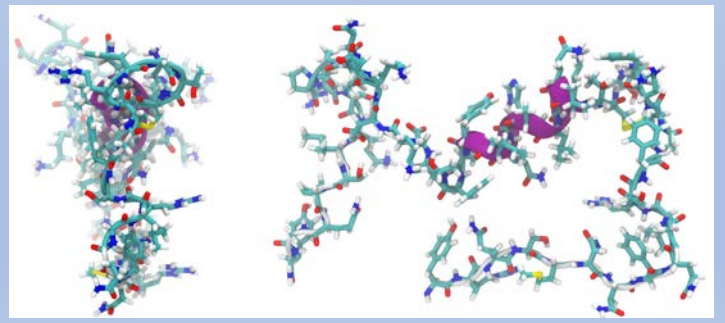
# Nuevos biomarcadores en ictus: Adrenomedulina y CCL5



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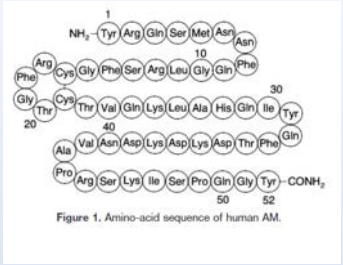
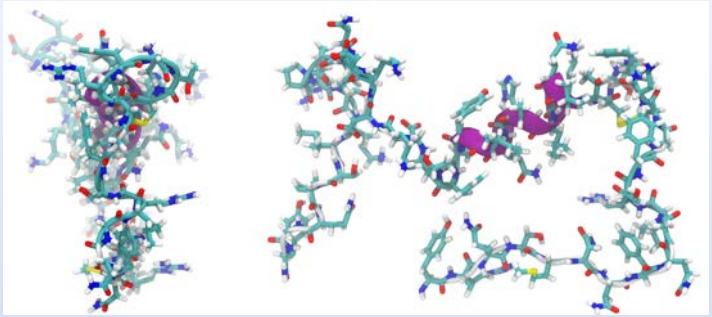
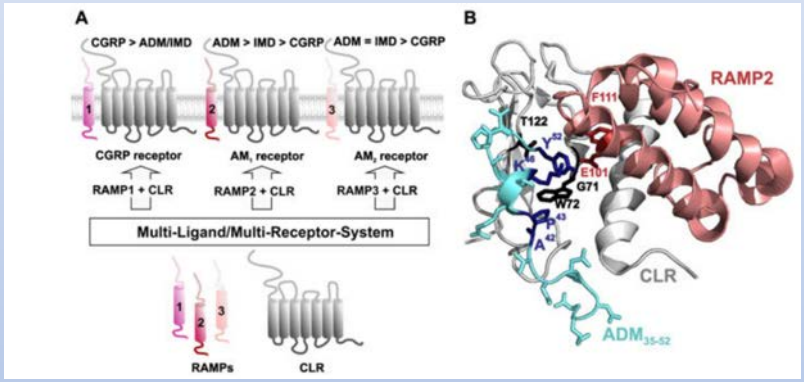
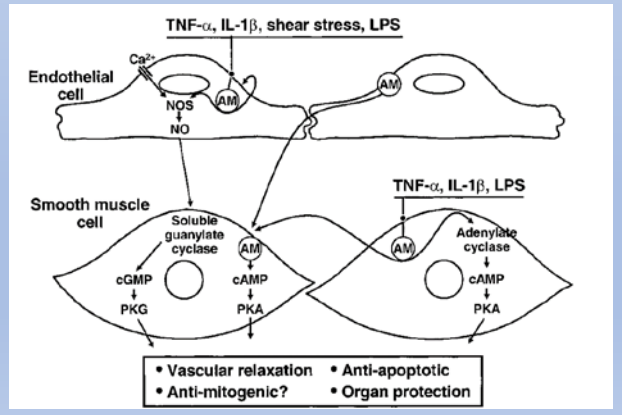
# Adrenomedulina



- Sintetizada en 1993 desde un freocomocitoma
- Gen AM expresado  principalmente en paredes arteriales
- Unión obligada entre receptor similar a calcitonina (CLR) y proteínas moduladoras actividad receptor (RAMP1-2-3)
- CLR/RAMP-1 → Receptor de CGRP
- CLR/RAMP-2 y RAMP-3→ Receptores AM
- Efecto vasodilatador
  - Adenilato ciclasa → AMPc (endotelio independiente)
  - eNOS→ ↑ NO



# Adrenomedulina: Funciones

| | |
|---|---|
| Vasculatura | Vasodilatación e hipotensíón<br>Estimulación síntesis NO<br>**<u>Inhibicion proliferación de células musculares lisas</u>**<br>Secreción endotelina<br>ANGIOGÉNESIS |
| Corazón | Inhibición hipertrofia y fibrosis<br>Inotrópico positivo |
| Riñón | Diuresis y natriuresis |
| Pulmón | Vasodilatación |
| Glándula adrenal | Inhibición aldosterona |
| Páncreas | Inhibición insulina |
| Plaquetas | Elevación AMPc |

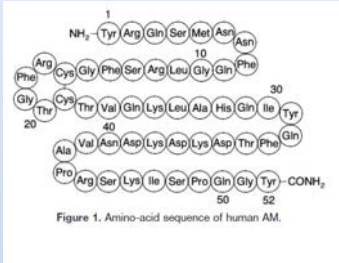
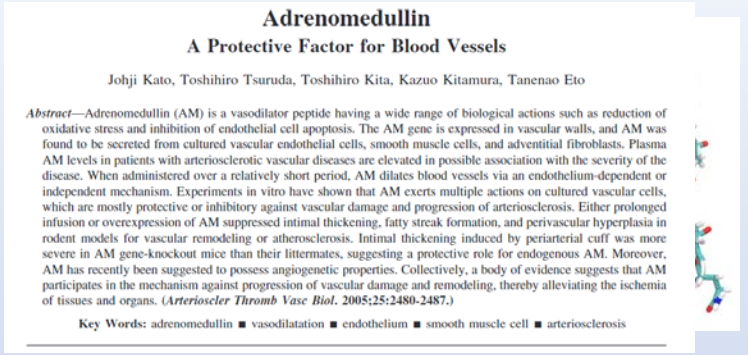


Figure 1. Amino-acid sequence of human AM.

