

Departamento de Imunologia



ICB



NEUROIMUNOLOGIA

Prof. Dr. Leandro Pires Araujo



Neuroimunologia

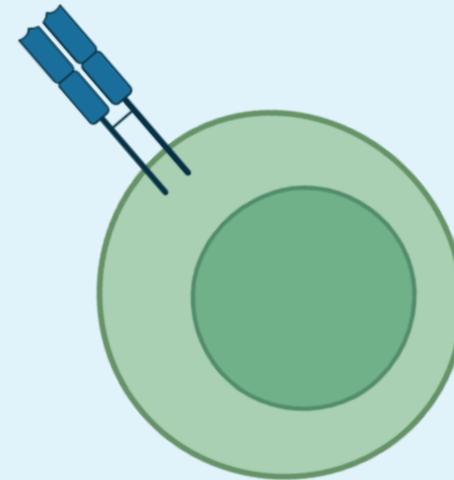
Conceitos Neuroimunologia

Vias de Comunicação

Mensageiros Químicos

Células imunológicas

Imunopatologias





Neuroimunologia

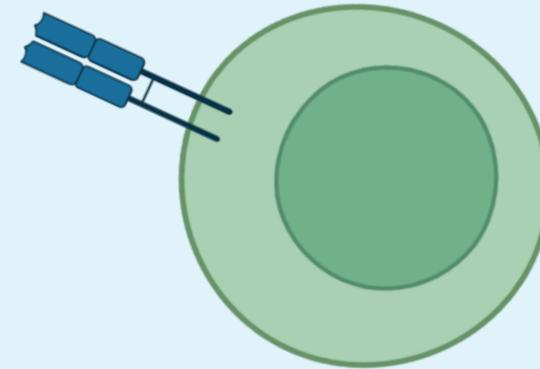
Conceitos Neuroimunologia

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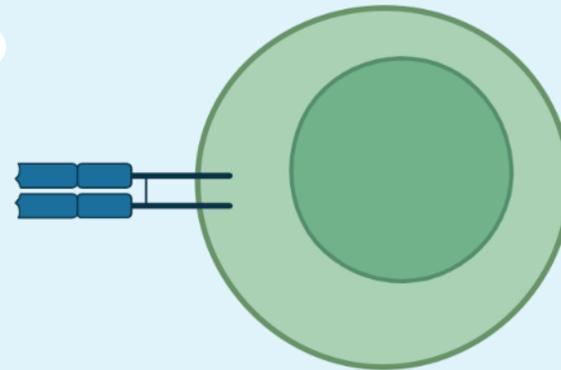


Neuroimunologia

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Células imunológicas

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Neuroimunologia

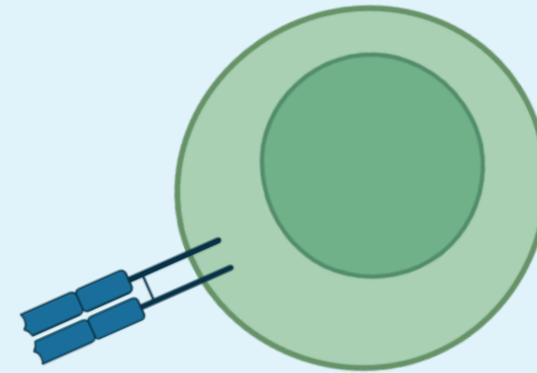
Conceitos Neuroimunologia

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Neuroimunologia

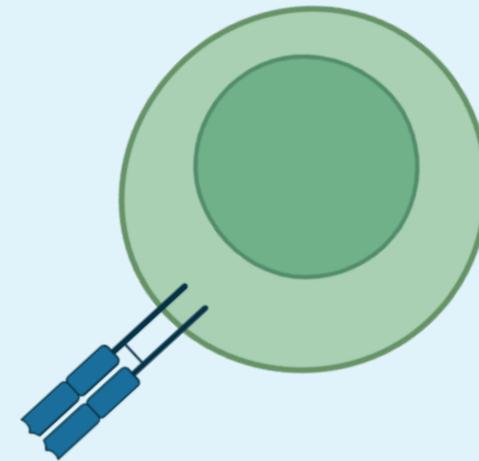
Conceitos Neuroimunologia

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Neuroimunologia

O que é neuroimunologia?

► Neuroimunomodulação

A neuroimunomodulação é a regulação bidirecional entre os sistemas nervoso e imunológico.

Sinais neurais influenciam as respostas imunes.

Sinais imunológicos afetam a função neural.

► **Comunicação bidirecional**

O sistema nervoso regula as respostas imunes por meio de neurotransmissores e neuropeptídeos, enquanto o sistema imunológico influencia a função cerebral por meio de citocinas e outras moléculas sinalizadoras.

► Homeostase e defesa

A neuroimunologia investiga como essa comunicação bidirecional ajuda a manter a homeostase e a defender o organismo contra infecções, lesões e estresse

► Doenças e disfunções

A neuroimunologia examina como a desregulação dessa interação pode contribuir para condições como esclerose múltipla, doença de Alzheimer, inflamação crônica e até distúrbios psiquiátricos, como a depressão.

Neuroinflamação e a Encefalomielite Autoimune Experimental

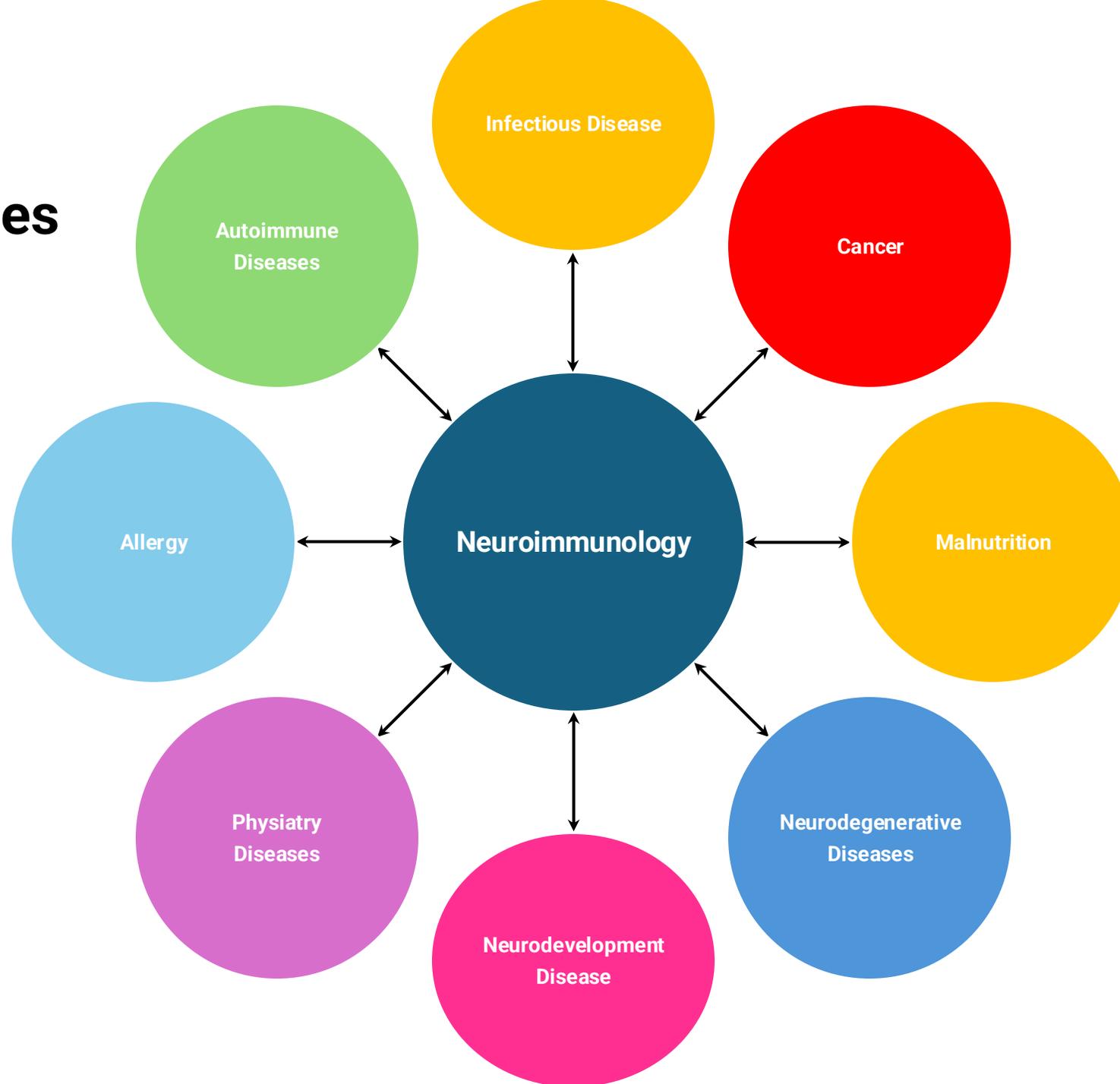


1885 - Development of the rabies vaccine by Louis Pasteur.

► Neuroimmunomodulation – Brief History

- 1984 - Norverva Spector organizes 1th International Neuroimmune modulation Symposium at NIH;
- 1990 - International Society for Neuroimmunomodulation
- The Journal of Neuroimmunology (1981), Brain, Behaviour and Immunity (1987), Neuroimmunomodulation (1994) and Journal of Neuroinflammation (2004)

Interações Neuroimunes



► Citocina imunoregulatórias

Immunoregulatory Feedback Between Interleukin-1 and Glucocorticoid Hormones

HUGO BESEDOVSKY, ADRIANA DEL REY, ERNST SORKIN,
CHARLES A. DINARELLO

The production and action of immunoregulatory cytokines, including interleukin-1 (IL-1), are inhibited by glucocorticoid hormones in vivo and in vitro. Conversely, glucocorticoid blood levels were increased by factors released by human leukocytes exposed to Newcastle disease virus preparations. This activity was neutralized by an antibody to IL-1. Therefore the capacity of IL-1 to stimulate the pituitary-adrenal axis was tested. Administration of subpyrogenic doses of homogeneous human monocyte-derived IL-1 or the pI 7 form of human recombinant IL-1 to mice and rats increased blood levels of adrenocorticotrophic hormone (ACTH) and glucocorticoids. Another monokine, tumor necrosis factor, and the lymphokines IL-2 and γ -interferon had no such effects when administered in doses equivalent to or higher than those of IL-1. The stimulatory effect of IL-1 on the pituitary-adrenal axis seemed not to be mediated by the secondary release of products from mature T lymphocytes since IL-1 was endocrinologically active when injected into athymic nude mice. These results strongly support the existence of an immunoregulatory feedback circuit in which IL-1 acts as an afferent and glucocorticoid as an efferent hormonal signal.

Administração de IL-1 e ACTH e Corticosterona

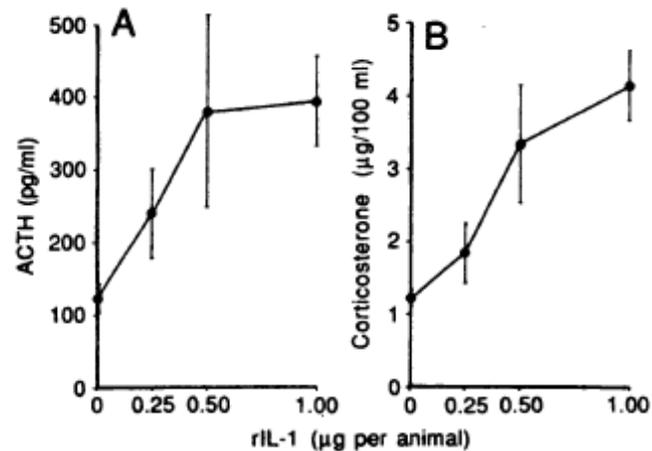


Fig. 1. Changes in ACTH and corticosterone blood levels in C3H/HeJ mice after injection of different doses of rIL-1. The rIL-1 was obtained as described in the legend to Table 2. C3H/HeJ mice were given different dilutions of rIL-1 injected intraperitoneally. Two hours later, the animals were killed and (A) ACTH and (B) corticosterone serum levels were determined by radioimmunoassay. Each point in the curves represents the mean \pm SEM of hormone determinations from seven or eight animals.

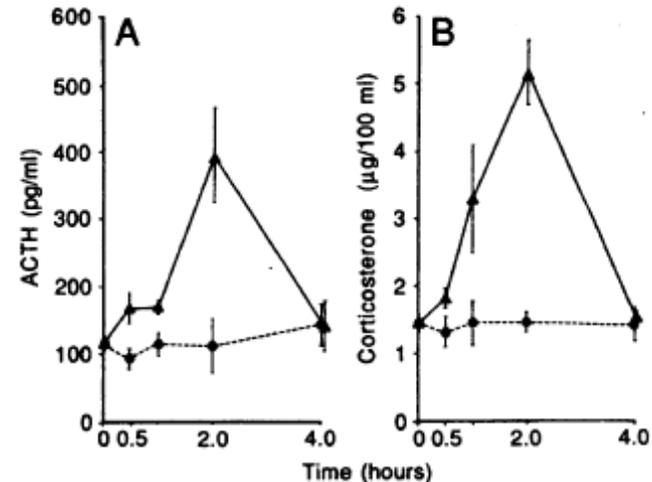


Fig. 2. Time course of increase in ACTH and corticosterone after rIL-1 administration to C3H/HeJ mice. The mice received 1 µg of rIL-1 in 0.5 ml of control medium (—) or 0.5 ml of control medium (---) injected intraperitoneally. At the time indicated, animals were killed, and (A) ACTH and (B) corticosterone serum levels were determined by radioimmunoassay. Each point in the curves represents the mean \pm SEM of hormone determinations from seven or eight animals.

Administração de IL-1 em camundongos Nude

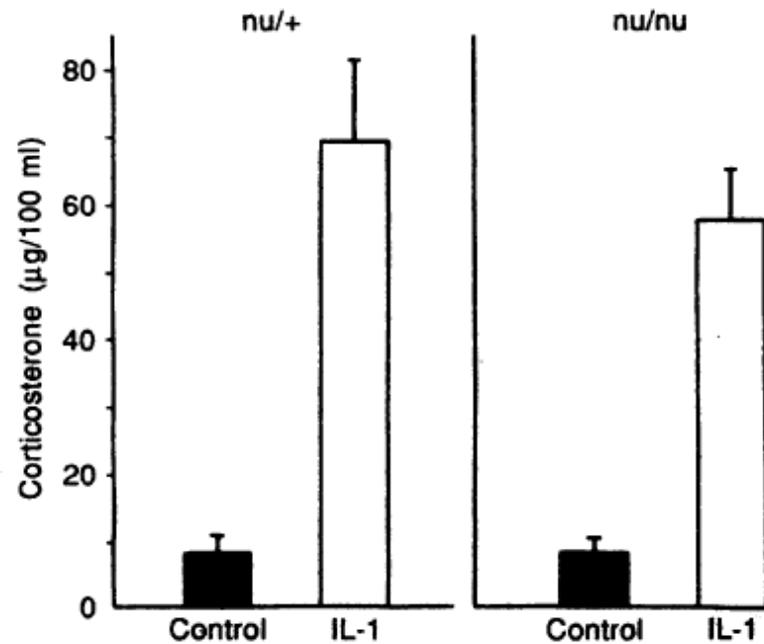
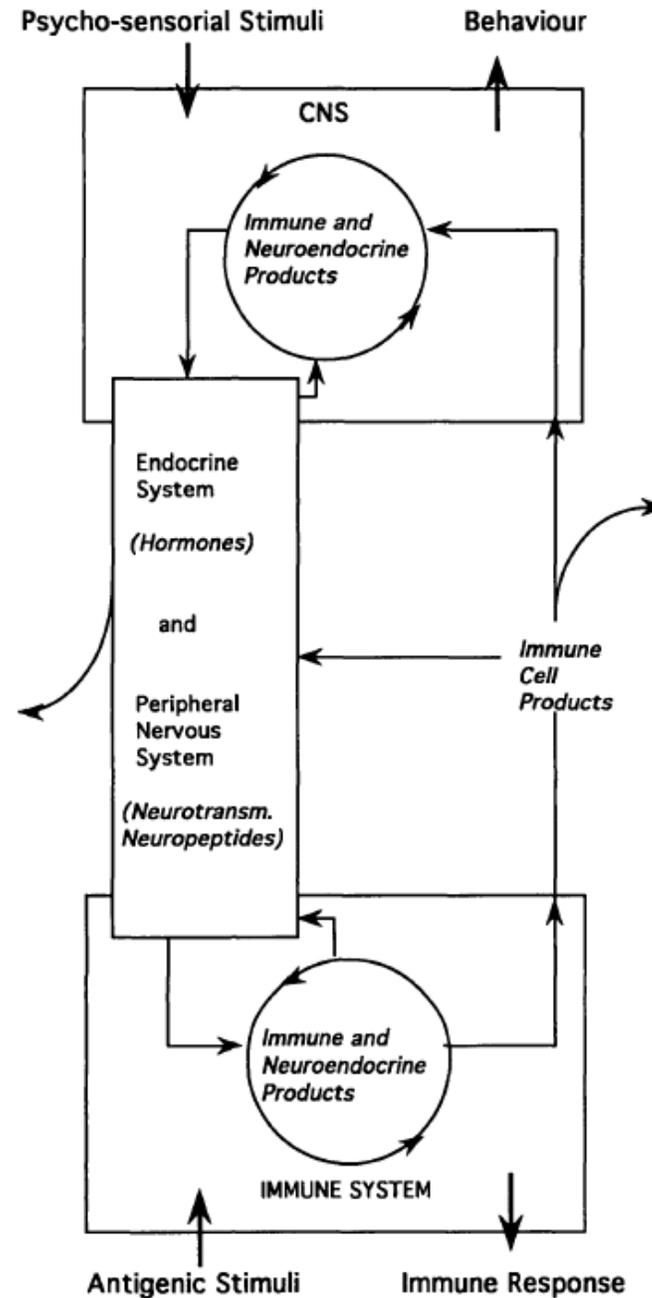


