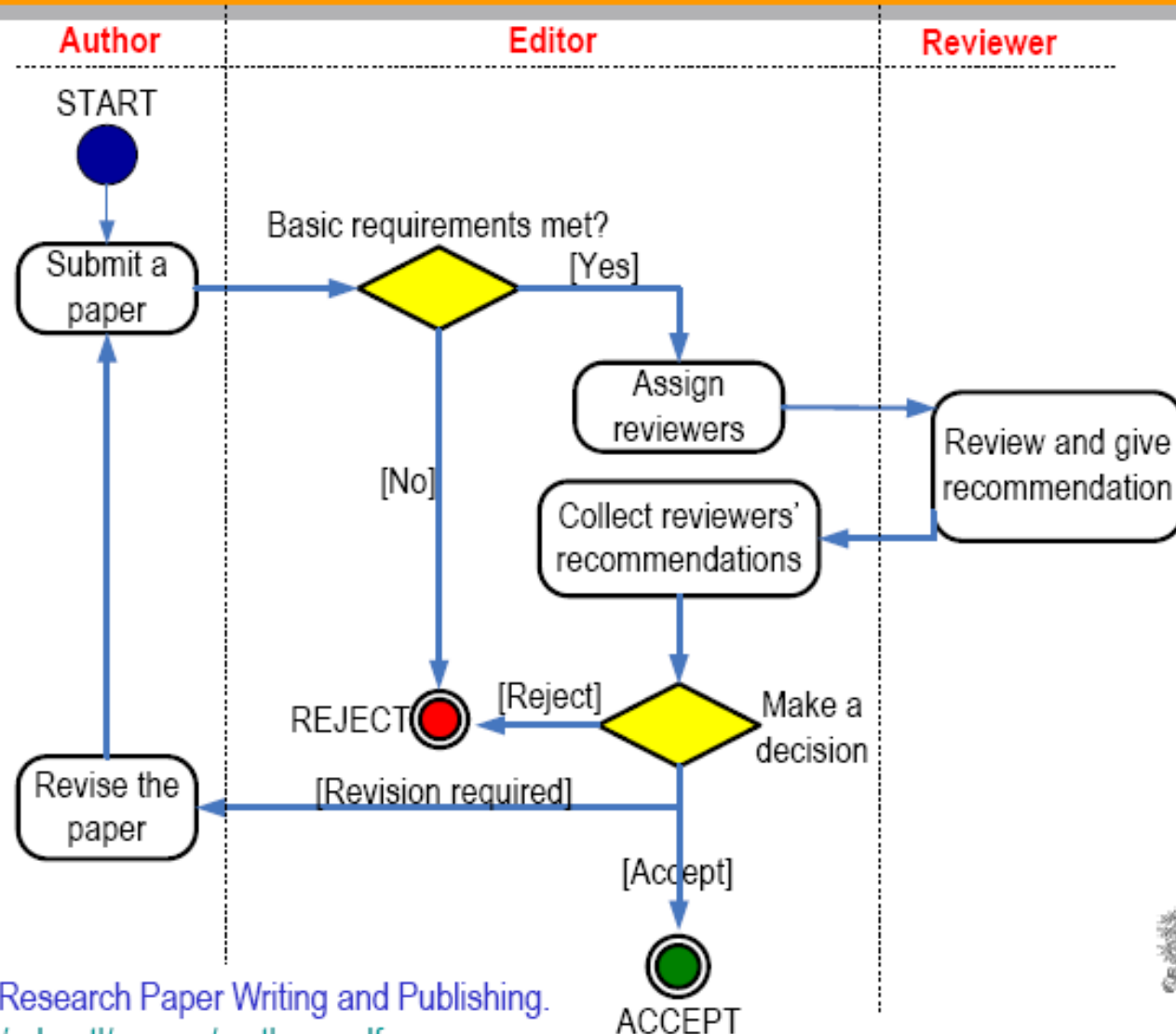


Most scientists regarded the new streamlined peer-review process as 'quite an improvement.'