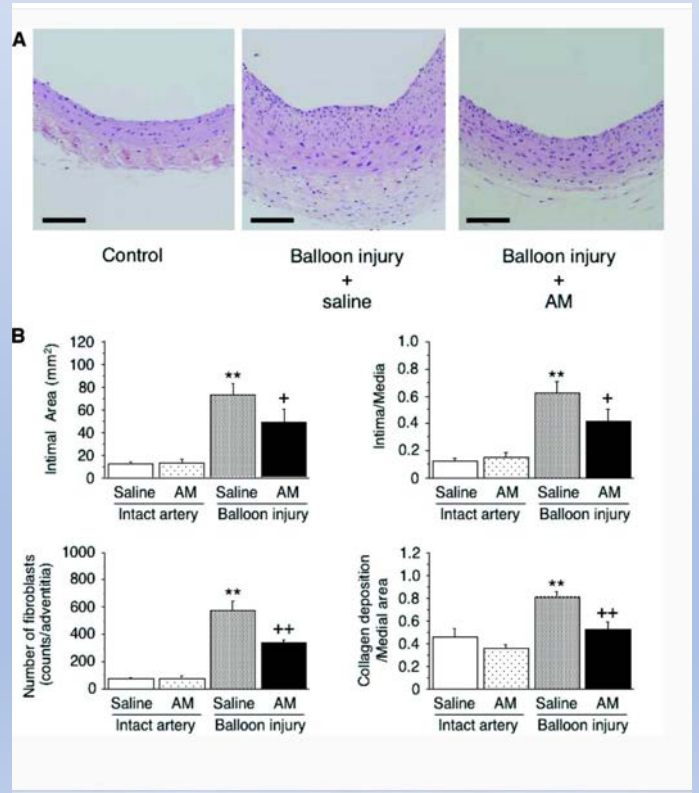

**Adrenomedullin**

**A Protective Factor for Blood Vessels**

Johji Kato, Toshihiro Tsuruda, Toshihiro Kita, Kazuo Kitamura, Tanenao Eto

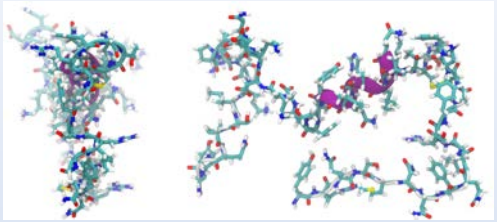
*Abstract*—Adrenomedullin (AM) is a vasodilator peptide having a wide range of biological actions such as reduction of oxidative stress and inhibition of endothelial cell apoptosis. The AM gene is expressed in vascular walls, and AM was found to be secreted from cultured vascular endothelial cells, smooth muscle cells, and adventitial fibroblasts. Plasma AM levels in patients with arteriosclerotic vascular diseases are elevated in possible association with the severity of the disease. When administered over a relatively short period, AM dilates blood vessels via an endothelium-dependent or independent mechanism. Experiments in vitro have shown that AM exerts multiple actions on cultured vascular cells, which are mostly protective or inhibitory against vascular damage and progression of arteriosclerosis. Either prolonged infusion or overexpression of AM suppressed intimal thickening, fatty streak formation, and perivascular hyperplasia in rodent models for vascular remodeling or atherosclerosis. Intimal thickening induced by periarterial cuff was more severe in AM gene-knockout mice than their littermates, suggesting a protective role for endogenous AM. Moreover, AM has recently been suggested to possess angiogenetic properties. Collectively, a body of evidence suggests that AM participates in the mechanism against progression of vascular damage and remodeling, thereby alleviating the ischemia of tissues and organs. (*Arterioscler Thromb Vasc Biol.* 2005;25:2480-2487.)

**Key Words:** adrenomedullin ■ vasodilatation ■ endothelium ■ smooth muscle cell ■ arteriosclerosis




1. Kato J, Tsuruda T, Kita T, Kitamura K, Eto T. Adrenomedullin: a protective factor for blood vessels. Arterioscler Thromb Vasc Biol. 2005 Dec;25(12):2480-7. doi: 10.1161/01.ATV.0000184759.91369.f8. Epub 2005 Sep 1. PMID: 16141406

# Adrenomedulina: Funciones (I)



REVIEW

OPEN ACCESS Check for updates

## Targeting the adrenomedullin-2 receptor for the discovery and development of novel anti-cancer agents

Ameera B. A. Jailani [a,*], Kamilla J. A. Bigos [a,*], Paris Avgoustou [a,*], Joseph L. Egan [b], Robert A. Hathway [b], Timothy M. Skerry [a,*] and Gareth O. Richards [a,*]

[a]Department of Oncology and Metabolism, University of Sheffield, Sheffield, UK; [b]Department of Chemistry, University of Sheffield, Sheffield, UK

Diana terapéutica: Cancer

*ntibiotics*

MDPI

## Mid-Regional Pro-Adrenomedullin as a Prognostic Factor for Severe COVID-19 ARDS

Etienne de Montmollin [1,2], Katell Peoc'h [3,4], Mehdi Marzouk [2], Stéphane Ruckly [1], Paul-Henri Wicky [2], Juliette Patrier [2], Pierre Jaquet [2], Romain Sonneville [1,2], Lila Bouadma [1,2] and Jean-François Timsit [1,2,*]

COVID-19

International Journal of *Molecular Sciences*

MDPI

*Article*

## Effects of Adrenomedullin on Atrial Electrophysiology and Pulmonary Vein Arrhythmogenesis

Chye-Gen Chin [1,2], Ahmed Moustafa Elimam [3], Fong-Jhih Lin [1,4], Yao-Chang Chen [4], Yung-Kuo Lin [2,5], Yen-Yu Lu [6], Satoshi Higa [7], Shih-Ann Chen [8,9], Ming-Hsiung Hsieh [2,5,*] and Yi-Jen Chen [1,2,*]