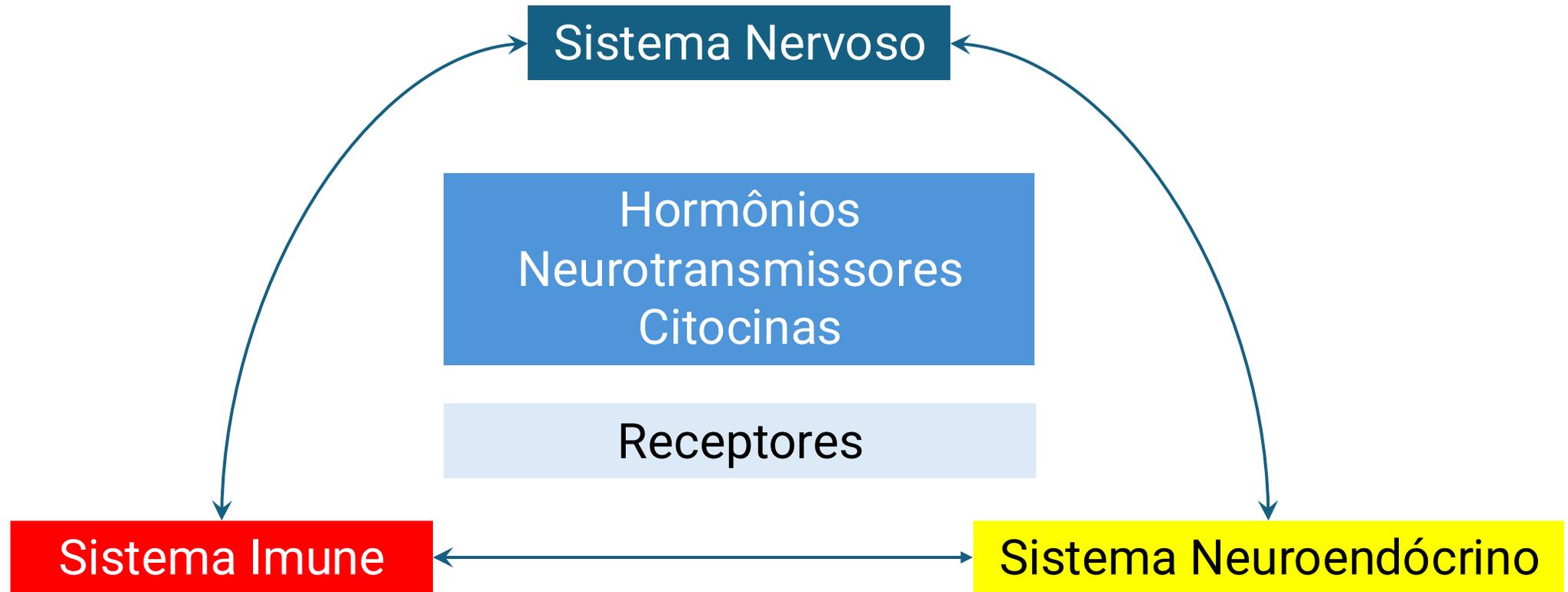
Fig. 3. Changes in corticosterone blood levels in athymic nude mice after administration of rIL-1.

Supernatant	n	Plasma corticosterone (µg/100 ml)
Control	9	12.50 ± 3.16
Control + anti-IL-1	12	12.51 ± 2.82
HPBL + NDV	11	52.99 ± 4.23
HPBL + NDV + anti-IL-1	13	14.47 ± 3.78

► A conversa entre Sistema Nervoso e Sistema Imune

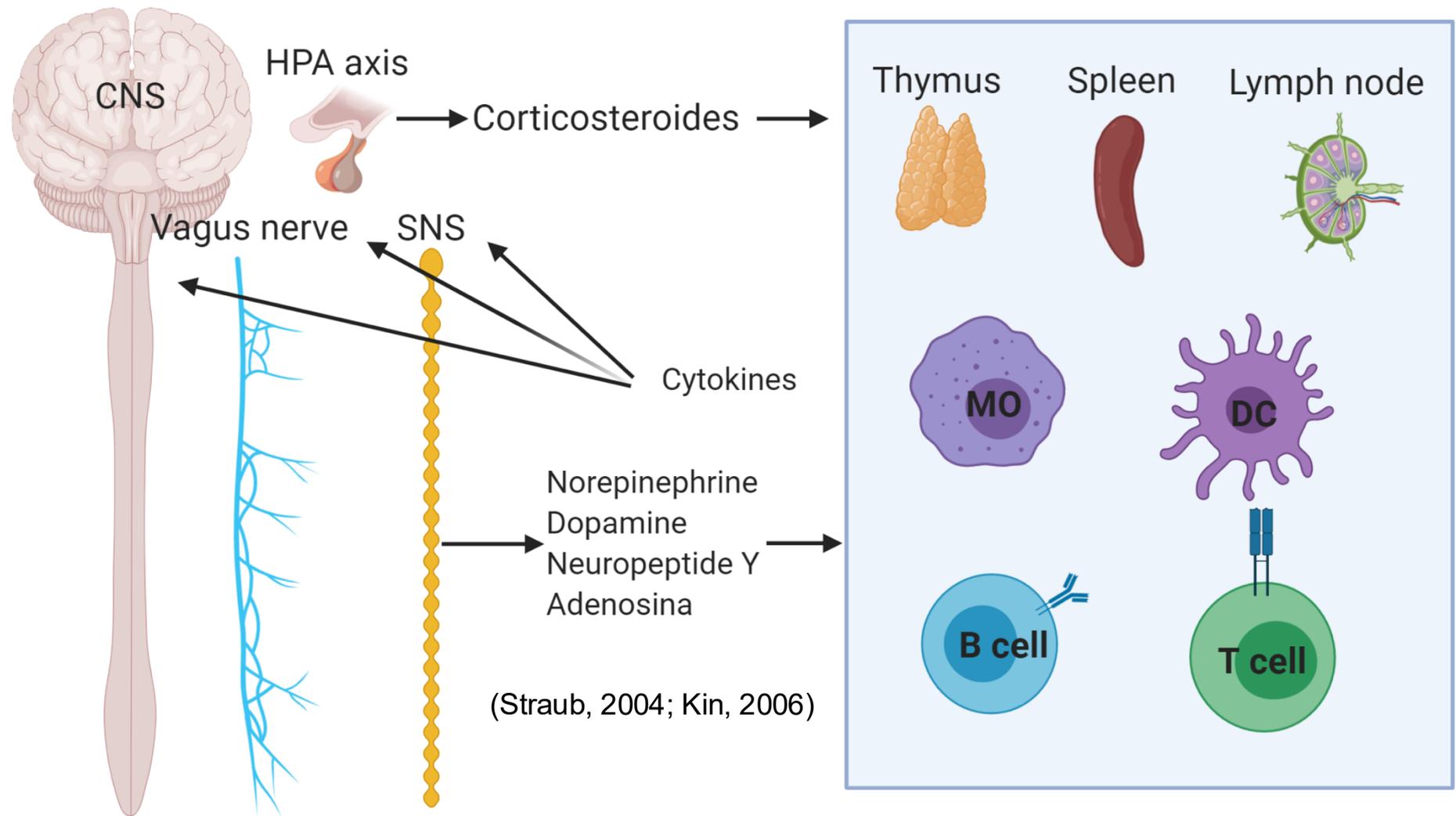


► Comunicação entre os sistemas nervoso e imunológico

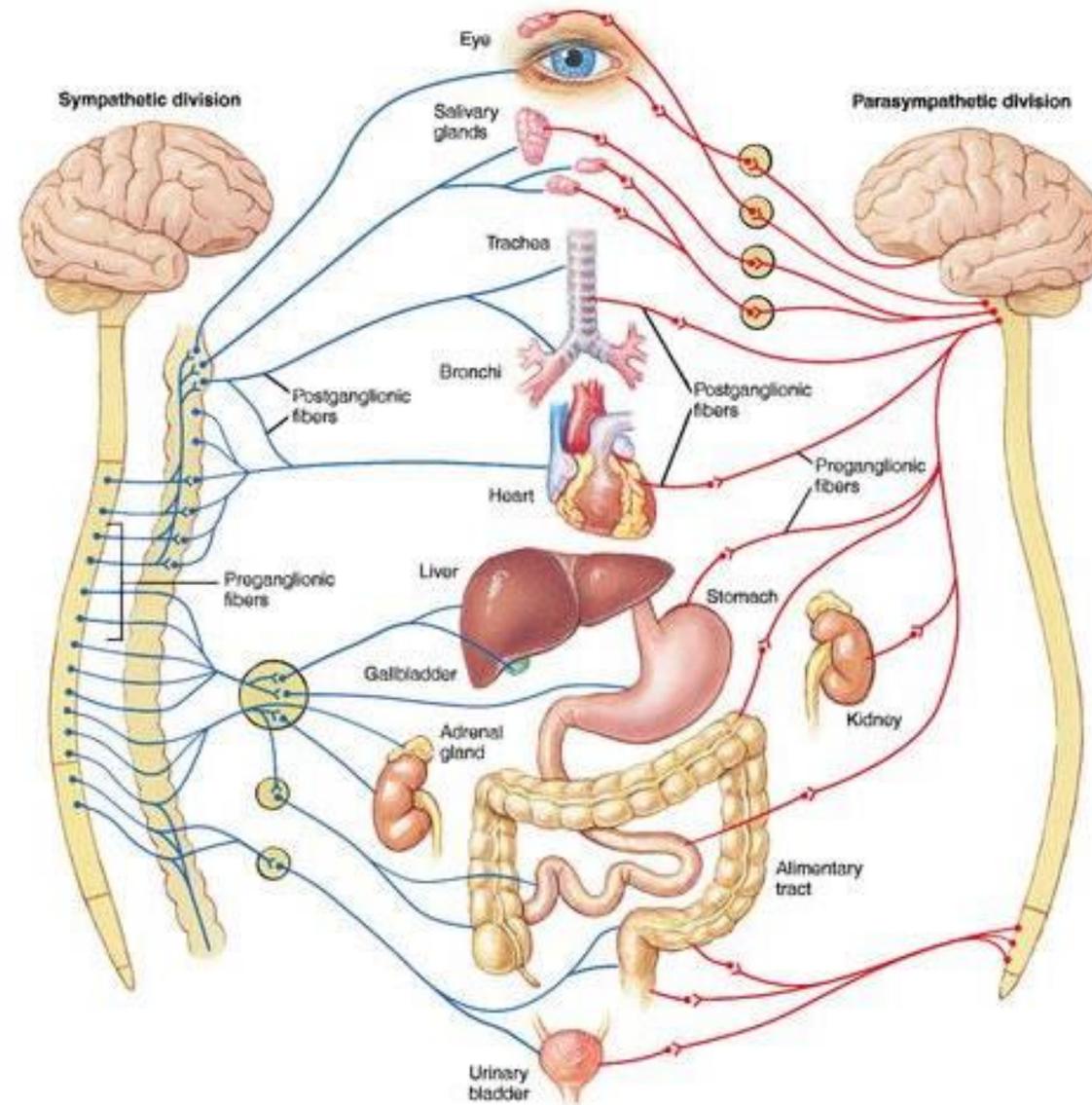


Nervous System

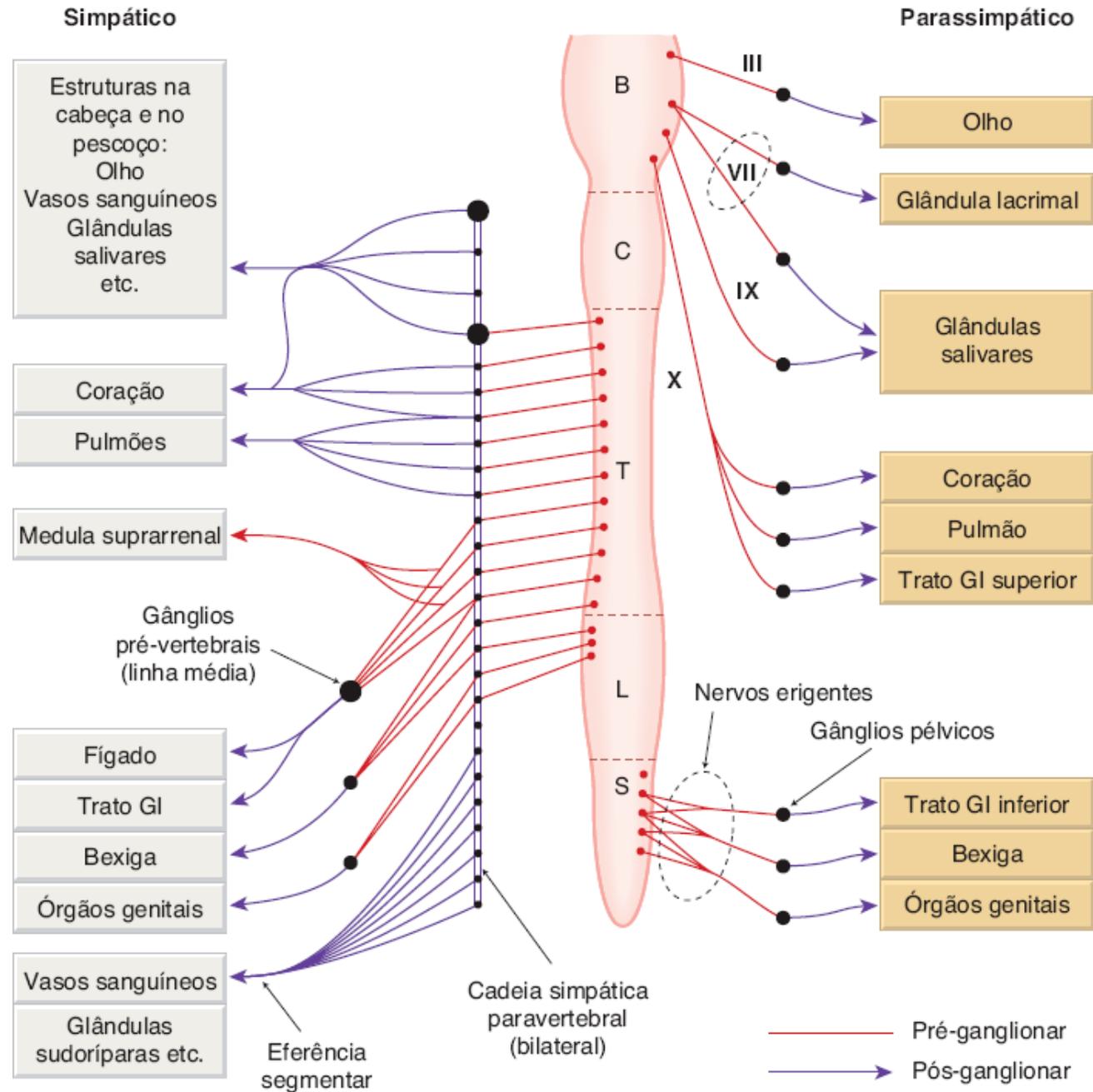
Immune System



Sistema Nervoso Autônomo



Sistema Nervoso Autônomo



Inervação dos tecidos linfoides e da mucosa

Sistema Nervoso Simpático (SNS)