É desta forma que o processo de revisão dos artigos costuma acontecer:



The Peer Review Process



Michael Derntl. Basics of Research Paper Writing and Publishing.
<http://www.pri.univie.ac.at/~derntl/papers/meth-se.pdf>



Pesquisa Bibliográfica no PubMed* passo a passo

<http://www.nlm.nih.gov/>

Com o cursor
seleccionar
“PubMed”

The screenshot shows the NCBI (National Center for Biotechnology Information) homepage. At the top, there is a navigation bar with 'NCBI', 'Resources', and 'How To'. Below this, a search bar is visible with 'PubMed' selected in a dropdown menu, indicated by a red arrow. The main content area features a 'UNITE' banner for a new NIH initiative to end structural racism. On the left, a 'Resource List (A-Z)' sidebar lists various databases. The central 'Welcome to NCBI' section provides an overview of the center's mission and links to 'About the NCBI', 'Mission', 'Organization', and 'NCBI News & Blog'. Below this, three main service areas are highlighted: 'Submit' (Deposit data or manuscripts into NCBI databases), 'Download' (Transfer NCBI data to your computer), and 'Learn' (Find help documents, attend a class or watch a tutorial). On the right, a 'Popular Resources' list includes PubMed, Bookshelf, PubMed Central, BLAST, Nucleotide, Genome, SNP, Gene, Protein, and PubChem. At the bottom, there is a section for 'NCBI News & Blog' with a link to 'Fungal Disease Awareness Week: fungal'.

* PubMed is a service of the [U.S. National Library of Medicine](http://www.nlm.nih.gov/)

PESQUISA POR TEMA

1ª Pesquisa:

Por tema, usando palavras chave (escritas em inglês)

Exemplo: Cell membrane

Pesquisa feita a 23.9.2021

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National Center for Biotechnology Information

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PubMed.gov

cell membrane

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RESULTS BY YEAR

1897 2022

TEXT AVAILABILITY

☐ Abstract

☐ Free full text

☐ Full text

ARTICLE ATTRIBUTE

☐ Associated data

ARTICLE TYPE

846,517 results

☐ **Cell membrane**-camouflaged nanoparticles for drug delivery.

1 Luk BT, Zhang L.

Cite J Control Release. 2015 Dec 28;220(Pt B):600-7. doi: 10.1016/j.jconrel.2015.07.019. Epub 2015 Jul 23.

PMID: 26210440 **Free PMC article.** Review.

Share

☐ **Compartmentalization of the Cell Membrane.**

2 Honigsmann A, Pralle A.

Cite J Mol Biol. 2016 Dec 4;428(24 Pt A):4739-4748. doi: 10.1016/j.jmb.2016.09.022. Epub 2016 Oct 5.

PMID: 27720722 Review.

Share

☐ **Cell membrane** modulation as adjuvant in cancer therapy.

3 Zalba S, Ten Hagen TL.

Cite Cancer Treat Rev. 2017 Jan;52:48-57. doi: 10.1016/j.ctrv.2016.10.008. Epub 2016 Nov 9.

PMID: 27889637 **Free PMC article.** Review.

Share

☐ **Are cell membrane** nanotubes the ancestors of the nervous system?

4 Nussenzweig HM.


Nesta pesquisa, nesta vista, têm acesso ao nº de artigos que existem com essas palavras (846 517), a título, nome dos autores, revista, volume, ano e págs; indicação se é de acesso livre, idioma (se diferente de inglês), de revisão...

2ª Pesquisa:


846 517 referências são muitas, por isso teremos de restringir a pesquisa aumentando o nº de palavras chave

Exemplo: Cell membrane **neuron**

Pesquisa feita a 23.9.2021

**National Library of Medicine**
National Center for Biotechnology Information

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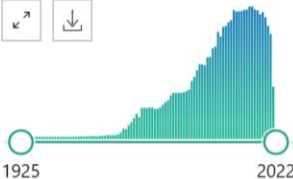
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RESULTS BY YEAR



1925 2022

TEXT AVAILABILITY

☐ Abstract

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ARTICLE ATTRIBUTE

☐ Associated data

ARTICLE TYPE

139,543 results

☐ 1

Communication networks in the brain: **neurons**, receptors, neurotransmitters, and alcohol.