CARDIOLOGÍA

PLOS ONE

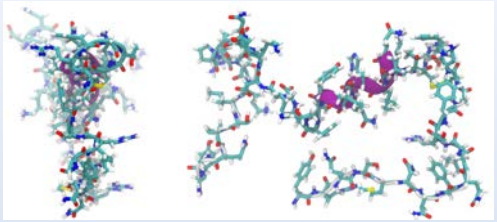
RESEARCH ARTICLE

## Bioactive adrenomedullin in sepsis patients in the emergency department is associated with mortality, organ failure and admission to intensive care

Oscar H. M. Lundberg[1,2]*, Mari Rosenqvist[3,4], Kevin Bronton[3,5], Janin Schulte[6], Hans Friberg[1,2], Olle Melander[3,4,5]

SEPSIS

# Adrenomedulina: Funciones (II)



NEURAL REGENERATION RESEARCH www.nrronline.org

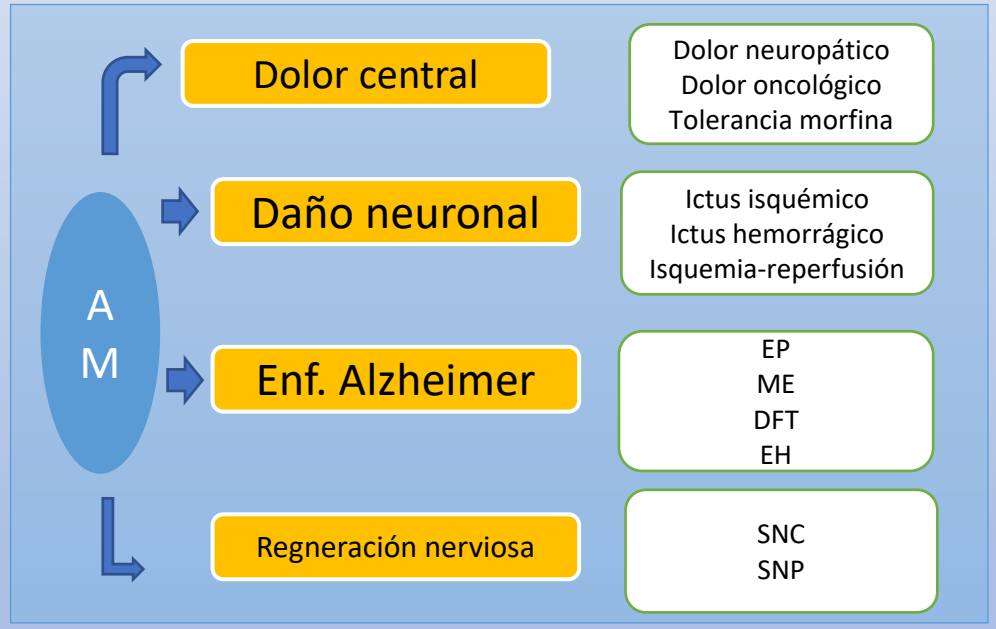
REVIEW

## Adrenomedullin: an important participant in neurological diseases

**Feng-Jiao Li, Si-Ru Zheng, Dong-Mei Wang***

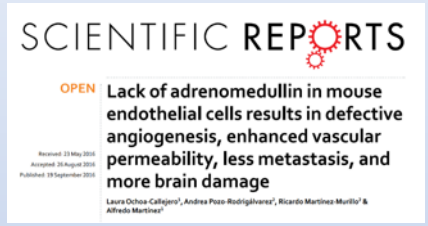
College of Life Sciences, Laboratory of Neuroendocrinology, Provincial Key Laboratory of Developmental Biology and Neuroscience, Fujian Normal University, Fuzhou, Fujian Province, China

***Funding:*** *This work was supported by the National Natural Science Foundation of China, No. 81400922 (to DMW), 81571084; the Natural Science Foundation of Fujian Province of China, No. 2018J01813 (to DMW); the College of Life Sciences of Fujian Normal University of China, No. FZSKG2018016 (to DMW).*



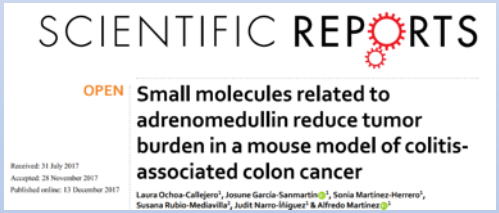
# Por qué adrenomedulina

- Angiogénesis
  - Unidad angiogénesis en CIBIR
    - Tumores gastrointestinales
    - Microbiota
    - Metástasis
    - Oncoprotección
- Enfermedades neurológicas
  - Enfermedad Alzheimer
  - DFT
  - Ictus isquémico


SCIENTIFIC REPORTS

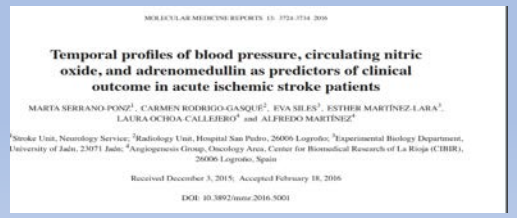
OPEN

Lack of adrenomedullin in mouse endothelial cells results in defective angiogenesis, enhanced vascular permeability, less metastasis, and more brain damage

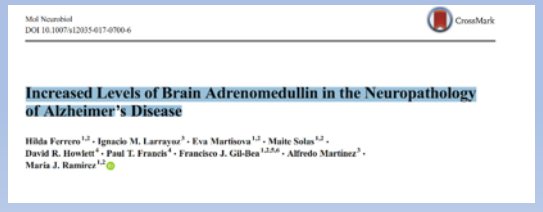

SCIENTIFIC REPORTS

OPEN

Small molecules related to adrenomedullin reduce tumor burden in a mouse model of colitis-associated colon cancer



MOLECULAR MEDICINE REPORTS

Temporal profiles of blood pressure, circulating nitric oxide, and adrenomedullin as predictors of clinical outcome in acute ischemic stroke patients

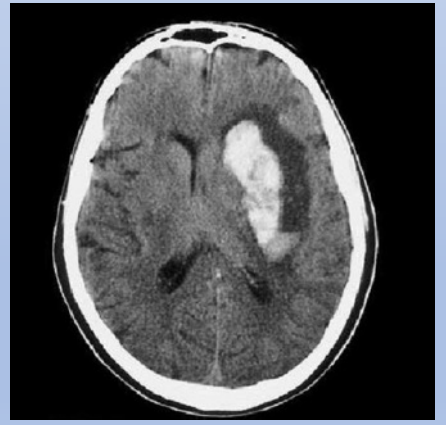

Mol Neurobiol

Increased Levels of Brain Adrenomedullin in the Neuropathology of Alzheimer's Disease

# HIPÓTESIS: Papel de la adrenomedulina en ictus hemorrágico

- ¿Tiene valor la AM en diagnóstico de ictus hemorrágico?