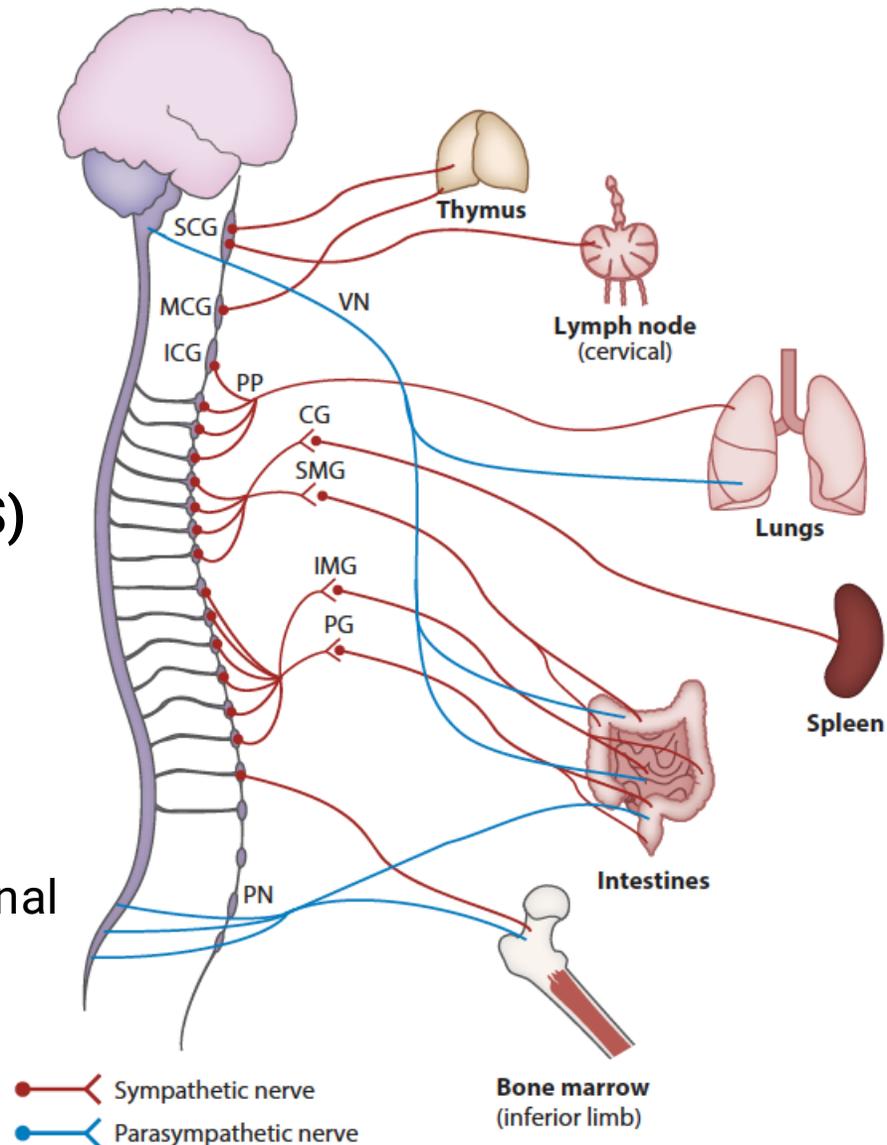
- medula espinhal toracolombar

Sistema Nervoso Parassimpático (PaNS)

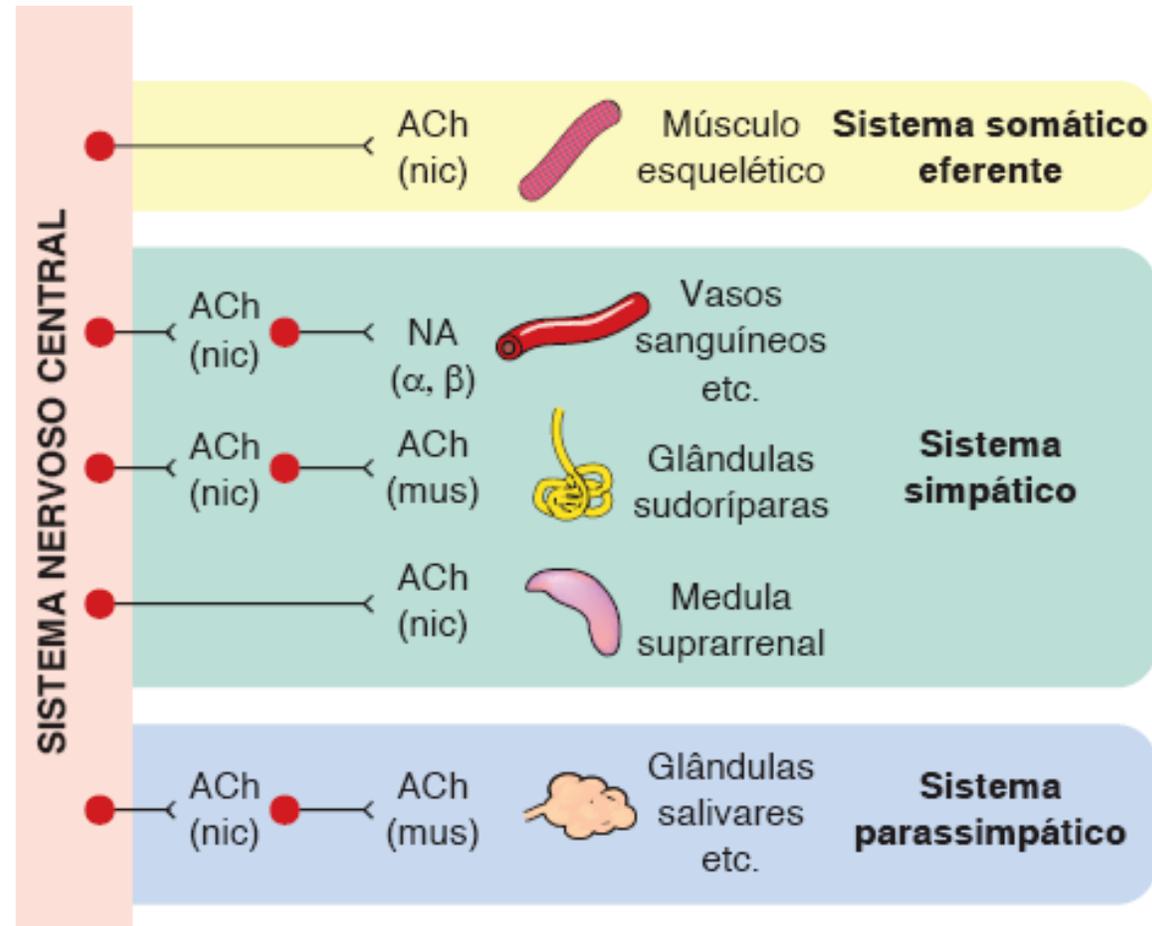
- nervos cranianos e medula espinhal sacral

Sistema Nervoso Entérico (ENS)

- dentro das paredes do trato gastrointestinal



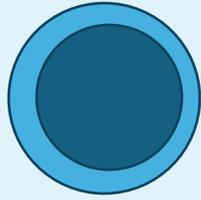
Mediadores químicos do Sistema Nervoso



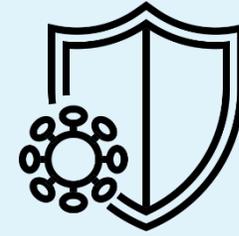
► Mediadores químicos do Sistema Nervoso

Role of some presynaptic inhibitory and stimulatory receptors in Ca^{2+} -dependent transmitter release from noradrenergic axon terminals in the CNS and periphery^a

Receptor Ligand	Receptor Subtype	Effect
Norepinephrine	α_2^b (A and C)	Inhibition
	β_2 (spleen ^b)	Potentiation
Acetylcholine	M_1	Potentiation
	M_2^b (M_3)	Inhibition
	N^b (neuronal)	Potentiation
Neuropeptide Y	Y_2 (spleen ^b)	Inhibition
Dopamine	D_2 (spleen ^b)	Inhibition
Adenosine	A_1^b	Inhibition
ATP	P_2	Potentiation
Opioid peptide ^b	μ	Inhibition
	δ	Inhibition
	κ	Inhibition
Prostaglandin	PGE_2 (thymus ^b)	Inhibition
Serotonin	$5-HT_{1B}$	Inhibition

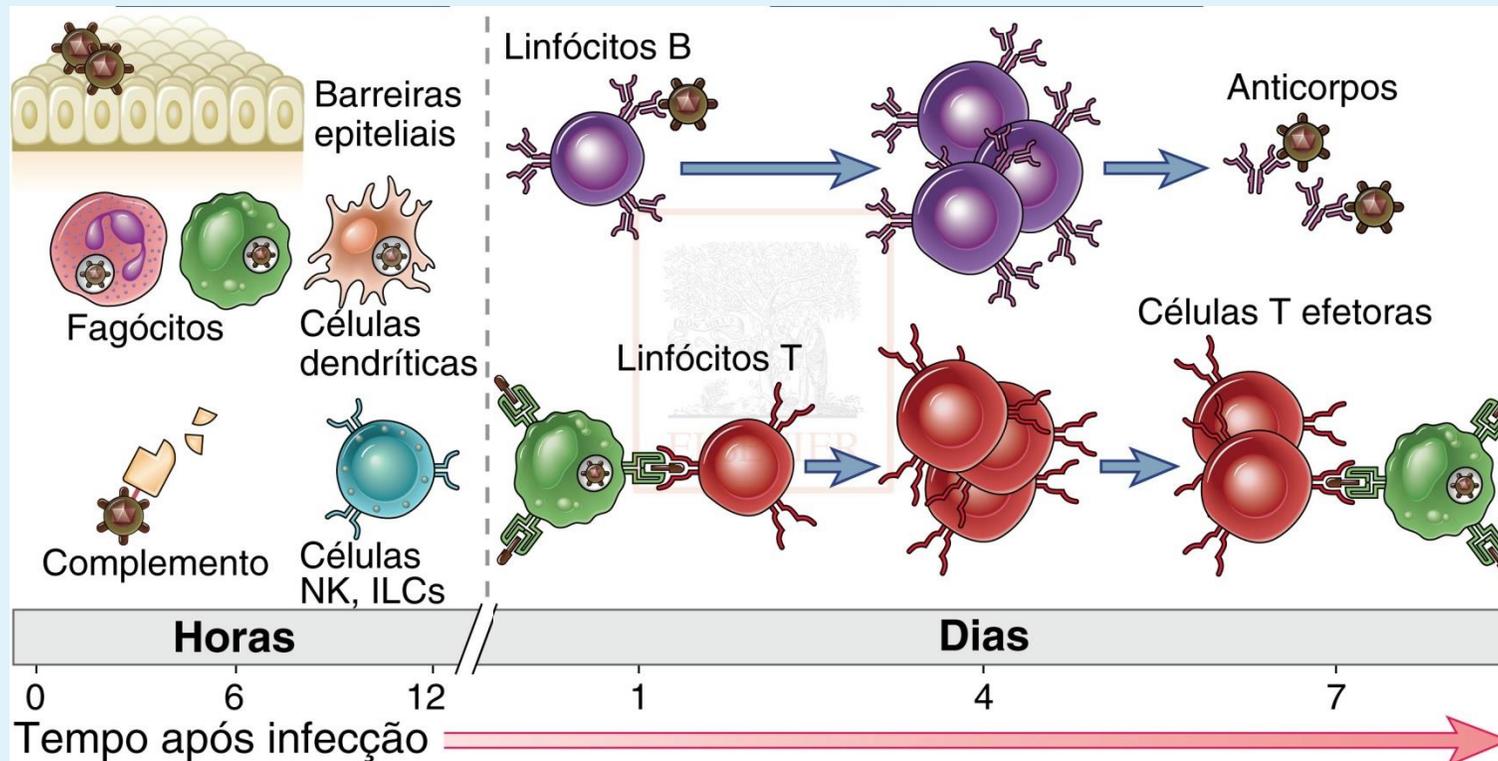
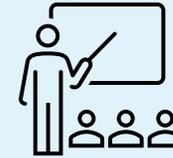


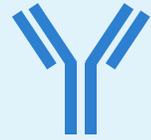
RESPOSTA IMUNE



INATA

ADAPTATIVA



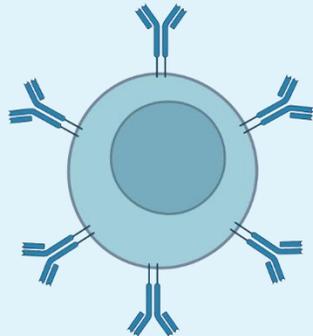


IMUNIDADE

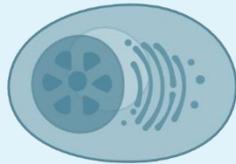


HUMORAL ADAPTATIVA

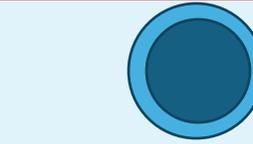
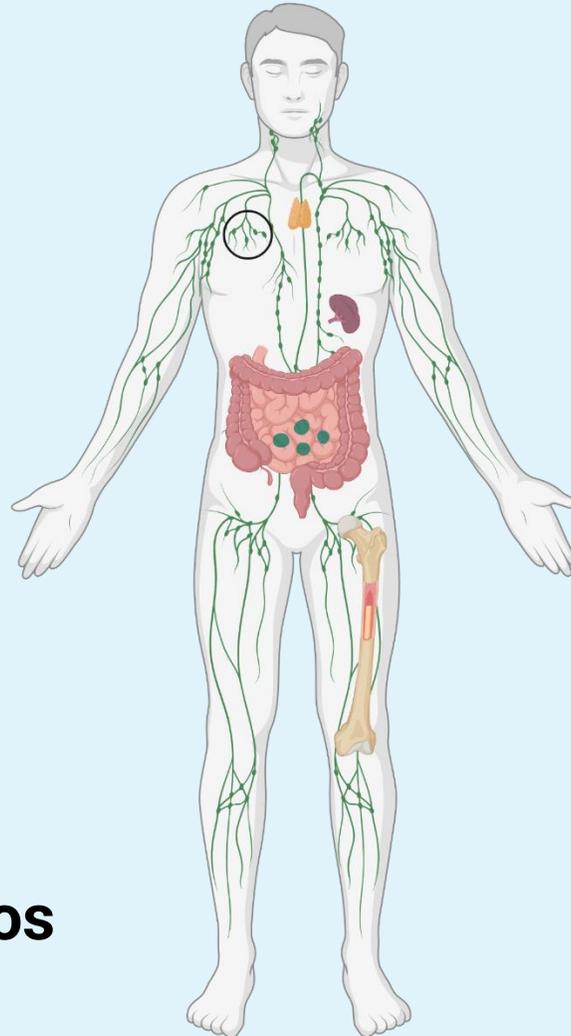
Linfócito B



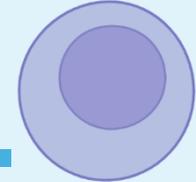
Plasmócitos



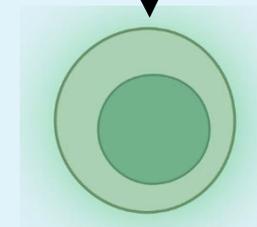
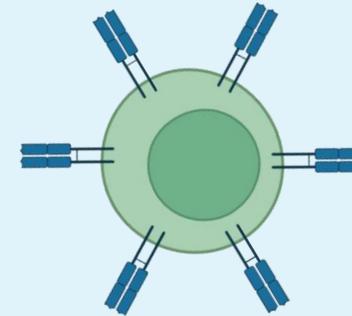
Anticorpos