Cite

Lovinger DM.

Share

Alcohol Res Health. 2008;31(3):196-214.

PMID: 23584863

Free PMC article.

Review.

☐ 2

Are **cell membrane** nanotubes the ancestors of the nervous system?

Cite

Nussenzveig HM.

Share

Eur Biophys J. 2019 Oct;48(7):593-598. doi: 10.1007/s00249-019-01388-x. Epub 2019 Jul 6.

PMID: 31280337

Review.

☐ 3

Clinical dose of lidocaine destroys the **cell membrane** and induces both necrosis and apoptosis in an identified *Lymnaea* **neuron**.

Cite

Onizuka S, Tamura R, Yonaha T, Oda N, Kawasaki Y, Shirasaka T, Shiraishi S, Tsuneyoshi I.

Share

J Anesth. 2012 Feb;26(1):54-61. doi: 10.1007/s00540-011-1260-y. Epub 2011 Oct 29.

PMID: 22038615

☐ Plasma **membrane** expansion: a **neuron's** Herculean task.


Nesta pesquisa, “reduzimos” para 139 543 referências, o que ainda é um nº muito elevado para consultarem para um trabalho de BC...

3ª Pesquisa:


139 543 referências são muitas, por isso teremos de restringir a pesquisa aumentando o nº de palavras chave

Exemplo: cell membrane **neuron sodium potassium pump**

Pesquisa feita a 23.9.2021

 **National Library of Medicine**
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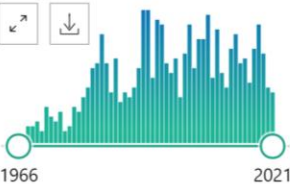
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RESULTS BY YEAR



19662021

TEXT AVAILABILITY

☐ Abstract

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ARTICLE ATTRIBUTE

☐ Associated data

699 results

☐ **Sodium/Potassium** homeostasis in the **cell**.

1

Clausen MJ, Poulsen H.

Cite

Met Ions Life Sci. 2013;12:41-67. doi: 10.1007/978-94-007-5561-1_3.

PMID: 23595670

Free article.

Share

☐ **Na(+)/K(+)-pump** and neurotransmitter **membrane** receptors.

2

Pivovarov AS, Calahorra F, Walker RJ.

Cite

Invert Neurosci. 2018 Nov 28;19(1):1. doi: 10.1007/s10158-018-0221-7.

PMID: 30488358

Free PMC article.

Review.

Share

☐ Direct influence of the **sodium pump** on the **membrane** potential of vomeronasal chemoreceptor **neurons** in frog.

3

Trotier D, Døving KB.

Cite

J Physiol. 1996 Feb 1;490 (Pt 3)(Pt 3):611-21. doi: 10.1113/jphysiol.1996.sp021171.

PMID: 8683461

Free PMC article.

Share


Nesta pesquisa, já reduzimos para 699 referências, o que é um nº ainda elevado para consultar e escolher as de interesse

4ª Pesquisa:


698 referências são muitas, por isso teremos de restringir a pesquisa aumentando o nº de palavras chave

Exemplo: cell membrane **neuron** **sodium potassium pump** **Bufalin**

Pesquisa feita a 23.9.2021

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cell membrane neuron sodium potassium pump bufalin

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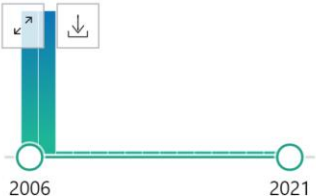
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RESULTS BY YEAR



TEXT AVAILABILITY

☐ Abstract

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ARTICLE ATTRIBUTE

☐ Associated data

2 results

☐ 1

Role of endosomal Na⁺-K⁺-ATPase and cardiac steroids in the regulation of endocytosis.

Cite Feldmann T, Glukmann V, Medvenev E, Shpolansky U, Galili D, Lichtstein D, Rosen H.