- ¿Tiene AM valor pronóstico en ictus hemorrágico?



# ADRENOMEDULINA. Material y métodos

Ictus hemorrágico n=64

d0 d1 d7

Vs

Voluntarios sanos (Banco de Sangre) n=50

| Característsticas clínicas | Ictus hemorrágicos | Voluntarios sanos | pValor |
|---|---|---|---|
| Edad (años) | 81 (72,2-87) | 46,5(40-54) | <0,001 |
| Sexo (varones) | 38 (59,4%) | 31 (62,0%) | 0,91 |
| Factores de riesgo | HTA 49 (76,6%)<br>DM 15 (23,4%)<br>DLP 20 (21,9%)<br>AF 18 (28,1%)<br>Ictus 16 (25%)<br>Demencia 8 (31,2%) | | |
| Rankin previo<br>0-1-2 54 (84,4%)<br>3-4 10 (15,6%)<br>5-6 0 | <br>54 (84,4%)<br>10 (15,6%)<br>0 | | |
| Localización hematoma | Profundo supratentorial 41 (64,1%)<br>Profundo infratentorial 6 (9,4%)<br>Lobar 14 (21,8%)<br>Mixto 3 (4,7%) | | |
| NIHSS ingreso<br>NIHSS al alta | 7,5 (2-16)<br>5 (2-6,7) | | |
| Volumen hematoma d0 (cm3)<br>Volumen hematoma d1 (cm3) | 4,5 (1-13,9)<br>4,6 (1-15,0) | | |

1. Julián-Villaverde FJ, Ochoa-Callejero L, Siles E, Martínez-Lara E, Martínez A. Adrenomedullin Is a Diagnostic and Prognostic Biomarker for Acute Intracerebral Hemorrhage. Curr Issues Mol Biol. 2021 Jun 11;43(1):324-334.

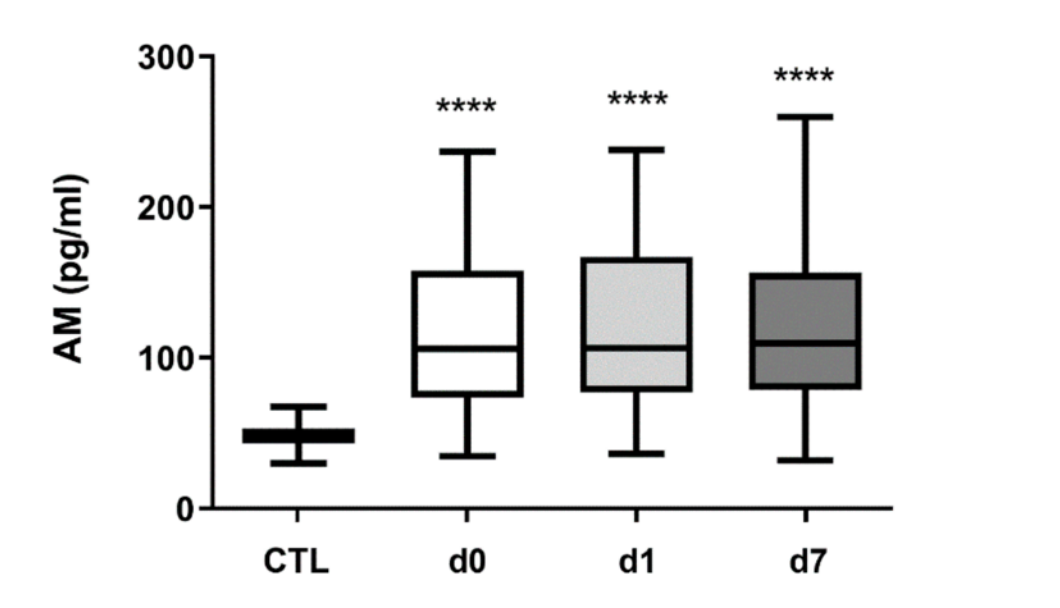
# ADRENOMEDULINA: DIAGNÓSTICO

*Article*

**Adrenomedullin Is a Diagnostic and Prognostic Biomarker for Acute Intracerebral Hemorrhage**

Francisco J. Julián-Villaverde [1], Laura Ochoa-Callejero [2], Eva Siles [3], Esther Martínez-Lara [3] and Alfredo Martínez [2,*]

RESULTADOS (1)




Niveles AM voluntarios sanos: 47,7 pg/ml (43,3-52,8)
Niveles AM al ingreso (d0): 105,8 pg/ml (74,6-157,8)
Niveles AM a las 24 horas (d1): 106,4 pg/ml (79,3-166,4)
Niveles AM a los 7 días* (d7): 109,7 pg/ml (79,2-154,4)

*Coeficiente de correlación de Spearman: r=-0,21; p=0,09

1. Julián-Villaverde FJ, Ochoa-Callejero L, Siles E, Martínez-Lara E, Martínez A. Adrenomedullin Is a Diagnostic and Prognostic Biomarker for Acute Intracerebral Hemorrhage. Curr Issues Mol Biol. 2021 Jun 11;43(1):324-334.