CELULAR



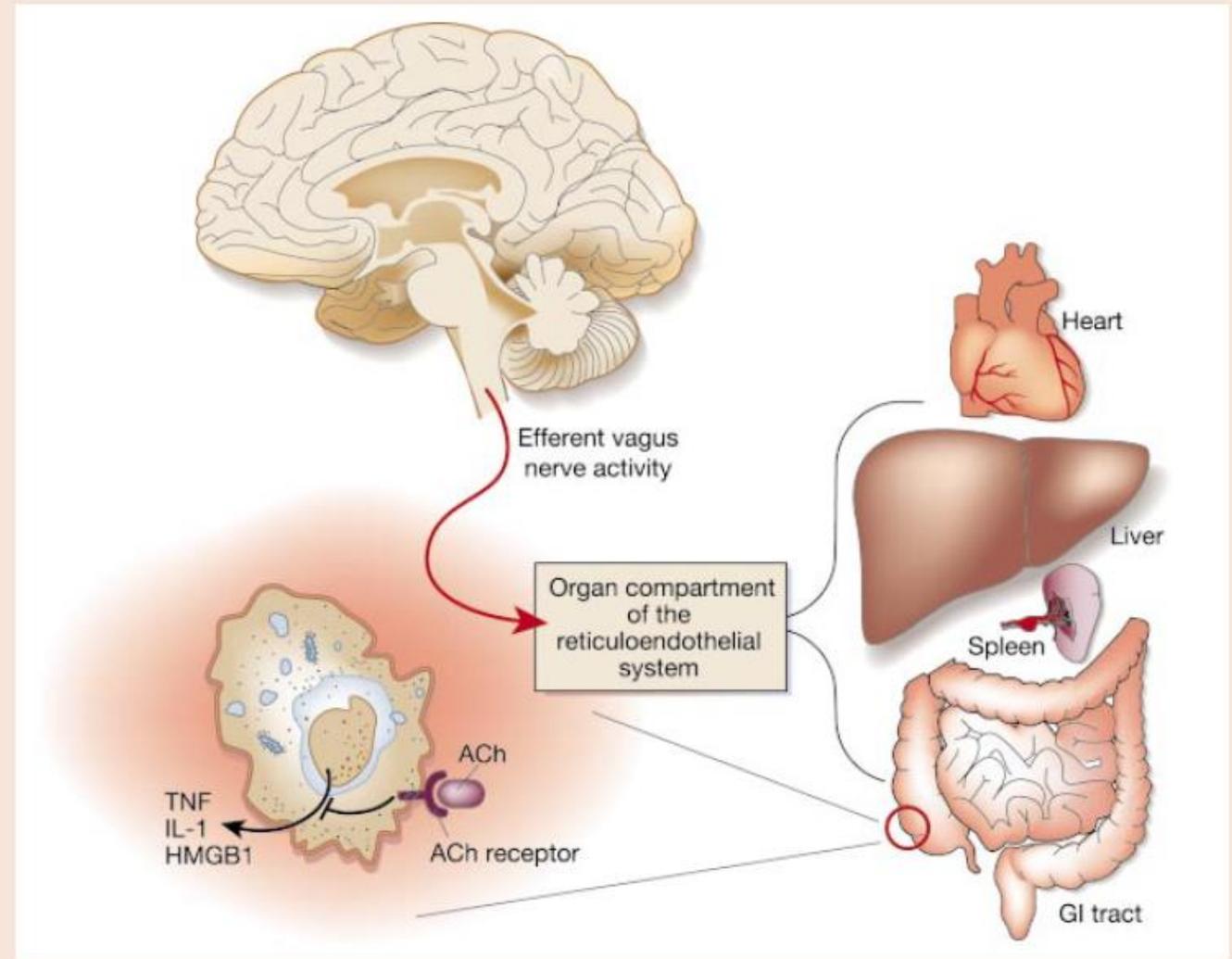
Linfócito T



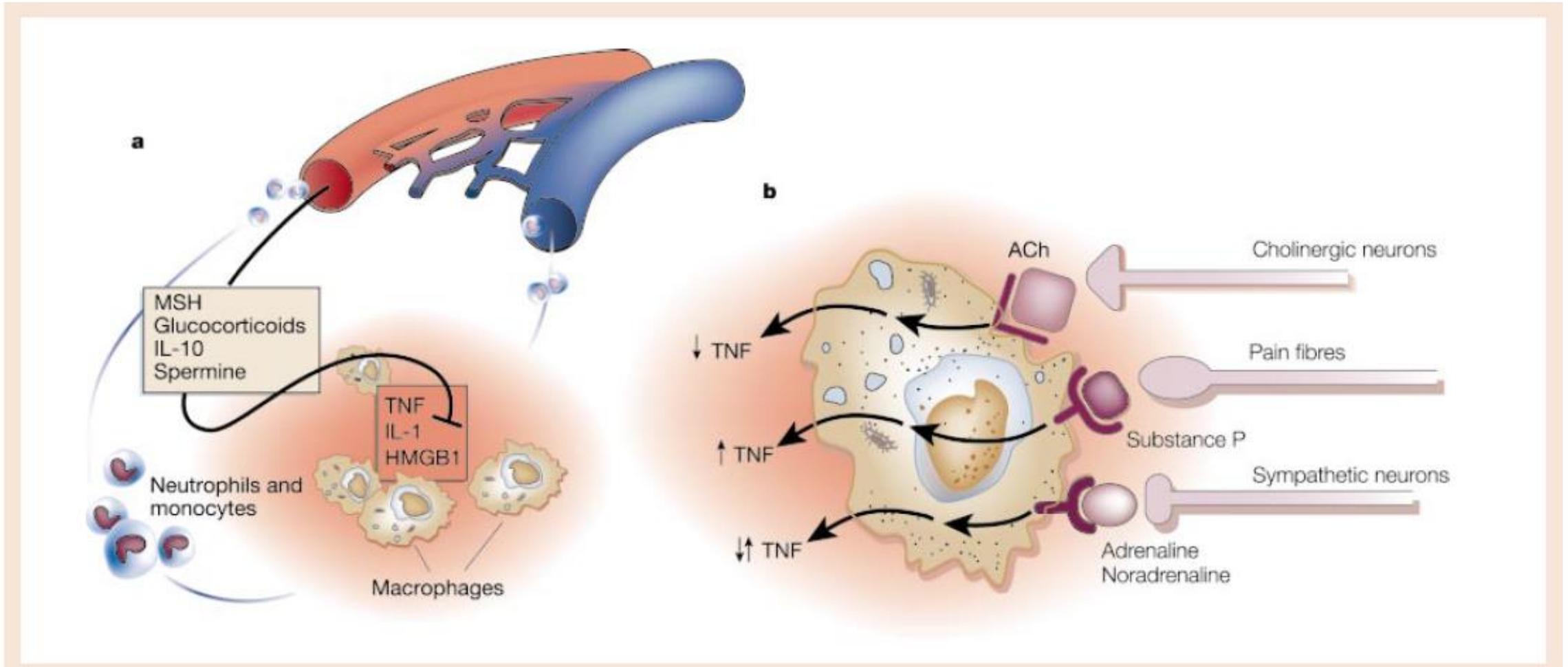
Célula T efetora

► Sistema Nervoso Parassimpático

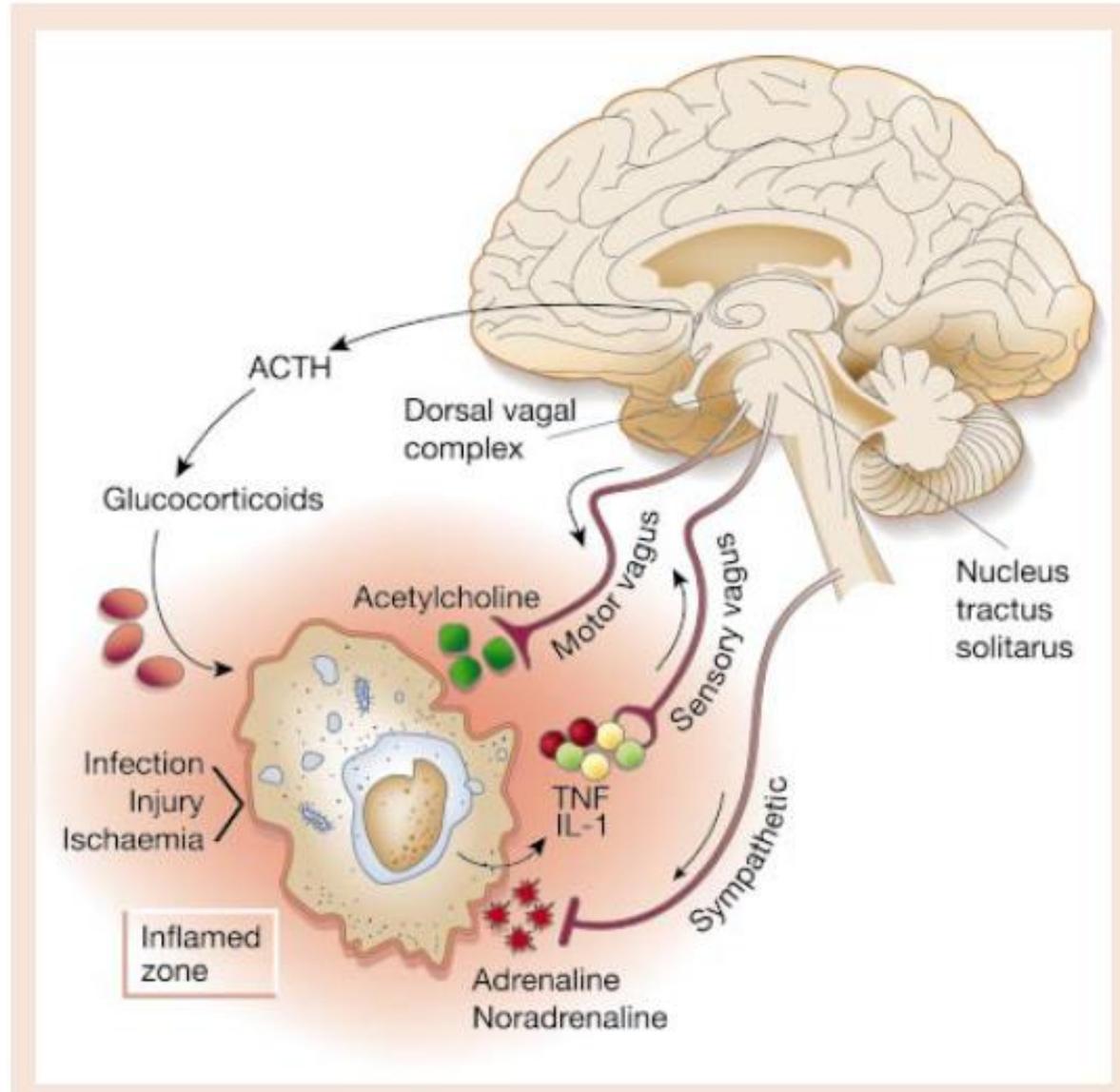
Figure 1 The cholinergic anti-inflammatory pathway. Efferent activity in the vagus nerve leads to acetylcholine (ACh) release in organs of the reticuloendothelial system, including the liver, heart, spleen and gastrointestinal tract. Acetylcholine interacts with α -bungarotoxin-sensitive nicotinic receptors (ACh receptor) on tissue macrophages, which inhibit the release of TNF, IL-1, HMGB1 and other cytokines.



