Block A: Membrane Biology & Biochemistry

Lipid signalling and sphingolipid function

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Programme of the week

• Monday
  - general discussion: cellular signalling
  - sphingosine-1-phosphate and neurodegeneration (Morbus Alzheimer)

• Tuesday
  - bioactive fatty acid derivatives: endocannabinoids and eicosanoids
  - sphingosine-1-phosphate and ceramide-1-phosphate in inflammation

• Thursday
  - Samira Marx: Targeting sphingosine-1-phosphate axis in cancer

• Friday
  - Saskia Neuert: Bioactive lipid mediators in skin inflammation and immunity
Outline of objectives

General aspects on cell signalling

Signalling via:
G-protein coupled receptors
Receptor tyrosine kinases
Nuclear receptors

Signalling lipids:
Fatty acids
Eicosanoids
Endocannabinoids
Sphingolipids (S1P, C1P)

Pathological implications:
Neurodegeneration (Alzheimer)
Inflammation
Cancer

References:


http://dx.doi.org/10.1016/j.plipres.2012.07.001


Programme

• Introduction
  - Morbus Alzheimer: numbers and facts
  - Sphingolipids: history, structure, metabolism

• Sphingosine-1-phosphate (S1P) - bane and blessing
  - biological activity and mechanism of action
  - CIMES, a synthetic sphingosine analogue

• S1P-lyase KO and conditional KO
  - molecular bases of S1P-induced neurotoxicity
  - S1P-lyase-deficiency and neurodegeneration
  - S1P-lyase-deficiency and synaptic plasticity

• Conclusion and outlook
1906: 37. Meeting of doctors for the insane of southwest Germany in Tübingen
Alois Alzheimer reports about “a peculiar affection of the cerebral cortex” Auguste D.


AD most common neurodegenerative disease worldwide 36 mill. cases (2030: 66 mill. 2050: 115 mill.)

Costs worldwide: 604 bill. USD in 2010 (1% of the global GDP)
Histopathological findings reported by A. Alzheimer (1906)

“Miliary foci distributed all over the cortex, caused by the infiltration of a peculiar substance into the cortex”

“Weird neurofibrillary changes, that appeared like very thick tangles filling not only the cell body but also neuronal processes”

Images C & D are from Holtzman et al. Sci Transl. Med. 2011, 3, 1-17
Key neuropathological elements of AD

BAP-tists: senile (neuritic) plaques: extracellular aggregates of β-amyloid

TAU-ists: Neurofibrillary tangles: intracellular bundles of hyperphosphorylated tau
Scheme of major proteolytic processing pathways of APP

A

APP<sub>S-β</sub>

β

β

γ

APP

APP CTF<sub>β</sub>

Aβ

B

APP<sub>S-α</sub>

α

γ

APP

APP CTF<sub>α</sub>

p3

van Echten-Deckert & Walter, Prog Lipid Res 2012
Sphingolipids: History

Johann Ludwig Wilhelm Thudichum
1884
Glycosphingolipids form cell type specific profiles

van Echten-Deckert & Herget, BBA 2006
Sphingolipids: Main metabolic pathways

De novo formation

Degradation

Recycling

Sulfatide

GalCer

GlcCer

LacCer

Gangliosides

van Echten-Deckert & Walter, Prog Lipid Res 2012
Physiological/clinical relevance of bioactive sphingolipids

Ser + FA-CoA
↓
↓
Sa
↓
Sphingomyelin
DHCer

GlcCer

Ceramide

C1P

S1P

MDR

GSL

apoptosis
differentiation
inflammation
insulin resistance
senescence
stress response

MDR

glucose tolerance

brain function
morphogenesis
tumour genesis

anti-apoptosis
proliferation
migration
inflammation
angiogenesis
wound healing

inflammation

angiogenesis
wound healing
Sphingolipids - Metabolism

De novo synthesis

Glycosphingolipids

Phosphosphingolipids

Recycling pathway

Degradation

Only one enzyme is known that cleaves the sphingoid backbone.
Dual Action of S1P: Extracellular Ligand and Intracellular Second Messenger

- Survival
- Differentiation
- Motility
- Cytoskeleton rearrangements
- Inflammation
- Angiogenesis

Sphingosine kinase

Sphingosine → S1P

S1P_1-5

Trimeric G-proteins

Adenylate-cyclase

PLCβ

Monomeric G-proteins

Intracellular targets?

- Proliferation
- Ca^{2+} homeostasis
- Anti-apoptosis
The ceramide/S1P-rheostat in cell growth regulation

Always applicable?
cis-4-Methylsphingosine (cimes) is a synthetic prodrug for a metabolically stable S1P-analogue
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Summary

Caspase-9
Caspase-3
neuronal apoptosis
p35
p25
CDK5
Rb
Z-LEHD-FMK
Caspase-12
tau
ER-stress
intracellular
extracellular
Ca²⁺
cell cycle reactivation

Hagen et al, Cell Death Differ, 2011
Conclusions and outlook

• Sphingosine-1-phosphate (S1P) is a neuronal death signal, when generated by SK2 and impaired degradation
• Calpain is an essential mediator of S1P-induced neurotoxicity
• On cellular and molecular level S1P neurotoxicity parallels that of Aβ
• S1P-lyase expression is correlated with neuronal death
• S1P-lyase deficiency is correlated with Alzheimer characteristics:
  • Hyperphosphorylation of tau
  • Impaired APP-processing
  • Elevated levels of cholesteryl-ester

S1P stimulates BACE1, the rate-limiting enzyme for Aβ production (Takasugi et al., 2011, J. Neurosci.)

Conditional knockout mouse: neuron-specific inactivation of S1P-lyase