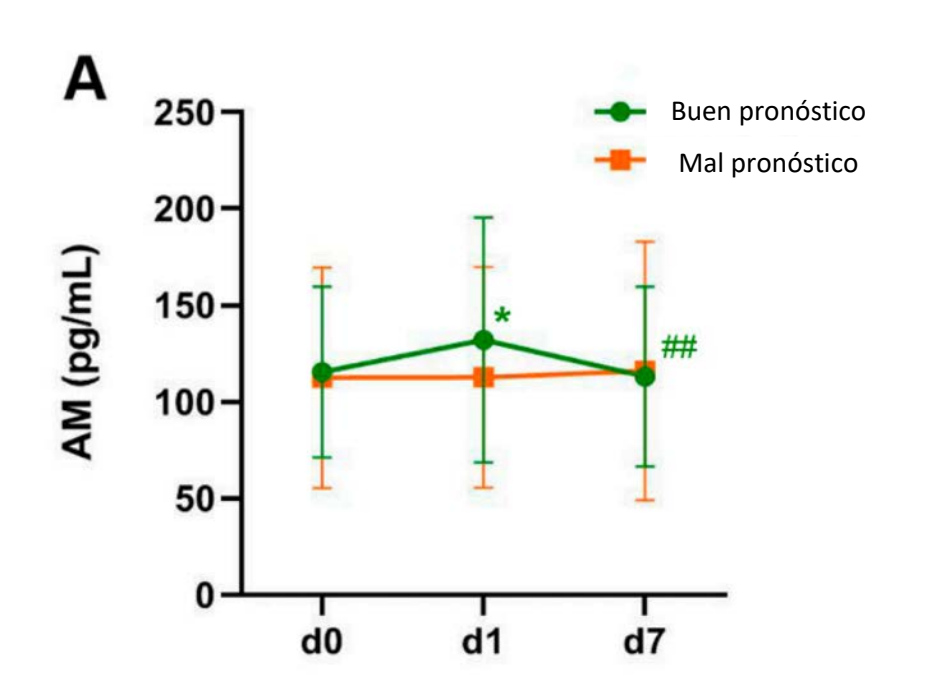
# ADRENOMEDULINA: PRONÓSTICO

*Article*

**Adrenomedullin Is a Diagnostic and Prognostic Biomarker for Acute Intracerebral Hemorrhage**

Francisco J. Julián-Villaverde [1], Laura Ochoa-Callejero [2], Eva Siles [3], Esther Martínez-Lara [3] and Alfredo Martínez [2,*]

- Buen pronóstico (NIHSS al alta ≤3) Vs Mal pronóstico NIHSS >3




RESULTADOS (2)

| NIHSS | AM d0 | AM d1 | AM d7 | pValor cambios |
|---|---|---|---|---|
| ≤3 | 115,515 pg/dL | 132,222pg/dL | 113,129pg/dL | <0,001 |
| >3 | 111,750 pg/dL | 111,285pg/dL | 115,170pg/dL | 0,61 |

INTERPRETACIÓN

AM en buen pronóstico: Eleva niveles d0 a d1; se normaliza d7

AM mal pronóstico: Niveles estables

*No diferencias en localización del hematoma (p 0.31) ni tamaño hematoma al ingreso (p 0.92)

1. Julián-Villaverde FJ, Ochoa-Callejero L, Siles E, Martínez-Lara E, Martínez A. Adrenomedullin Is a Diagnostic and Prognostic Biomarker for Acute Intracerebral Hemorrhage. Curr Issues Mol Biol. 2021 Jun 11;43(1):324-334.

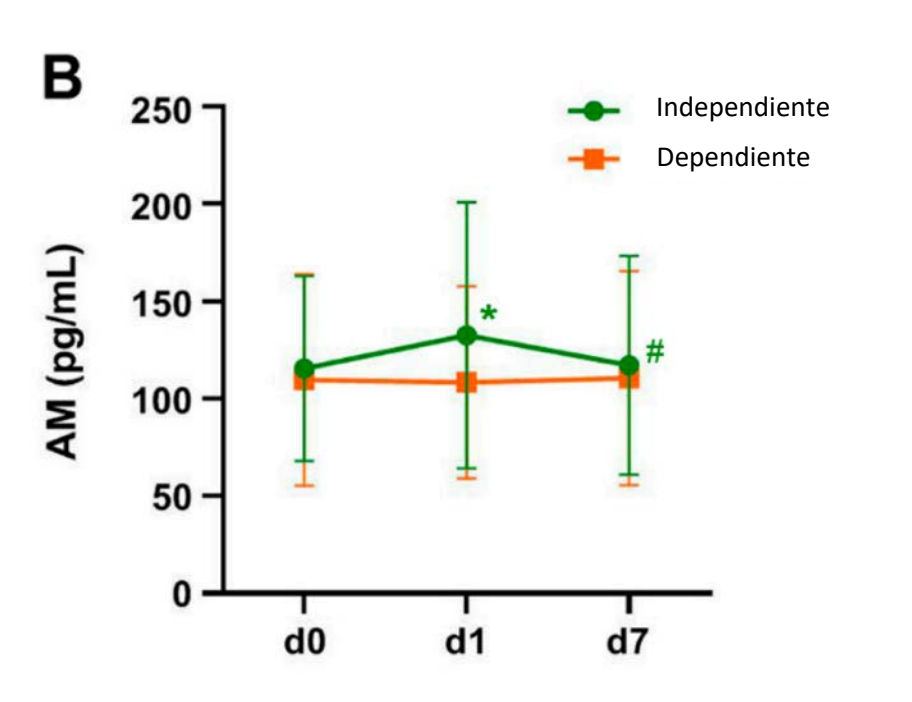
# ADRENOMEDULINA: PRONÓSTICO

*Article*

**Adrenomedullin Is a Diagnostic and Prognostic Biomarker for Acute Intracerebral Hemorrhage**

Francisco J. Julián-Villaverde [1], Laura Ochoa-Callejero [2], Eva Siles [3], Esther Martínez-Lara [3] and Alfredo Martínez [2,*]

- mRankin 3m( Independiente ≤ 2 Vs Dependiente ≥3)




RESULTADOS (3)

| RANKIN | AM d0 | AM d1 | AM d7 | pValor cambios |
|---|---|---|---|---|
| ≤2 | 115,509 pg/dL | 132,666 pg/dL | 117,132 pg/dL | <0,006 |
| >2 | 109,638 pg/dL | 108,494 pg/dL | 110,509 pg/dL | 0,79 |