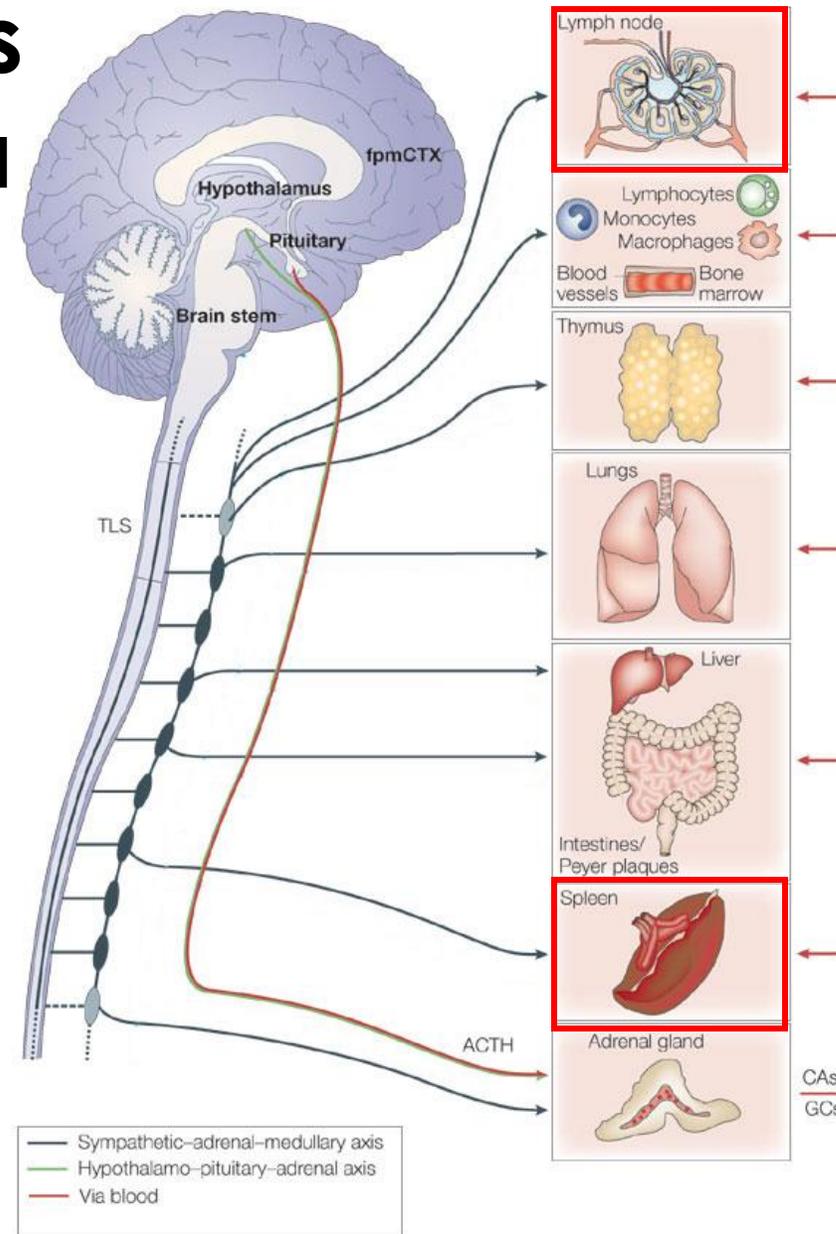
Sistema Nervoso Autônomo



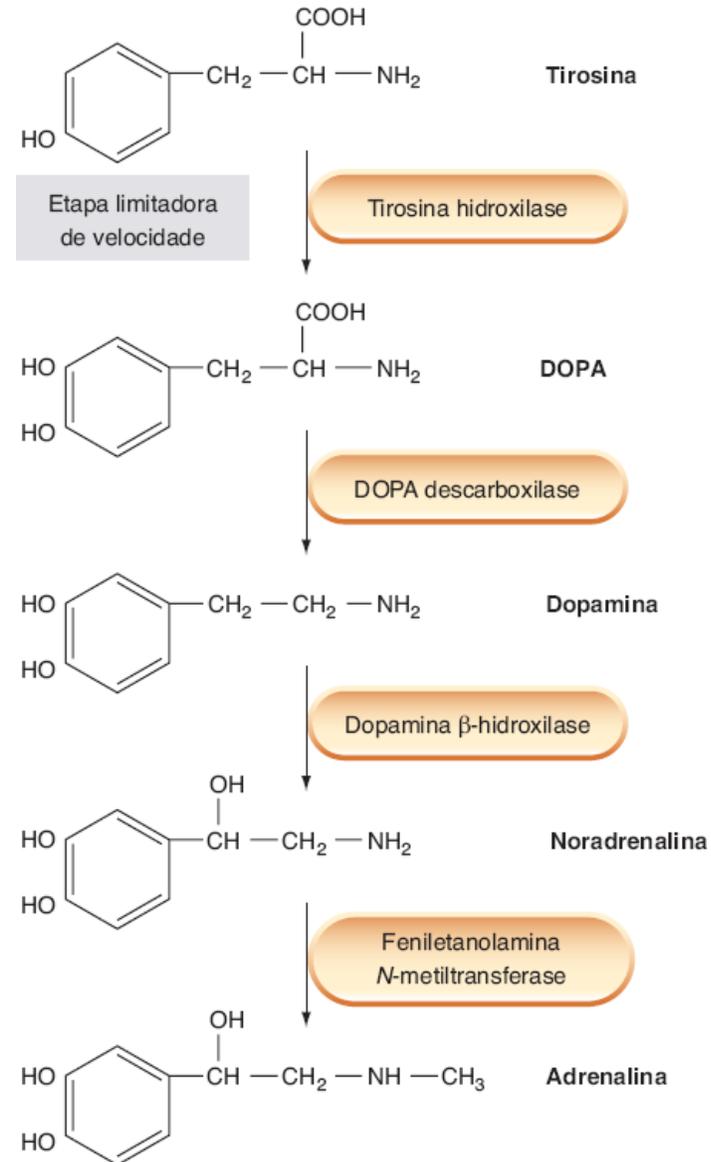
Reflexo anti-inflamatório



► Inervação dos órgãos linfoides pelo Sistema Nervoso Simpático



► Estrutura das principais catecolaminas



► Classificação dos receptores adrenérgicos

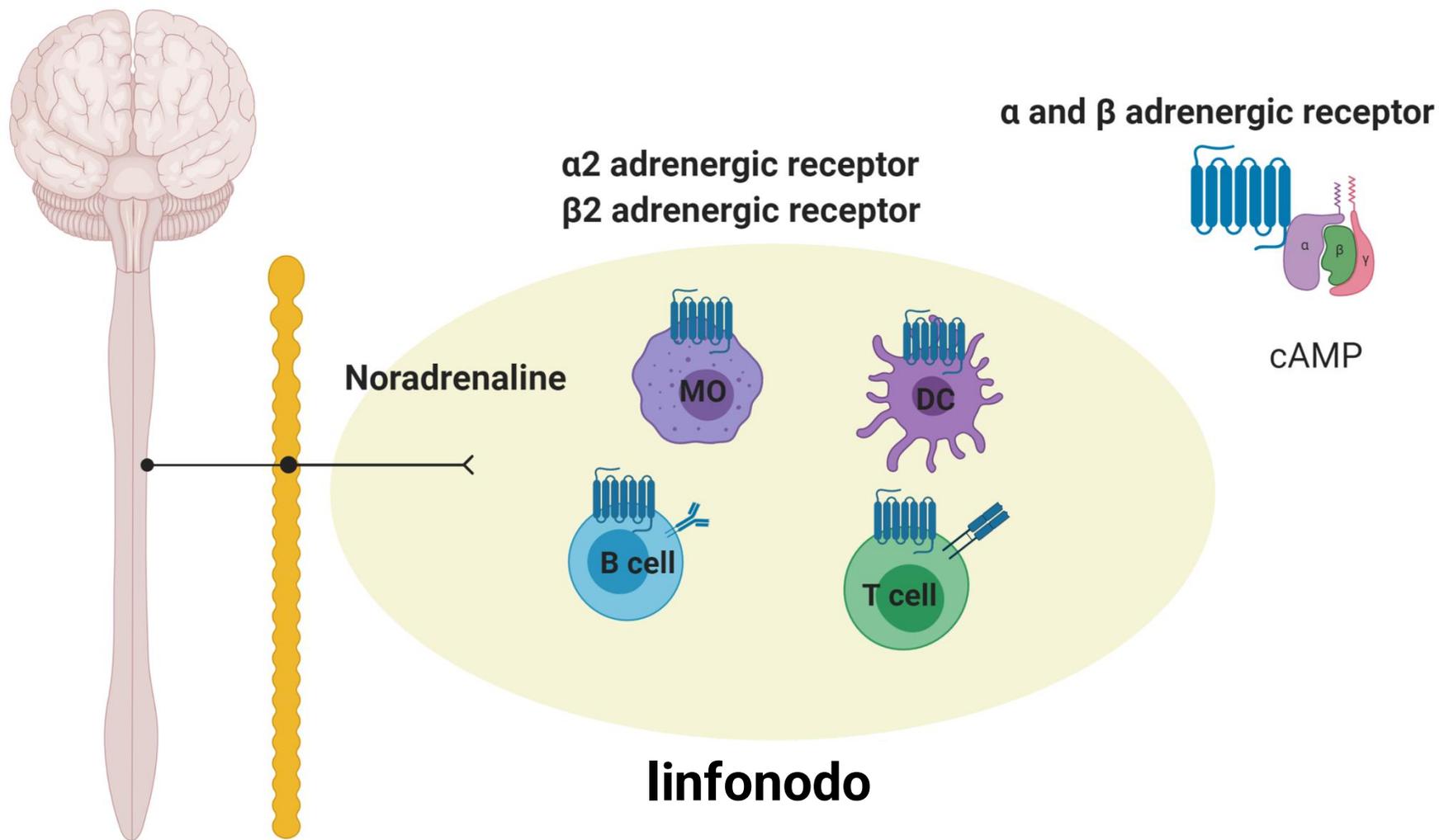


Classificação dos receptores adrenérgicos

- A principal classificação farmacológica em subtipos α e β baseou-se, a princípio, na ordem de potência entre agonistas e, depois, em antagonistas seletivos
- Subtipos de receptores adrenérgicos:
 - Dois subtipos principais de receptor α -adrenérgicos, α_1 e α_2 , cada um dividido em três subtipos adicionais (α_{1A} , α_{1B} , α_{1D} e α_{2A} , α_{2B} , α_{2C})
 - Três subtipos de receptores β -adrenérgicos (β_1 , β_2 , β_3)
 - Todos pertencem à superfamília de receptores acoplados à proteína G (ver Capítulo 3)
- Segundos mensageiros:
 - Os receptores α_1 ativam a fosfolipase C por meio da G_q , produzindo trifosfato de inositol e diacilglicerol como segundos mensageiros
 - Os receptores α_2 modulam os canais de Ca^{2+} e de K^+ por meio de subunidades β_a da proteína G e inibem a adenilato ciclase por meio da α_i (todavia, o AMPc citoplasmático nas terminações nervosas em geral está baixo em condições basais, o que limita a importância desse segundo mecanismo)
 - Todos os tipos de receptores β estimulam a adenilato ciclase por G_s
- Os principais efeitos da ativação dos receptores são:
 - Receptores α_1 : vasoconstrição, relaxamento do músculo liso gastrointestinal e glicogenólise hepática
 - Receptores α_2 : inibição da liberação de transmissores (incluindo a liberação de noradrenalina e de acetilcolina dos nervos autônomos), causada pela abertura dos canais de K^+ e inibição dos canais de Ca^{2+} ; agregação plaquetária; contração do músculo liso vascular; inibição da liberação de insulina
 - Receptores β_1 : aumento da frequência e da força cardíacas
 - Receptores β_2 : broncodilatação, vasodilatação, relaxamento do músculo liso visceral, glicogenólise hepática, tremor muscular
 - Receptores β_3 : lipólise e termogênese, relaxamento do músculo detrusor da bexiga.

Painel de leitura do documento

► Expressão dos receptores adrenérgicos nas células do sistema imune

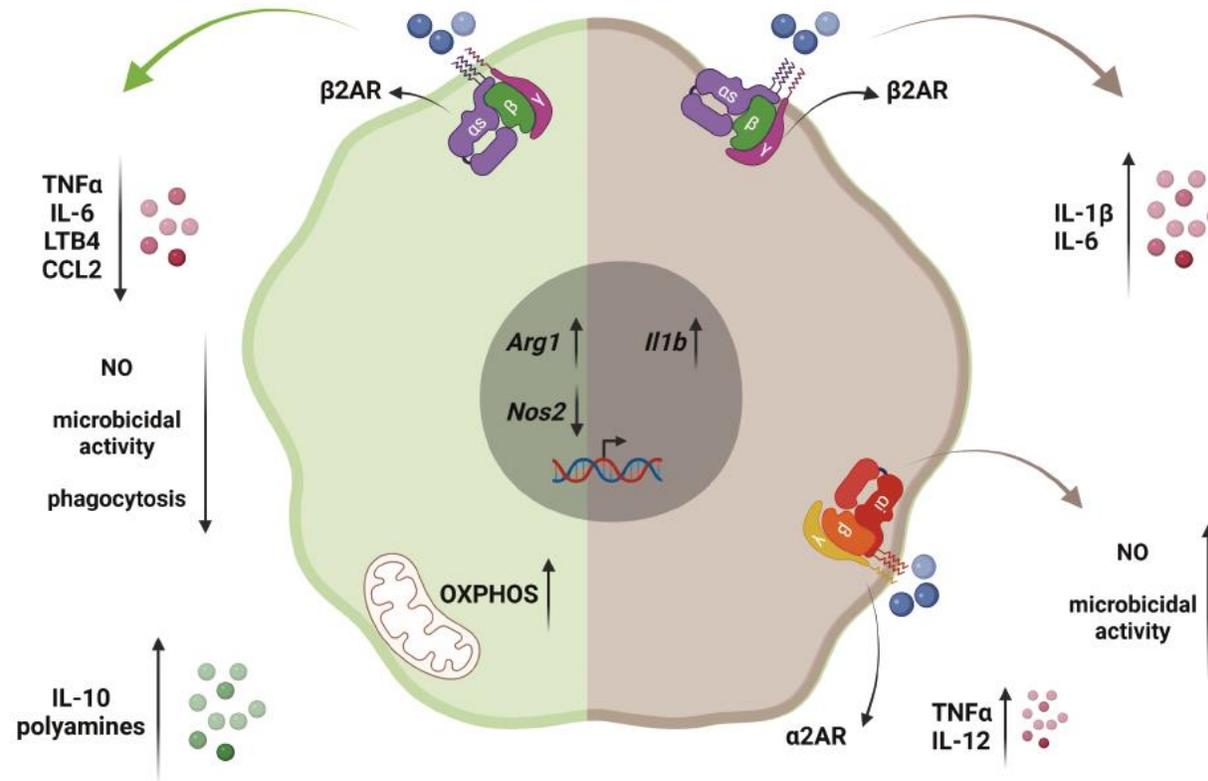


Expressão dos receptores adrenérgicos nas células imunológicas

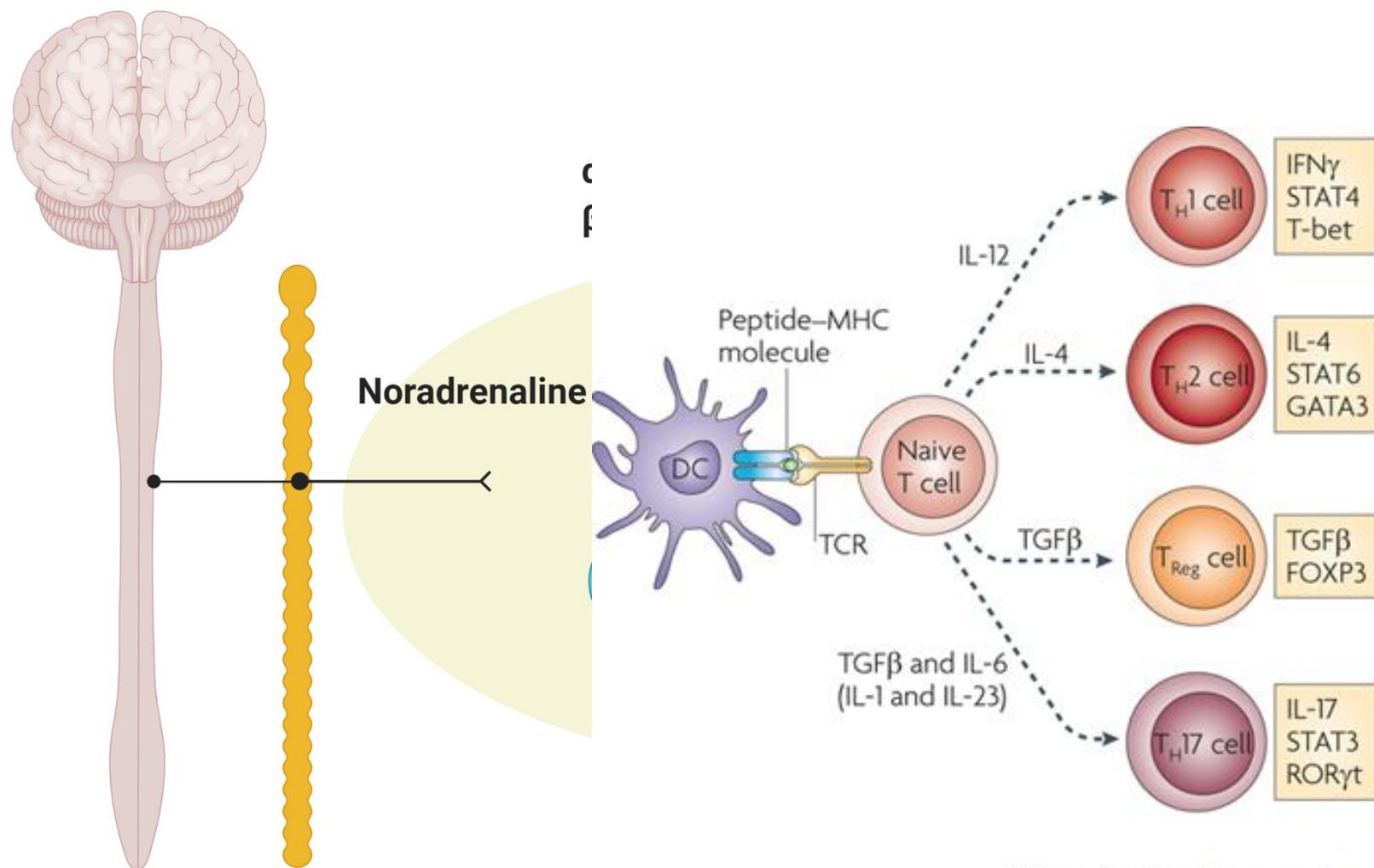
Table 1 Adrenergic receptors

Receptor family	Subtypes	Ligand affinity	Canonically coupled G protein	Main outcomes
$\alpha 1$	$\alpha 1a$ $\alpha 1b$ $\alpha 1c$	NORADRENALINE > ADRENALINE	Gq	phospholipase C beta (PLC- β) activation; \uparrow DAG and \uparrow IP3
$\alpha 2$	$\alpha 2a$ $\alpha 2b$ $\alpha 2c$		Gi	\downarrow cAMP
β	$\beta 1$ $\beta 2$ $\beta 3$	ADRENALINE > NORADRENALINE	Gs	\uparrow cAMP \rightarrow protein kinase A (PKA) and/or exchange protein directly activated by cAMP (EPAC)