Am J Physiol Cell Physiol. 2007 Sep;293(3):C885-96. doi: 10.1152/ajpcell.00602.2006. Epub 2007 Jun 6.

Share PMID: 17553933 **Free article.**

☐ 2

Short-term effects of cardiac steroids on intracellular membrane traffic in neuronal NT2 cells.

Cite Rosen H, Glukmann V, Feldmann T, Fridman E, Lichtstein D.

Cell Mol Biol (Noisy-le-grand). 2006 Dec 30;52(8):78-86.


Share PMID: 17535740

Nesta pesquisa, já reduzimos para 2 referências, o que é um nº excelente para consultar

Nesta vista temos acesso a título, nome dos autores, revista, volume, ano e págs; indicação se é de acesso livre, idioma (se diferente de inglês), de revisão...

- ☐ [Multidrug resistance in Salmonella enterica serovar typhi isolated from patients with typhoid fever complications in Lagos, Nigeria.](#) ← **Título**
8. Akinyemi KO, Smith SI, Oyefolu AO, Coker AO. ← **Autores**
Public Health. 2005 Apr;119(4):321-7. ← **Nome da revista, ano de publicação, volume e pags**
PMID: 15733694 [PubMed - indexed for MEDLINE]
[Related citations](#)
- ☐ [\[The increase of plasmid DNA copy number is a possible mechanism of the amplification of bacteria anti-lysozyme activity under the effect of chloramphenicol\].](#)
2. Andriushchenko SV, Bukharin OV, Perunova NB, Ivanova EV.
Zh Mikrobiol Epidemiol Immunobiol. 2011 Nov-Dec;(6):8-13. Russian. ← **Idioma (quando é diferente de inglês)**
PMID: 22308720 [PubMed - indexed for MEDLINE]
[Related citations](#)
- ☐ [Simple and rapid preparation of plasmid template by a filtration method using microtiter filter plates.](#)
19. Itoh M, Carninci P, Nagaoka S, Sasaki N, Okazaki Y, Ohsumi T, Muramatsu M, Hayashizaki Y.
Nucleic Acids Res. 1997 Mar 15;25(6):1315-6.
PMID: 9092649 [PubMed - indexed for MEDLINE] Free PMC Article ← **Se é de acesso livre e gratuito**
[Related citations](#)
- ☐ [\[Construction of Streptococcus mutans surface protein antigen eukaryotic expression vector pcDNA3-PAC. I. Extraction and purification of plasmid DNA pPC41 and pcDNA3\].](#)
11. Liu J, Liu T, Zhou X, Liu L, Jia W, Zhan L.
Hua Xi Kou Qiang Yi Xue Za Zhi. 1999 Nov;17(4):361-3. Chinese. ← **Idioma (quando é diferente de inglês)**
PMID: 12539388 [PubMed - indexed for MEDLINE] Free Article
[Related citations](#)
- ☐ [Isolation of plasmids from E. coli by alkaline lysis.](#)
10. Ehrh S, Schnappinger D.
Methods Mol Biol. 2003;235:75-8. No abstract available. ← **Quando o Abstract não está disponível**
PMID: 12904648 [PubMed - indexed for MEDLINE]
[Related citations](#)

Continuação da pesquisa: acesso a abstract (resumo) e eventualmente ao artigo na forma completa (se for de livre acesso ou se estivermos ligados à PubMed por um servidor que tenha pago o acesso às revistas (ex. na FCT temos acesso a muitas revistas; em casa podem ligar-se por VPN)

☐ [Role of endosomal Na⁺-K⁺-ATPase and cardiac steroids in the regulation of endocytosis.](#) 

1

Cite Feldmann T, Glukmann V, Medvenev E, Shpolansky U, Galili D, Lichtstein D, Rosen H.

Am J Physiol Cell Physiol. 2007 Sep;293(3):C885-96. doi: 10.1152/ajpcell.00602.2006. Epub 2007 Jun 6.