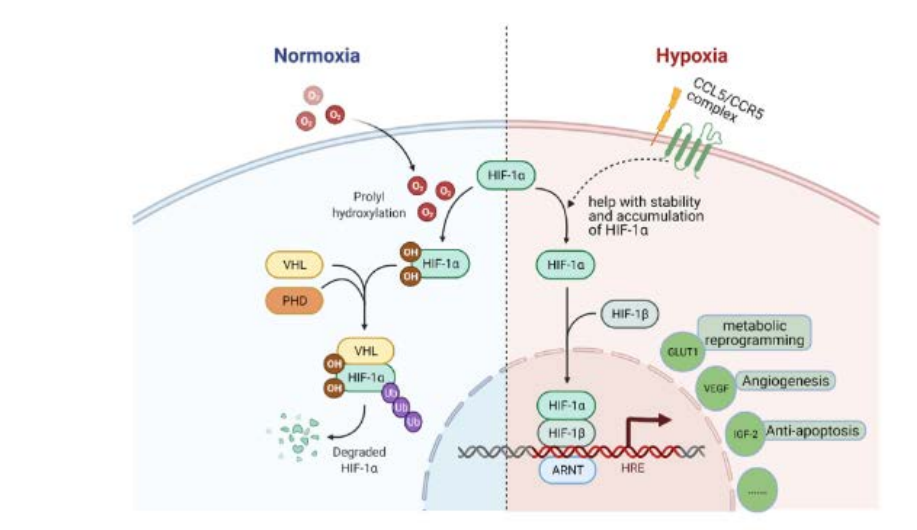
DISCUSIÓN (2)

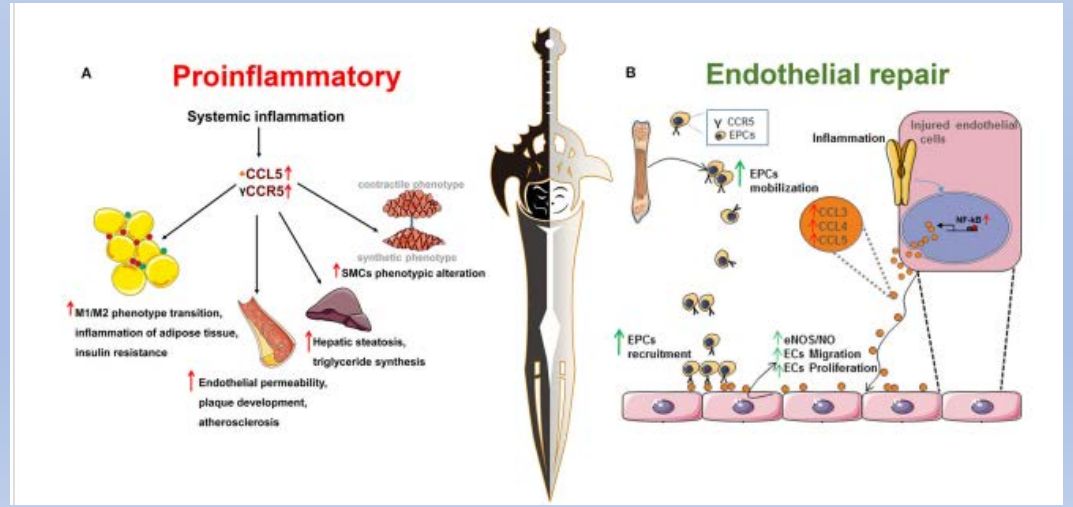
AM en pacientes independientes 3 meses: Eleva niveles día d0 a d1; se normaliza d7

AM en pacientes dependientes 3 meses : Niveles estables.

1. Julián-Villaverde FJ, Ochoa-Callejero L, Siles E, Martínez-Lara E, Martínez A. Adrenomedullin Is a Diagnostic and Prognostic Biomarker for Acute Intracerebral Hemorrhage. Curr Issues Mol Biol. 2021 Jun 11;43(1):324-334.

# CCL5 (RANTES) en PATOLOGÍA VASCULAR




CCL5. Quimiokina implicada en

- Progresión placa de ateroma
- Daño miocárdico
- Muerte súbita en pacientes con SCA

- Expresada en
  - Macrófagos
  - Linf-T
  - NK
  - Células endoteliales
  - Células no inflamatorias ( Astrocitos, neuronas)

- Funciones
  - ↑ Reclutamiento Cels. Progenitoras
  - ↑ Mecanismos reparación daños endotelial
  - Inhibición CCL5
    - ↓ Inflamación
    - ↑ Daño endotelial

# CCL5 (RANTES) EN PATOLOGÍA VASCULAR

International Journal of *Molecular Sciences*

MDPI

*Article*

**CCL5 Levels Predict Stroke Volume Growth in Acute Ischemic Stroke and Significantly Diminish in Hemorrhagic Stroke Patients**

**Francisco José Julián-Villaverde [1], Marta Serrano-Ponz [2], Enrique Ramalle-Gómara [3], Alfredo Martínez [4,†] and Laura Ochoa-Callejero [4,5,*,†]**

1 Stroke Unit, Neurology Service, Hospital San Pedro, 26006 Logroño, Spain
2 Neurology Service, Hospital Universitario Miguel Servet, 50009 Zaragoza, Spain
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4 Angiogenesis Group, Oncology Area, Center for Biomedical Research of La Rioja (CIBIR), 26006 Logroño, Spain
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* Correspondence: locallejero@riojasalud.es; Tel.: +34-941278775; Fax: +34-941278887
† These authors contributed equally to this work.