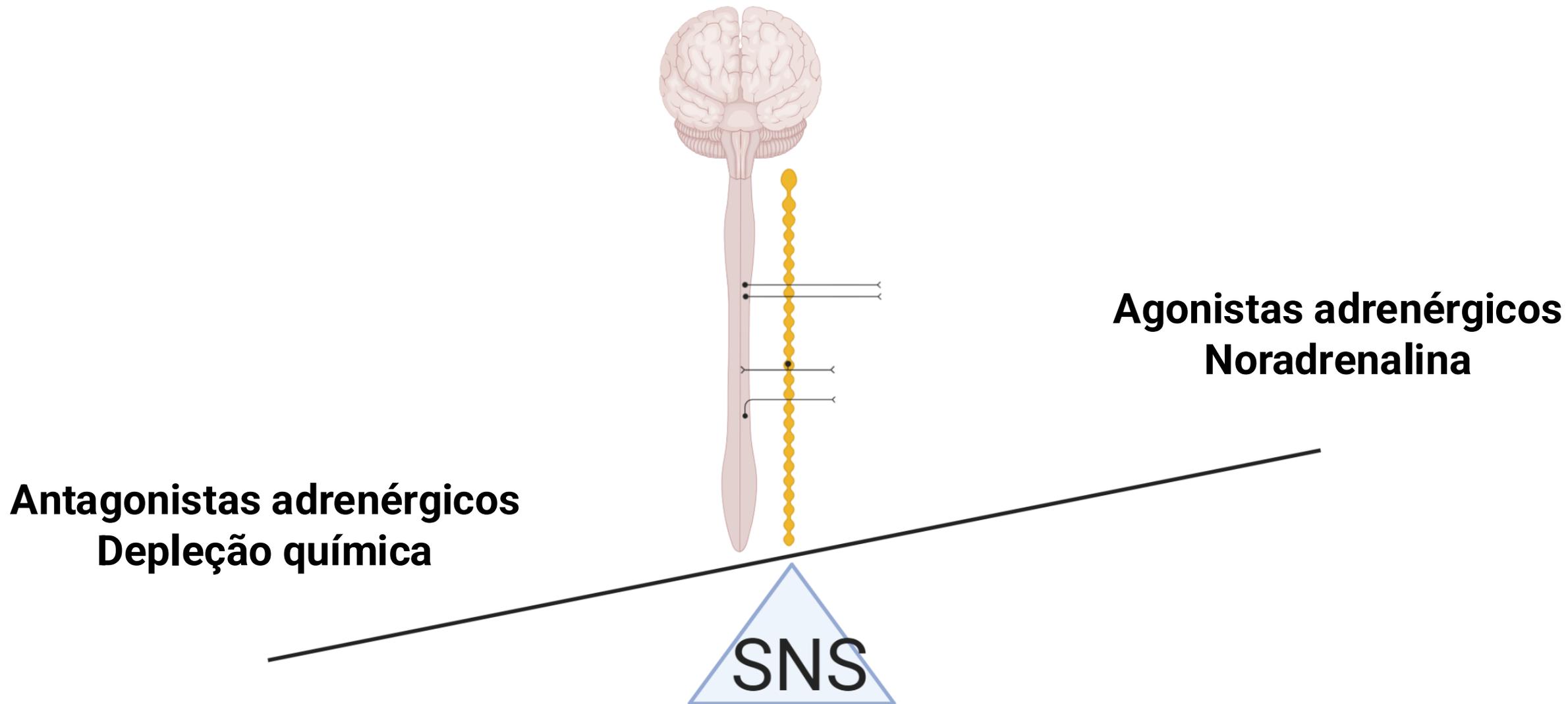
Papel distinto dos receptores adrenérgicos nas células imunológicas



► SNS e a geração da resposta imune adaptativa



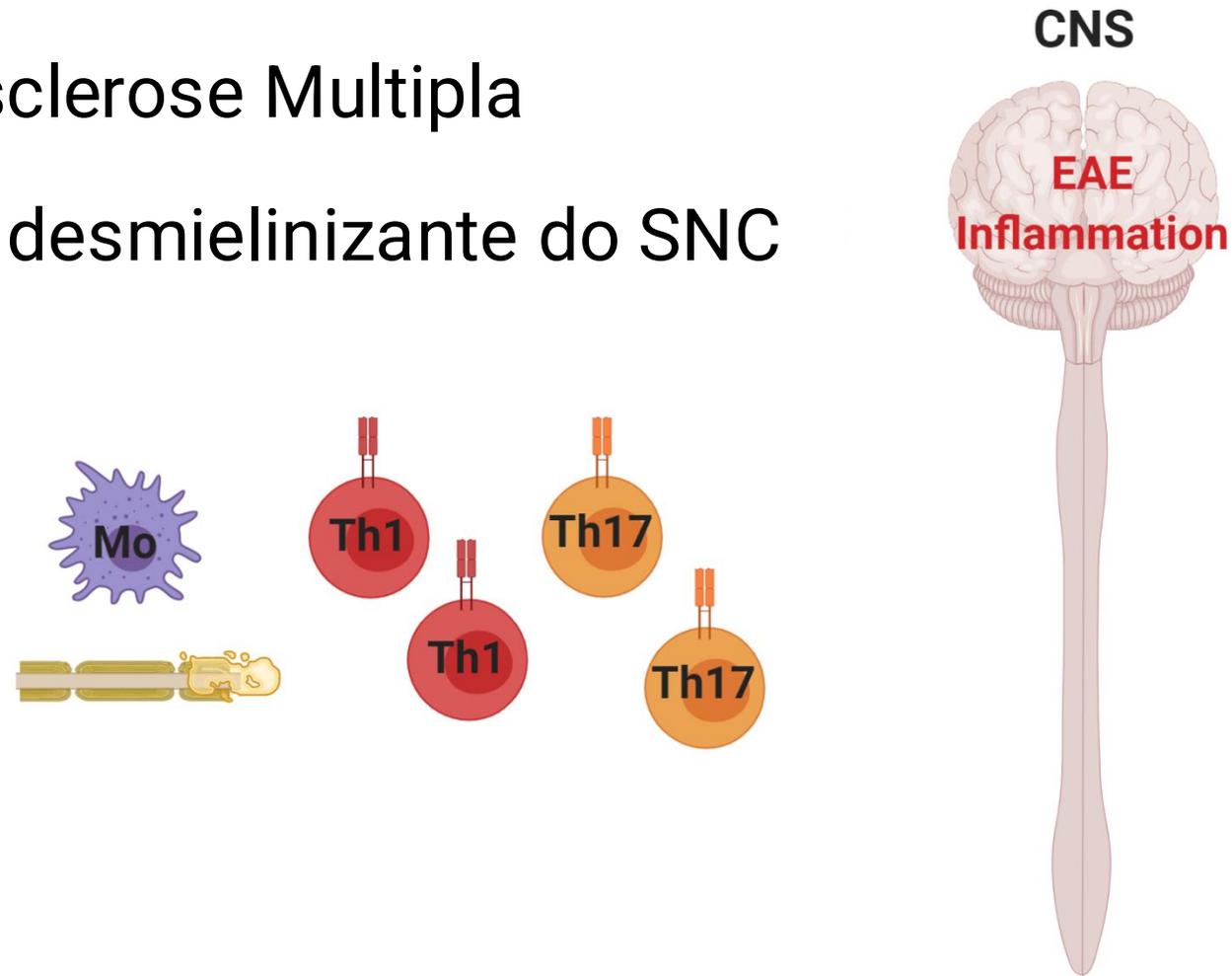
► Estratégias para avaliar a função do SNS



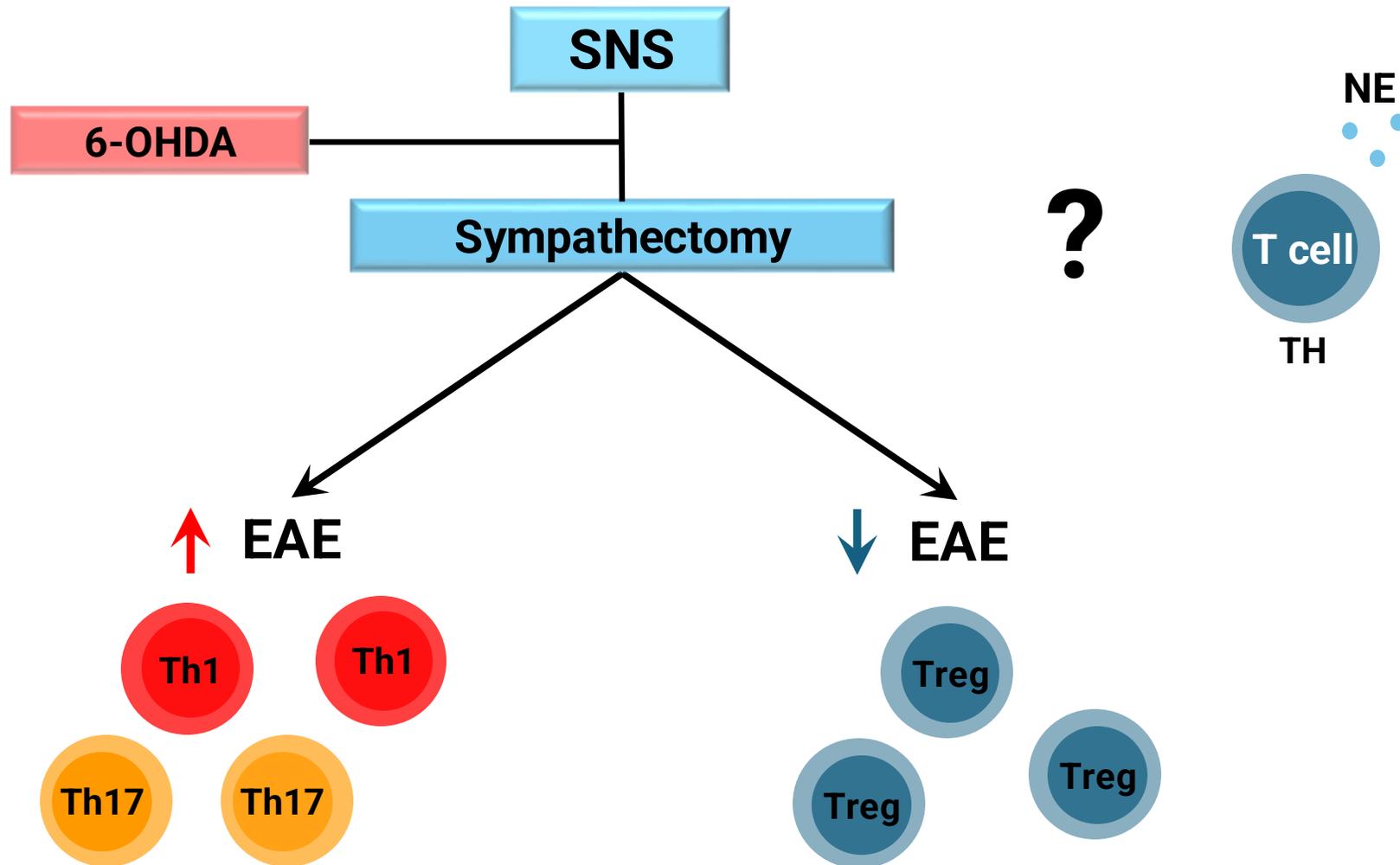
▶ Encefalomielite Autoimune Experimental (EAE)

Modelo animal da Esclerose Múltipla

Doença inflamatória desmielinizante do SNC



Sistema nervoso simpático e EAE



Indução Ativa e Passiva da EAE

Active Induction

Day 0: Myelin antigen/CFA



Day 10: Onset EAE

Passive Induction

Day 0: Myelin antigen/CFA



Day 10: Isolate lymph node and spleen cells. Restimulate T cells with myelin antigen (T_H -17-promoting reagents can be included in this step)

Day 12: Irradiate recipient mice
~400 rad

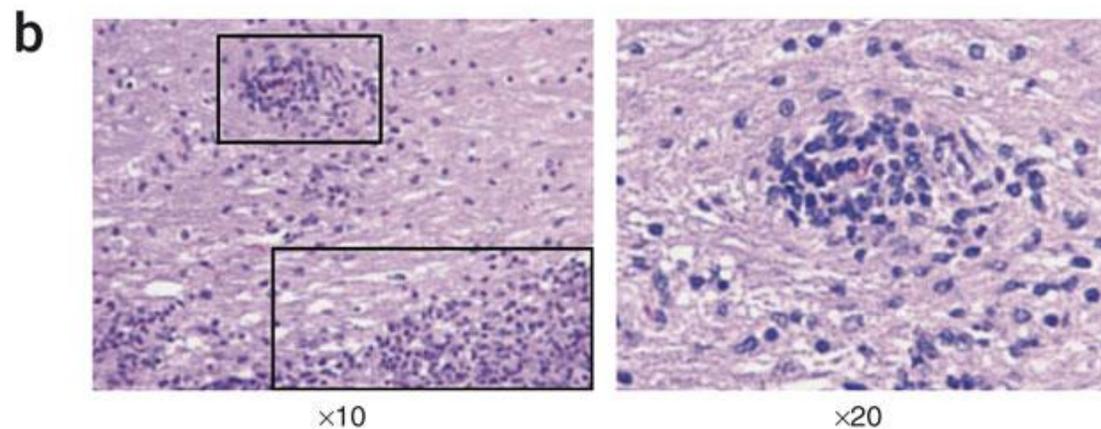
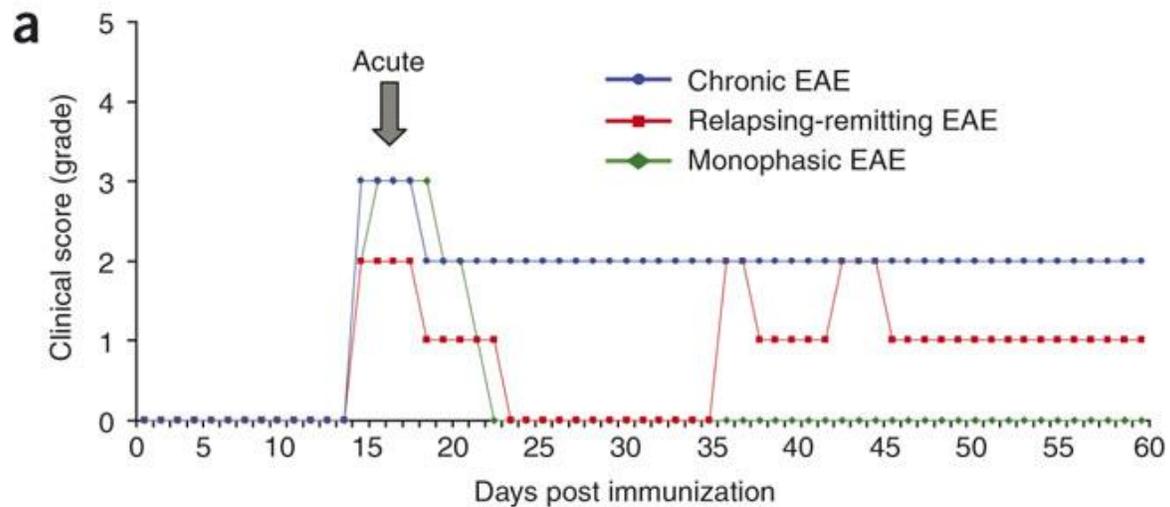


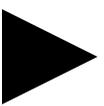
Day 13: Transfer T cells



EAE

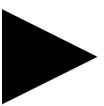
Modelos de EAE em roedores





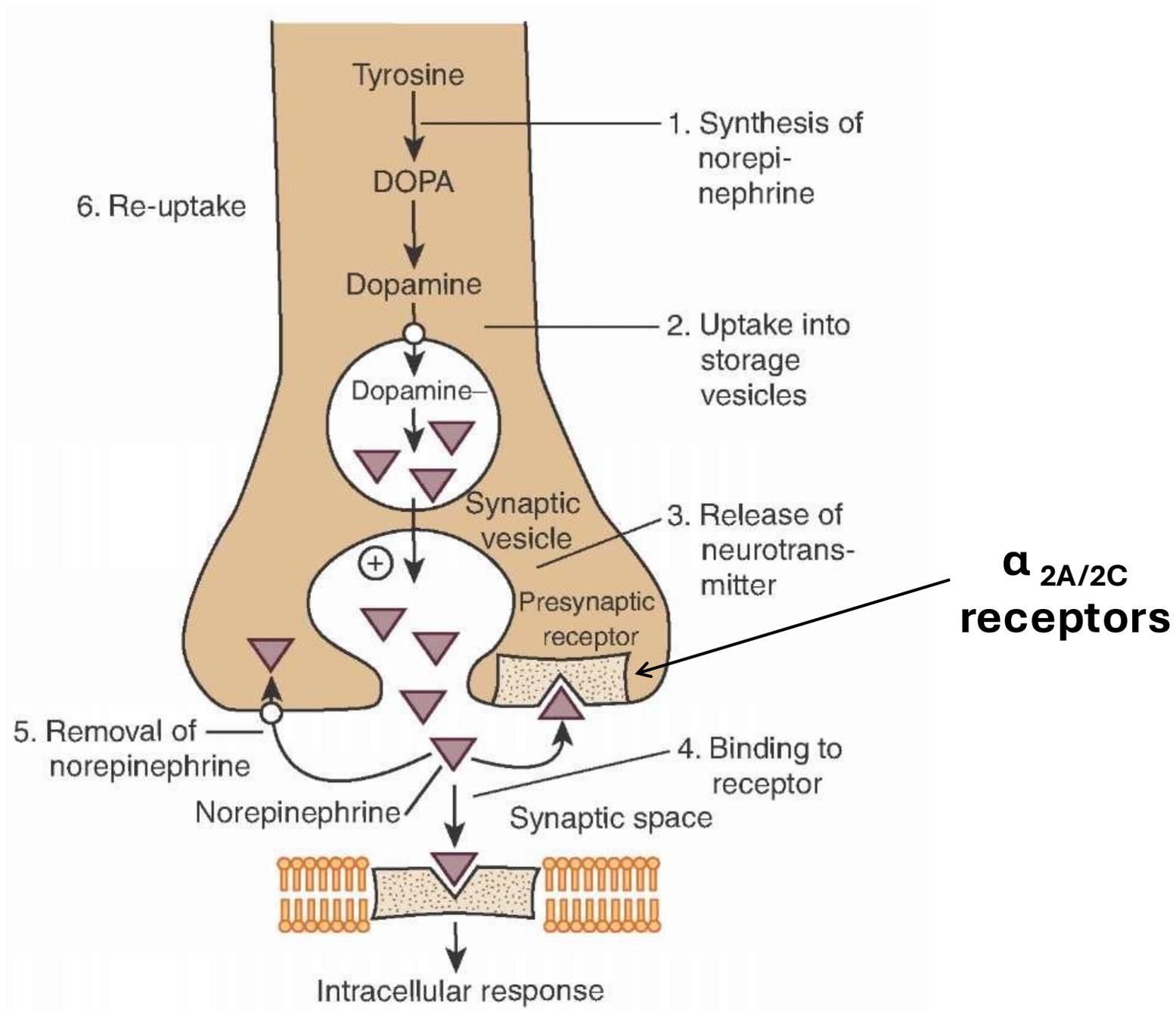
Objetivo

Avaliar o efeito do aumento da atividade do sistema nervoso simpático (SNS) durante o curso da encefalomielite autoimune experimental (EAE)