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Clicar em cima do título do artigo que parece ser interessante

Aparece o Abstract / Resumo

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> Am J Physiol Cell Physiol. 2007 Sep;293(3):C885-96. doi: 10.1152/ajpcell.00602.2006. Epub 2007 Jun 6.

Role of endosomal Na⁺-K⁺-ATPase and cardiac steroids in the regulation of endocytosis

Tomer Feldmann¹, Vladimir Glukmann, Eleonora Medvenev, Uri Shpolansky, Dana Galili, David Lichtstein, Haim Rosen



Affiliations + expand

PMID: 17553933 DOI: 10.1152/ajpcell.00602.2006

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Ler o Abstract / Resumo e se tiver interesse, clicar nos links da seta azul para abrir o artigo na forma completa

FULL TEXT LINKS




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ACTIONS

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Abstract

Similar articles

Aparece o artigo ou acesso ao artigo na sua forma completa (html). Para aceder ao artigo no formato PDF, procurar o link “Download PDF”

The screenshot shows a web browser with two tabs open, both titled 'Role of endosomal Na+-K+-ATPase'. The address bar shows the URL: journals.physiology.org/doi/full/10.1152/ajpcell.00602.2006?rfr_dat=cr_pub++0pubmed&url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org. The website header includes navigation links like 'JOURNALS', 'JOURNAL HOME', 'ISSUES', 'COLLECTIONS', 'INFORMATION', 'ABOUT', 'SUBMIT', and 'SUBSCRIBE'. A search bar is also present. The main content area displays the article title 'Role of endosomal Na⁺-K⁺-ATPase and cardiac steroids in the regulation of endocytosis' under the category 'MEMBRANE TRANSPORTERS, ION CHANNELS, AND PUMPS'. The authors listed are Tomer Feldmann, Vladimir Glukmann, Eleonora Medvenev, Uri Shpolansky, Dana Galili, and others. The publication date is 01 SEP 2007. A red arrow points to the 'PDF (797 KB)' link, which is accompanied by icons for a document, a wrench, and a share button. Below the title, there is an 'Abstract' section. On the right side of the page, there is a sidebar with a 'Call for Papers' for 'Inter-Organ Communication in Homeostasis and Disease' with a submission deadline of 30th June 2022, and information about 'Physiological Reports' Volume 293, Issue 3, September 2007, Pages C885-C896.

Se não tiverem acesso ao artigo esta página (ou a do PDF) não abre sem um login e password, ou sem pagarem o artigo.
Se for o caso, podem procurar a morada electrónica do autor de correspondencia (normalmente a informação está nesta fase da pesquisa) e enviar um e-mail cordial a pedir uma cópia do artigo. Geralmente os autores enviam.

Quando temos acesso ao artigo, conseguimos ter o PDF com todas as secções. A partir daqui podemos guardar, imprimir, etc...

Role of endosomal Na⁺-K⁺-ATPase and cardiac steroids in the regulation of endocytosis

Tomer Feldmann,¹ Vladimir Glukmann,¹ Eleonora Medvenev,¹ Uri Shpolansky,² Dana Galili,² David Lichtstein,² and Haim Rosen¹

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Feldmann T, Glukmann V, Medvenev E, Shpolansky U, Galili D, Lichtstein D, Rosen H. Role of endosomal Na⁺-K⁺-ATPase and cardiac steroids in the regulation of endocytosis. *Am J Physiol Cell Physiol* 293: C885–C896, 2007. First published June 6, 2007; doi:10.1152/ajpcell.00602.2006.—Plasma membrane Na⁺-K⁺-ATPase, which drives potassium into and sodium out of the cell, has important roles in numerous physiological processes. Cardiac steroids (CS), such as ouabain and bufalin, specifically interact with the pump and affect ionic homeostasis, signal transduction, and endocytosed membrane traffic. CS-like compounds are present in mammalian tissues, synthesized in the adrenal gland, and considered to be new family of steroid hormones. In this study, the mechanism of Na⁺-K⁺-ATPase involvement in the regulation of endocytosis is explored. We show that the effects of various CS on changes in endosomal pH are mediated by the pump and correspond to their effects on endosomal membrane traffic. In addition, it was found that CS-induced changes in endocytosed membrane traffic were dependent on alterations in [Na⁺] and [H⁺] in the endosome. Furthermore, we show that various CS differentially regulate endosomal pH and membrane traffic. The results suggest that these differences are due to specific binding characteristics. Based on our observations, we propose that Na⁺-K⁺-ATPase is a key player in the regulation of endosomal pH and endocytosed membrane traffic. Furthermore, our results raise the possibility that CS-like hormones regulate differentially intracellular membrane traffic.