ELSEVIER

Clinica Chimica Acta

Volume 412, Issues 11–12, 12 May 2011, Pages 1112-1115

# The RANTES gene promoter polymorphisms are associated with the risk of atherothrombotic cerebral infarction in Northern Han Chinese

Xue Qin [a], Zhiyi He [a], Dongxue Zhao [b], Lei Li [a], Liying Yuan [a]

Published: 25 January 2009

# Regulatory T cells are key cerebroprotective immunomodulators in acute experimental stroke

Arthur Liesz, Elisabeth Suri-Payer, Claudia Veltkamp, Henrike Doerr, Clemens Sommer, Serge Rivest, Thomas Giese & Roland Veltkamp

*Nature Medicine* **15**, 192–199 (2009) | Cite this article

# CCL5 (RANTES) EN PATOLOGÍA VASCULAR

Ictus isquémico (n=36). Ictus hemorrágico (n= 64)
Muestras d0; d1; d7

International Journal of *Molecular Sciences*

MDPI

*Article*

## CCL5 Levels Predict Stroke Volume Growth in Acute Ischemic Stroke and Significantly Diminish in Hemorrhagic Stroke Patients

**Francisco José Julián-Villaverde [1], Marta Serrano-Ponz [2], Enrique Ramalle-Gómara [3], Alfredo Martínez [4,†] and Laura Ochoa-Callejero [4,5,*,†]**

1 Stroke Unit, Neurology Service, Hospital San Pedro, 26006 Logroño, Spain
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3 Department of Epidemiology, La Rioja Government, 26071 Logroño, Spain
4 Angiogenesis Group, Oncology Area, Center for Biomedical Research of La Rioja (CIBIR), 26006 Logroño, Spain
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* Correspondence: locallejero@riojasalud.es; Tel.: +34-941278775; Fax: +34-941278887
† These authors contributed equally to this work.

**Table 1.** Clinical characteristics of the 36 ischemic patients included in the study.

| | | |
|---|---|---|
| **Age (Years), Median (Q1–Q3)** | | 75 (63.5–79) |
| **Sex (M)** | | 20 (55.5%) |
| **Risk factors** | | |
| | **Arterial hypertension** | 25 (69.4%) |
| | **Diabetes mellitus** | 12 (33.3%) |
| | **Dyslipidemia** | 20 (55.5%) |
| | **Atrial fibrillation** | 6 (16.6%) |
| | **Previous stroke** | 7 (19.4%) |
| **Previous treatment** | | |
| | **Antihypertensives** | 22 (61.1%) |
| | **Statins** | 14 (38.8%) |
| | **Antiaggregants** | 14 (38.8%) |
| | **Anticoagulants** | 9 (25.0%) |
| **TOAST** | | |
| | **Atherothrombotic** | 11 (30.5%) |
| | **Cardioembolic** | 16 (44.4%) |
| | **Lacunar** | 2 (5.5%) |
| | **Cryptogenic** | 5 (13.8%) |
| | **Undetermined etiology** | 2 (5.5%) |
| **mRankin** | | |
| Basal | **0–1–2** | 32 (88.8%) |
| | **3–4** | 4 (11.1%) |
| | **5–6** | 0 (0.0%) |
| 3 months | **0–1–2** | 21 (58.3%) |
| | **3–4** | 10 (27.7%) |
| | **5–6** | 5 (13.8%) |
| **NIHSS, median (Q1–Q3)** | | |
| Basal | | 6 (2–13.2) |
| Hospital discharge | | 1 (0–8) |
| 3 months | | 0 (0–5.2) |
| **Infarct volume at d0 ($cm^3$), median (Q1–Q3)** | | 4.9 (1.3–22.6) |
| **Infarct volume at d7 ($cm^3$), median (Q1–Q3)** | | 3.2 (1.4–20.8) |
| **CCL5 at d0 (ng/mL), median (Q1–Q3)** | | 42.3 (24.3–50.6) |
| **CCL5 at d1 (ng/mL), median (Q1–Q3)** | | 43.1 (25.6–56.4) |
| **CCL5 at HD (ng/mL), median (Q1–Q3)** | | 60.4 (35.4–71.9) |

**Table 2.** Clinical characteristics of the 64 hemorrhagic patients included in the study.

| | | |
|---|---|---|
| **Age (Years), Median (Q1–Q3)** | | 81 (72.7–87) |
| **Sex (M)** | | 38 (59.4%) |
| **Risk factors** | | |
| | **Arterial hypertension** | 49 (76.6%) |
| | **Diabetes mellitus** | 15 (23.4%) |
| | **Dyslipidemia** | 20 (31.2%) |
| | **Atrial fibrillation** | 18 (28.1%) |
| **Previous treatment** | | |
| | **Antihypertensives** | 45 (70.3%) |
| | **Statins** | 21 (32.8%) |
| | **Antiaggregants** | 19 (29.7%) |
| | **Anticoagulants** | 20 (31.5%) |
| **TOAST** | | |
| | **Supratentorial** | 41 (64.1%) |
| | **Infratentorial** | 6 (9.4%) |
| | **Lobar** | 14 (21.9%) |
| | **Mixed** | 3 (4.7%) |
| **mRankin** | | |
| Basal | **0–1–2** | 54 (84.4%) |
| | **3–4** | 10 (15.6%) |
| | **5–6** | 0 (0.0%) |
| 3 months | **0–1–2** | 28 (43.7%) |
| | **3–4** | 12 (18.7%) |
| | **5–6** | 24 (37.5%) |
| **NIHSS, median (Q1–Q3)** | | |
| Basal | | 7 (2–16) |
| Hospital discharge | | 2.5 (1–6.2) |
| 3 months | | 1.5 (0–3) |
| **Hematoma at d0 ($cm^3$), median (Q1–Q3)** | | 4.5 (1–13.9) |
| **Hematoma at d1 ($cm^3$), median (Q1–Q3)** | | 4.1 (1–10.9) |
| **CCL5 at d0 (ng/mL), median (Q1–Q3)** | | 29.7 (18.2–45.6) |
| **CCL5 at d1 (ng/mL), median (Q1–Q3)** | | 28.9 (22.5–40.5) |
| **CCL5 at HD (ng/mL), median (Q1–Q3)** | | 33.9 (22.0–51.1) |

# CCL5 (RANTES): Resultados

International Journal of *Molecular Sciences*

MDPI

*Article*

**CCL5 Levels Predict Stroke Volume Growth in Acute Ischemic Stroke and Significantly Diminish in Hemorrhagic Stroke Patients**