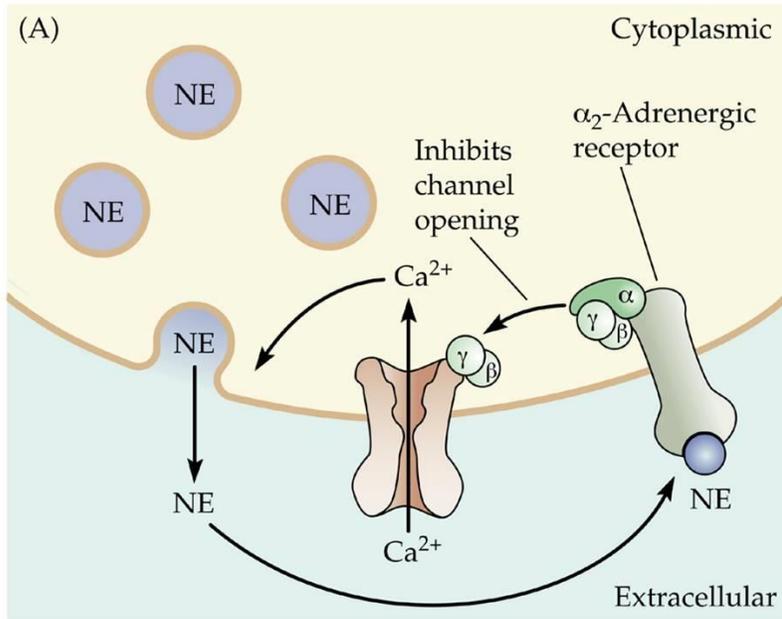


Hipóteses

- 1) A ausência dos receptores alfa 2-adrenérgicos (ADRA2) nas células imunológicas interfere no desenvolvimento da EAE;
- 2) A hiperatividade do sistema nervoso simpático modula a EAE via receptor beta2-adrenérgico (ADRB2);



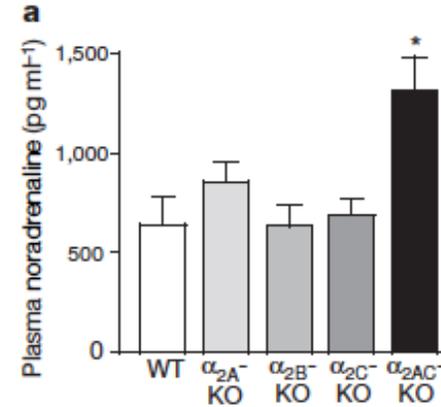
Hyperactivity of the SNS



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α_2 Receptors

Activation of the receptor decreases production of cAMP, leading to an inhibition of further release of norepinephrine from the neuron.



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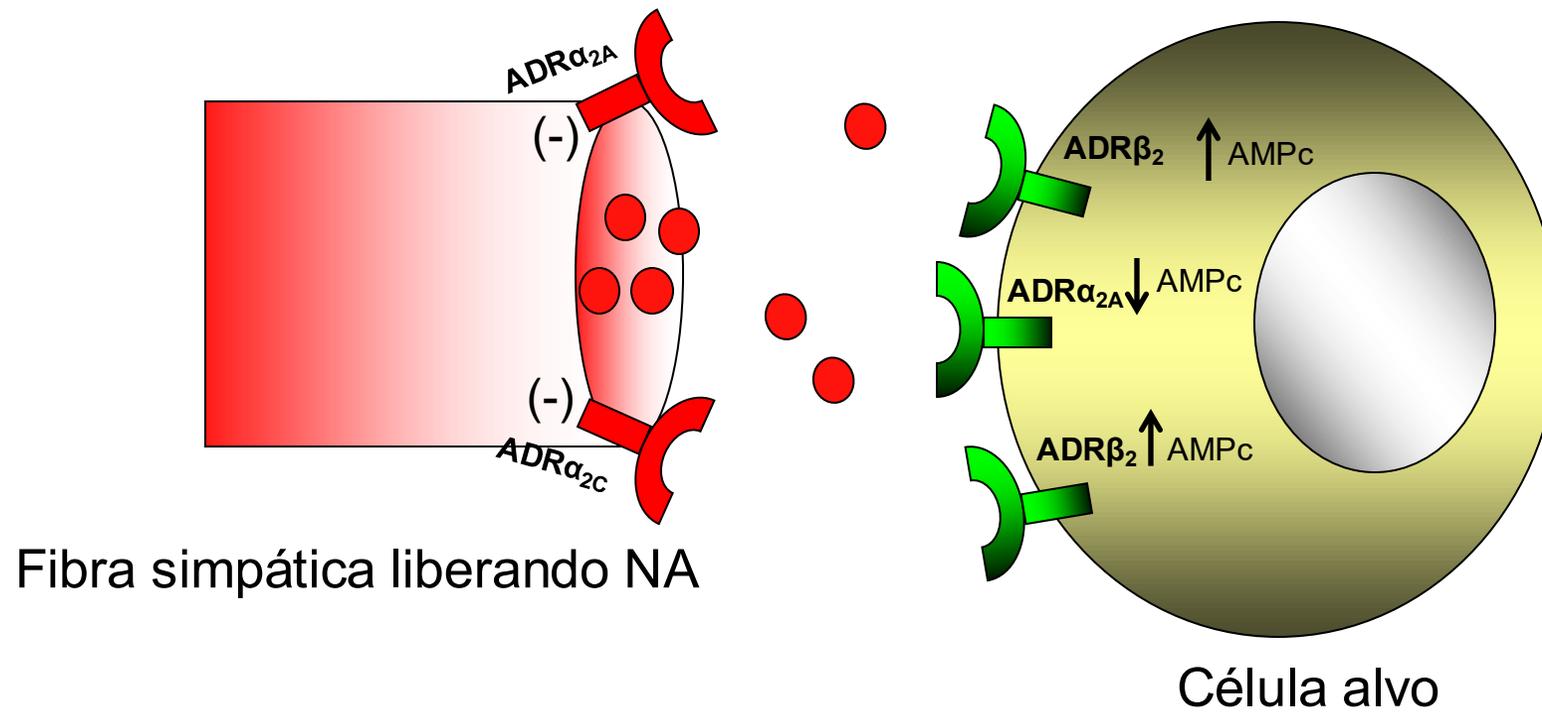
Two functionally distinct α_2 -adrenergic receptors regulate sympathetic neurotransmission

Lutz Hein[†], John D. Altman[†] & Brian K. Kobilka[†]

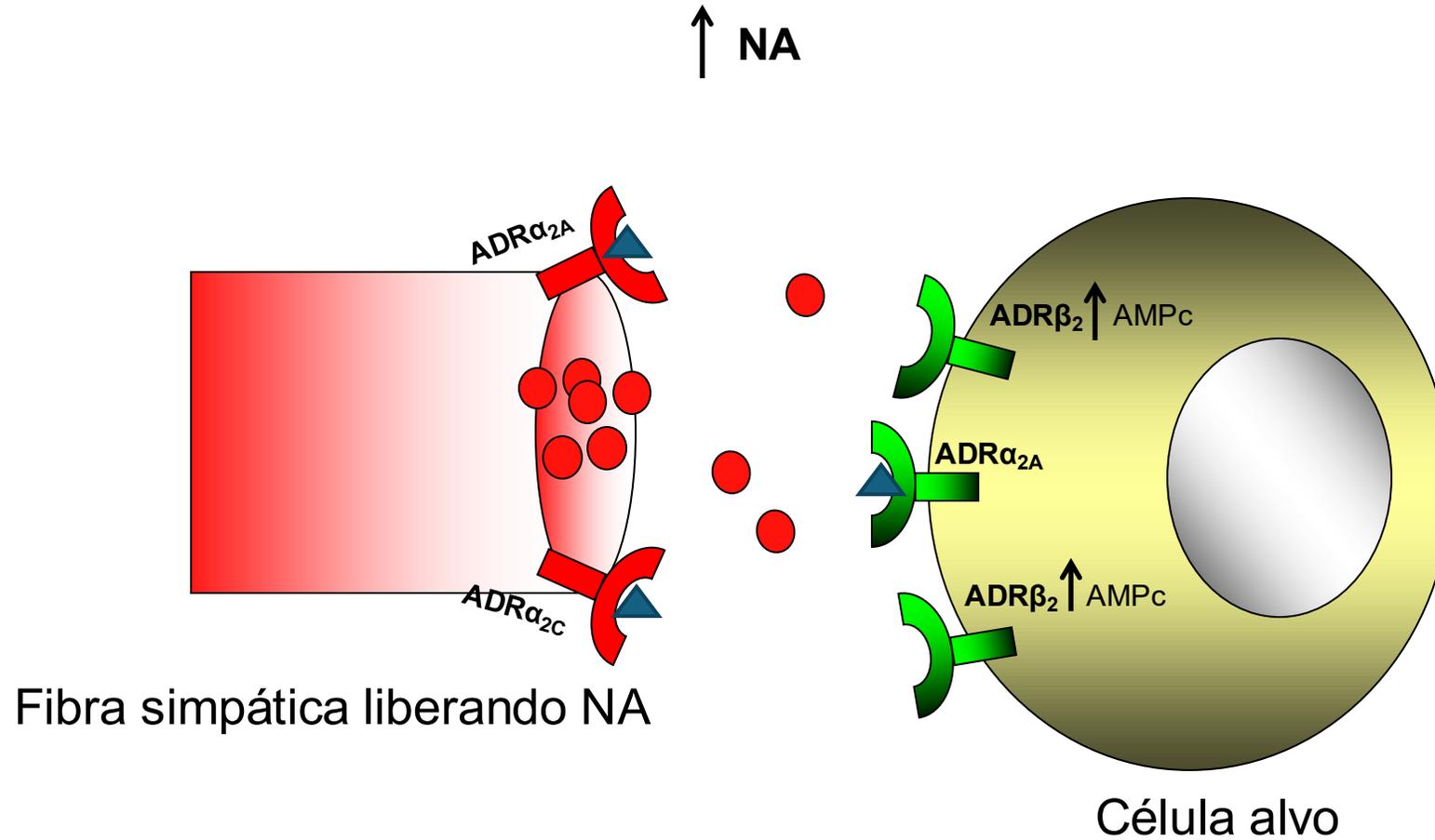
NATURE | VOL 402 | 11 NOVEMBER 1999 |

$Adra2ac^{-/-}$ mice miss the negative feedback

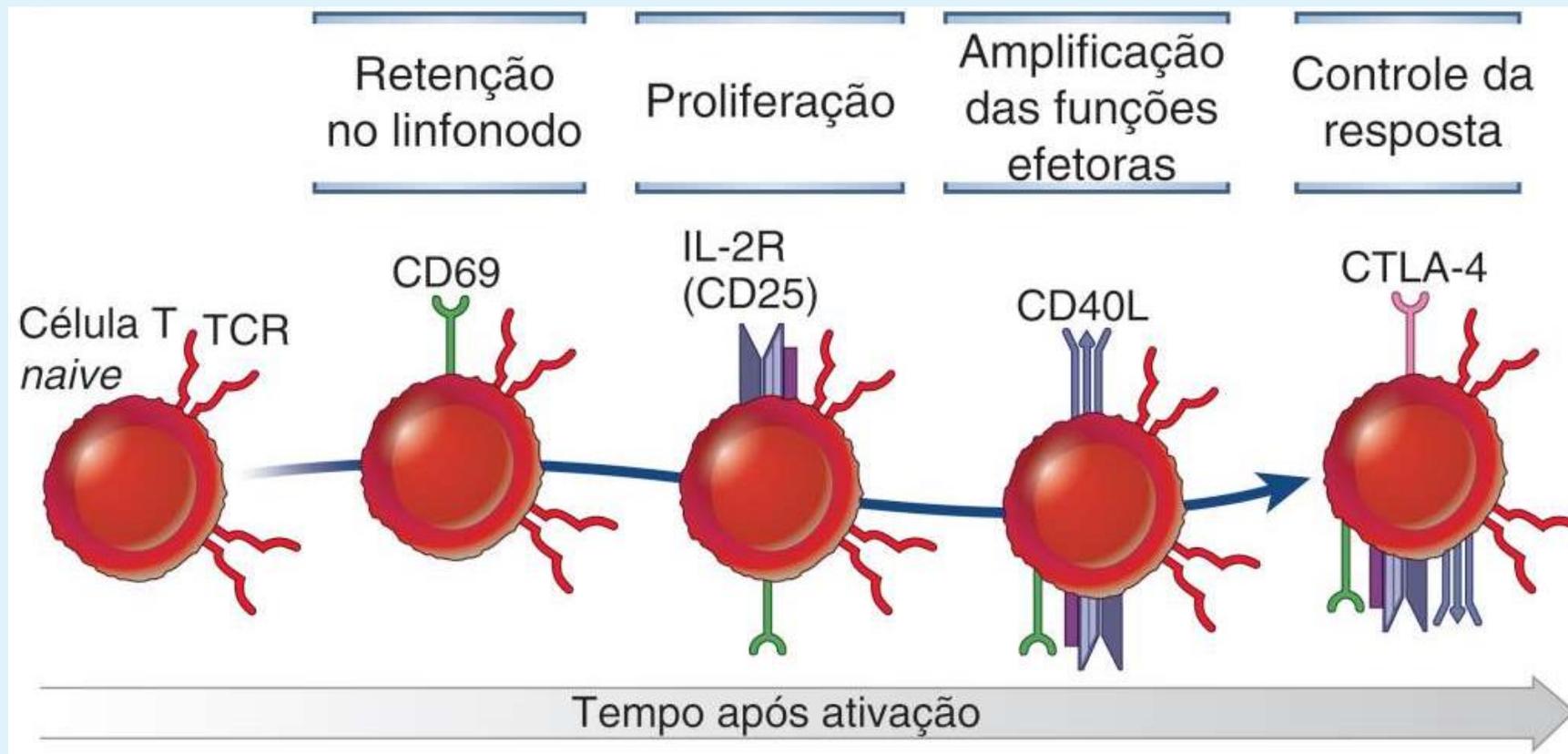
▶ Liberação de noradrenalina (NA) pelo SNS