bufalin; ouabain; endosomal pH

IONIC ELECTROCHEMICAL GRADIENTS ACROSS cellular membranes (e.g., H⁺ in the mitochondria or Na⁺, K⁺, and Ca²⁺ in the plasma membrane) are major driving forces for numerous cellular functions. These gradients are established and controlled by primary active transporters such as Na⁺-, K⁺-, H⁺-, or Ca²⁺-activated ATPases. Plasma membrane Na⁺-K⁺-ATPase hydrolyzes ATP and uses the free energy generated to drive potassium into the cell and sodium out of the cell, against their electrochemical gradients. Consequently, this enzyme has an important role in regulating cell volume, the plasma membrane electrical potential ($\Delta\psi$), and cytoplasmic pH and Ca²⁺ levels through Na⁺/H⁺ and Na⁺/Ca²⁺ exchangers, respectively (for reviews, see Refs. 16 and 25). Na⁺-K⁺-ATPase is a heteromeric protein composed of a catalytic α -subunit that binds Na⁺, K⁺, and ATP and β - and γ (FXYD)-subunits that can modulate substrate affinity (1, 15, 25, 42). It is well established that specific steroids, originally identified in plants and amphibians (e.g., digitalis, cardenolides, and bufadienol-

ides), collectively termed here cardiac steroids (CS), bind to a specific site on the α -subunit and inhibit ATP hydrolysis and ion transport (4). The pharmacological profile of these steroids as Na⁺-K⁺-ATPase inhibitors has been extensively studied and well defined (28, 34). In the past decade, several groups have identified CS-like compounds in animal and human tissues, and their synthesis in and release from the adrenal gland was proven (for reviews, see Refs. 13 and 20). The endogenous CS-like compounds are considered to function as hormones and have been implicated in salt and water homeostasis and the regulation of blood pressure (5, 9, 39).

Recent studies have supported the notion that Na⁺-K⁺-ATPase participates in physiological processes distinct from its role in ion homeostasis: research on heart tissue, kidney and lung epithelial cells, and smooth muscle cells have implied that Na⁺-K⁺-ATPase interacts with other proteins as an intracellular signal transducer, thereby affecting numerous cellular functions (3, 48). In addition, CS have been shown to induce intracellular slow Ca²⁺ oscillations associated with the activation of NF- κ B (24). Furthermore, ouabain-induced toxicity in OS cells was directly associated to signal transduction mechanisms and dissociated from the inhibition of ATPase activity by the steroid (44).

Endocytosis is a process in which cells internalize material from the environment and from cell surface receptors. It has been well established that after internalization of extracellular components by clathrin-coated vesicles (CCVs), receptor-ligand complexes, membrane proteins, and lipids are delivered to early endosomes in the peripheral cytoplasm. Early endosomes are multifunctional organelles that regulate the sorting and transport of membrane components between the plasma membrane and various intracellular compartments. These include recycling and late endosomes, lysosomes, and the trans-Golgi network. The prevalent model suggests that combinations of different members of highly conserved protein families [soluble *N*-ethylmaleimide-sensitive factor attachment protein (SNARE)], coat complexes, Rho and Rab] in distinct membrane compartments are the basis for sorting specificity (12, 23, 31).

Recently, we discovered that CS, at physiological concentrations (nM), induce changes in intracellular membrane traffic by inhibiting recycling within the late endocytic pathway (35). The ability of CS to induce these changes in membrane traffic in human cells was markedly reduced following transfection with the rat Na⁺-K⁺-ATPase α_1 -subunit, which has a low-

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