Francisco José Julián-Villaverde [1], Marta Serrano-Ponz [2], Enrique Ramalle-Gómara [3], Alfredo Martínez [4,†] and Laura Ochoa-Callejero [4,5,*,†]

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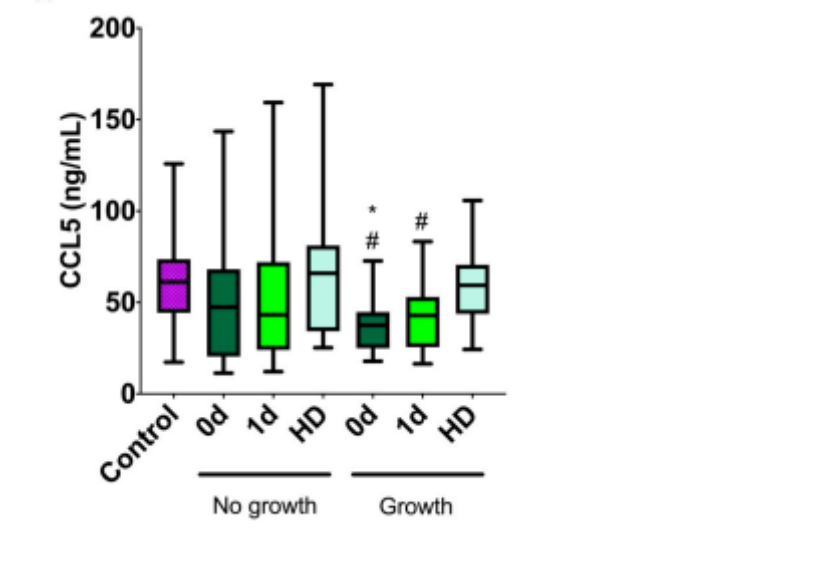
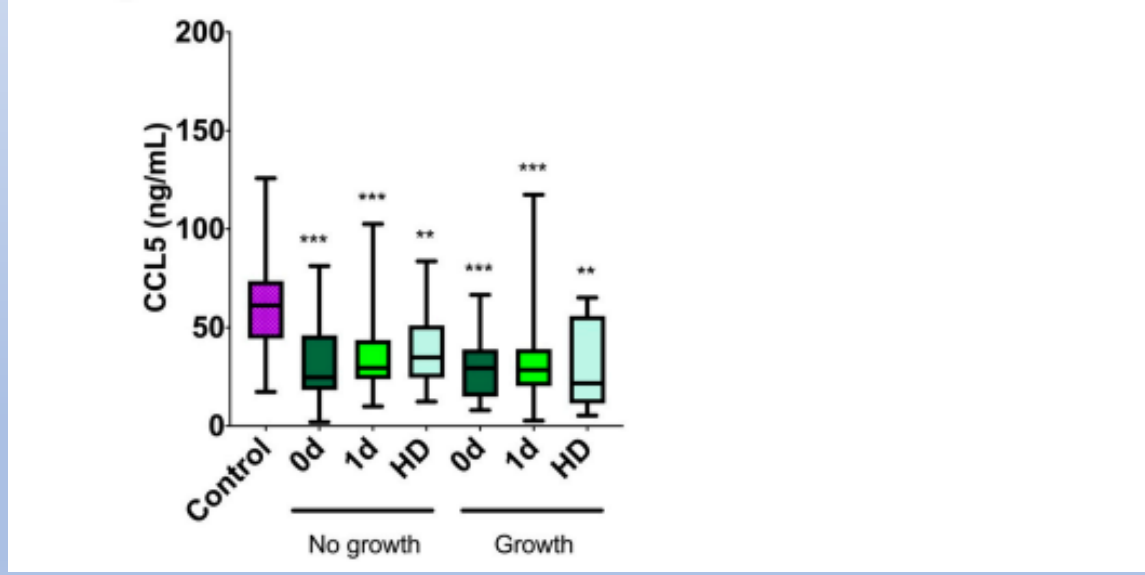
† These authors contributed equally to this work.

Crecimiento tamaño infarto y CCL5




CCL5 d0 (↓↓) predice crecimiento de lesión isquémica

Crecimiento tamaño hematoma y CCL5



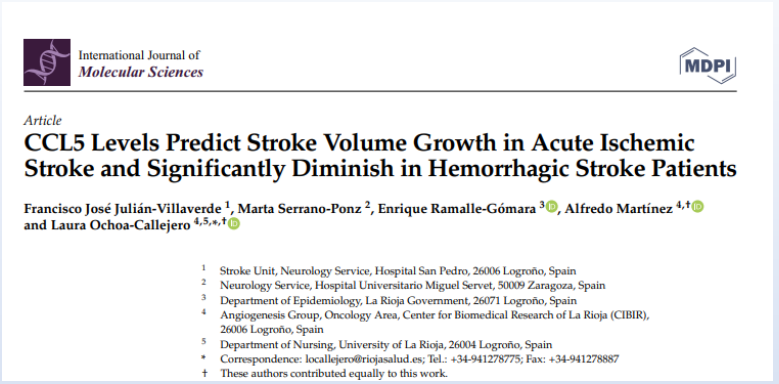

No diferencias en crecimiento hematoma
Niveles de CCL5 ↓↓en ictus hemorrágicos Vs sanos

# CONCLUSIONES

*Article*

**Adrenomedullin Is a Diagnostic and Prognostic Biomarker for Acute Intracerebral Hemorrhage**

Francisco J. Julián-Villaverde [1], Laura Ochoa-Callejero [2], Eva Siles [3], Esther Martínez-Lara [3] and Alfredo Martínez [2,*]



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- AM potencial como biomarcador diagnóstico en ictus hemorrágico
- Perfil temporal de niveles de AM es marcador pronóstico
  - Buen pronostico:  Asciende 1as 24 horas y normaliza en d7
  - Mal pronóstico: Valores estables
- CCL5 potencial marcador mal pronóstico en ictus isquémico
- CCL5 como marcador diagnóstico en ictus hemorrágico ?

# MUCHAS GRACIAS