Liberação de NA na hiperatividade do SNS

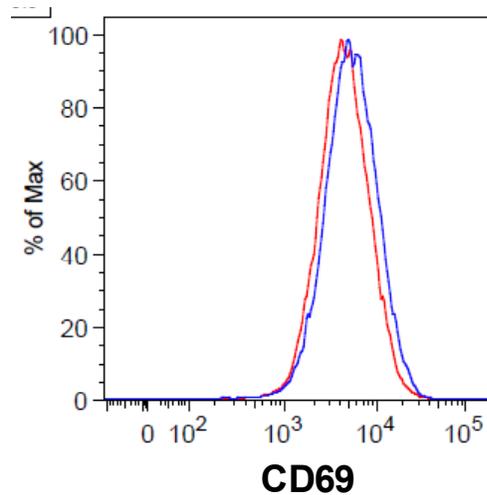
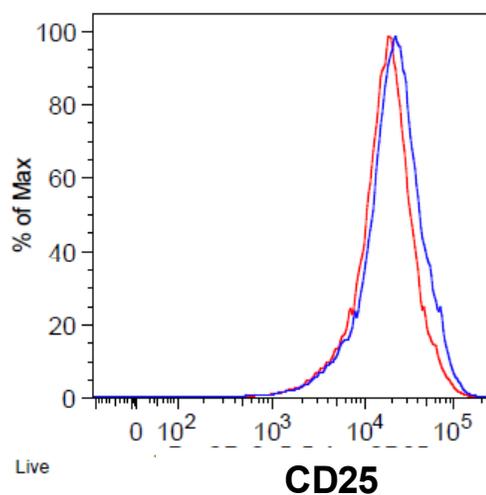


► Marcadores de ativação das células T

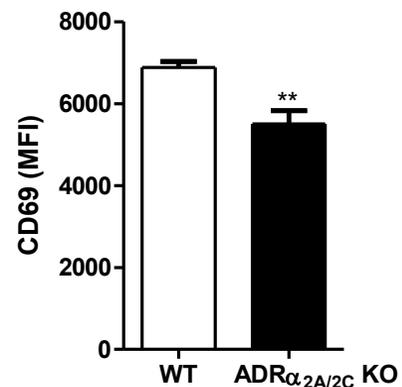
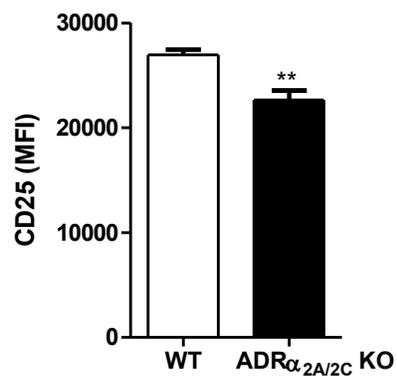


Ativação das células T CD4⁺ WT e KO *in vitro*

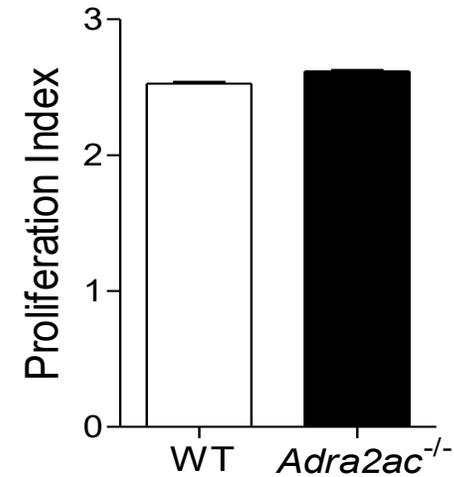
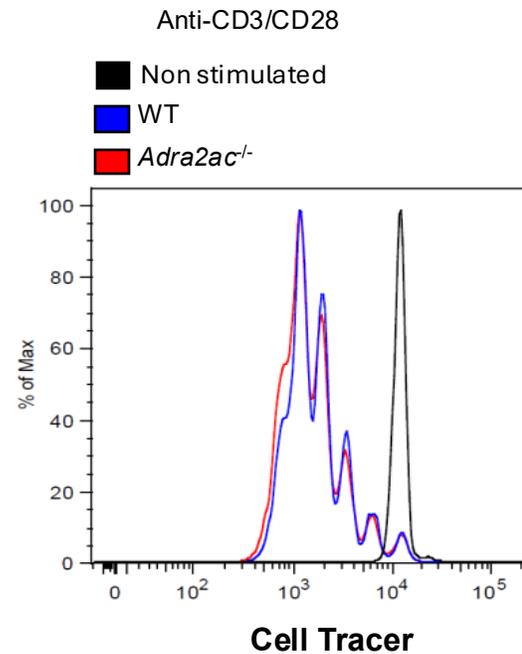
- Anti-CD3/CD28



■ WT
■ ADR $\alpha_{2A/2C}$ KO

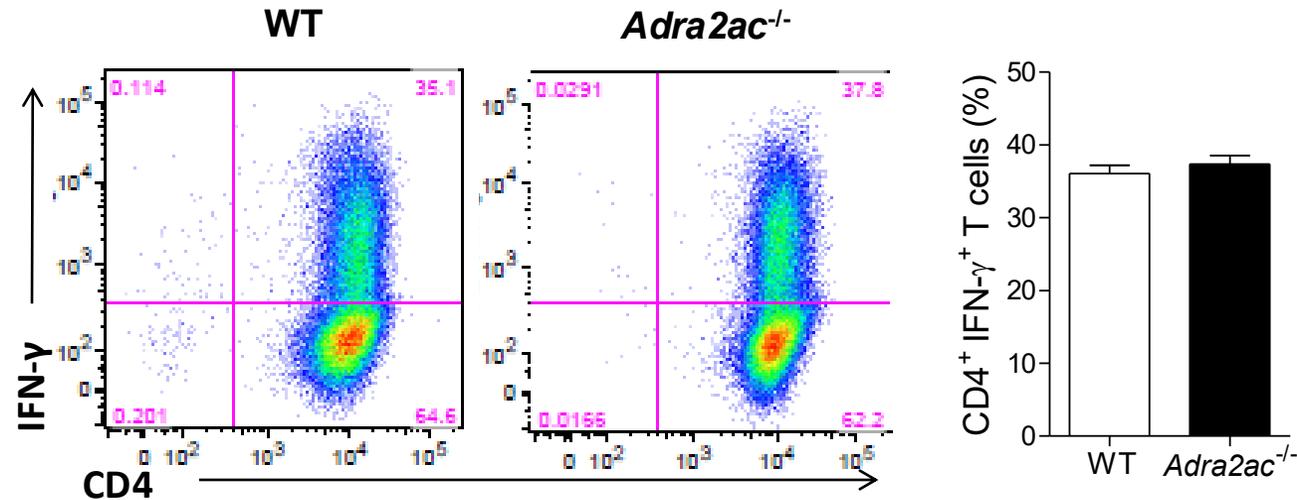


Ausência dos receptores alfa2ac adrenérgicos na proliferação das células T CD4+

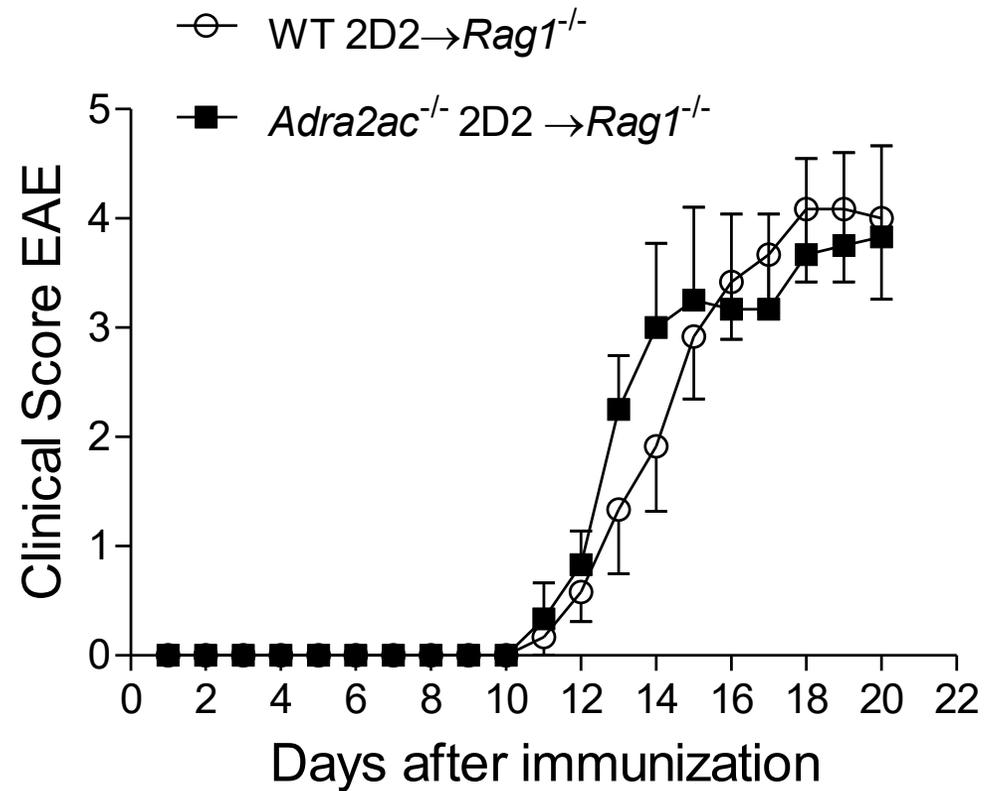


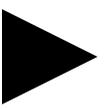
Ausência dos ADRA2AC polarização das células T CD4+

Diferenciação de Th1



Ausência dos ADRA2AC nas células T CD4+ *in vivo*





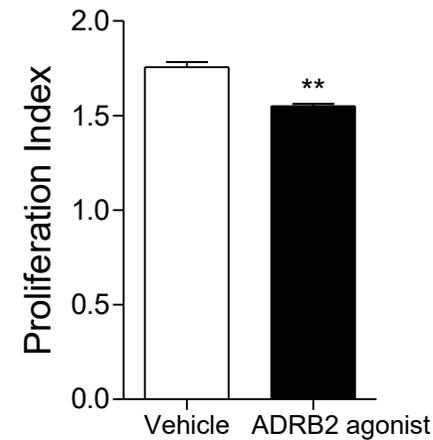
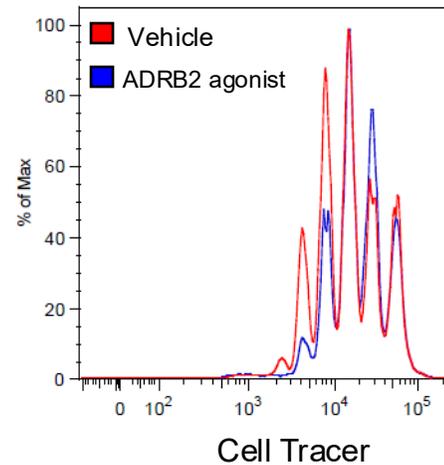
Hipóteses

1) A ausência dos receptores alfa2-adrenérgicos nas células imunológicas interfere no desenvolvimento da EAE;

2) A hiperatividade do sistema nervoso simpático modula a EAE via receptor beta2-adrenérgico (ADRB2);

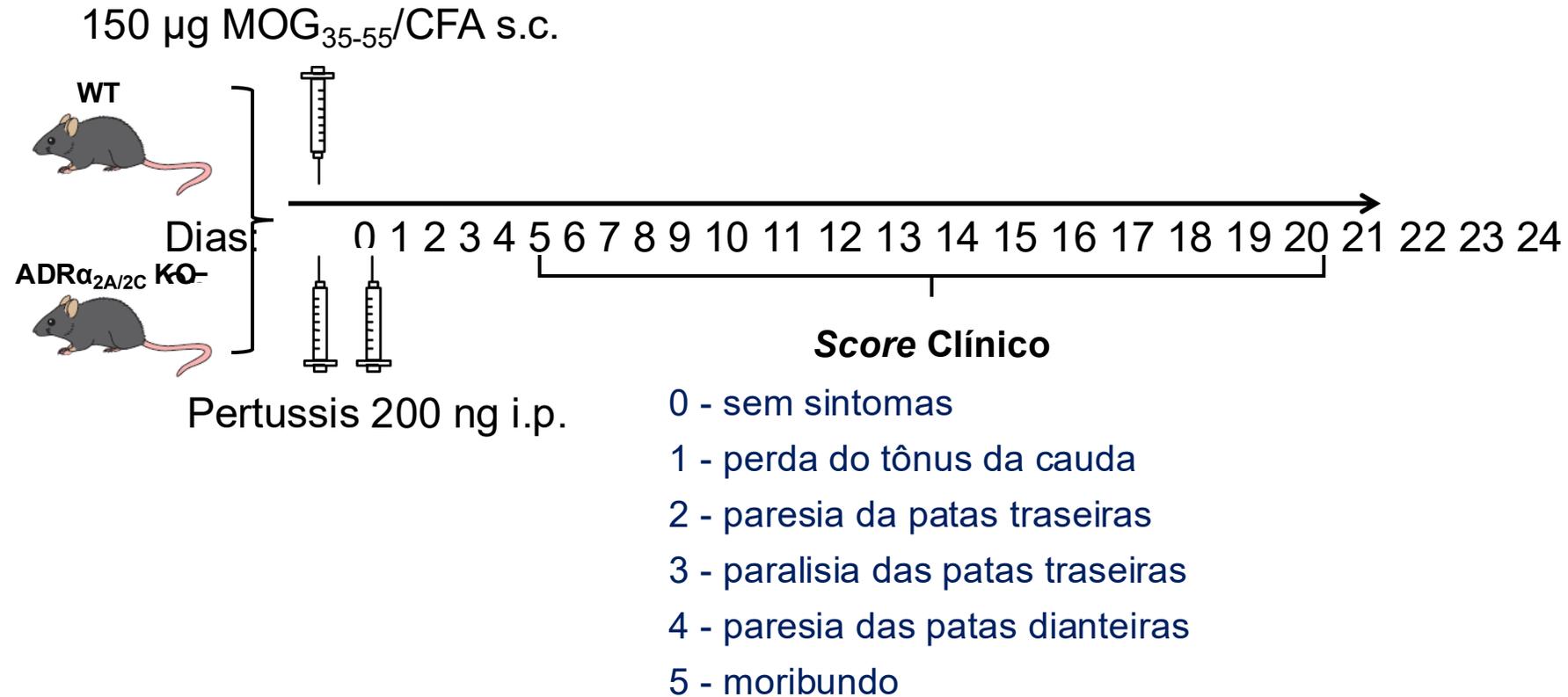
Sinalização via ADRB2 reduz a proliferação de células T CD4+

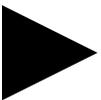
In vitro



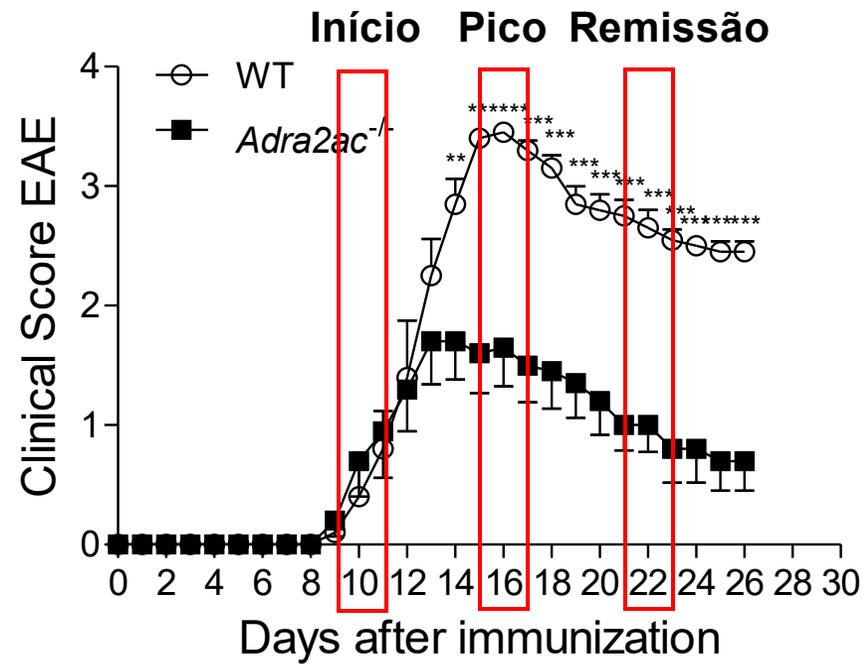
Modelo de encefalomielite autoimune experimental (EAE)

Camundongos: WT e $ADRA_{2A/2C}$ KO

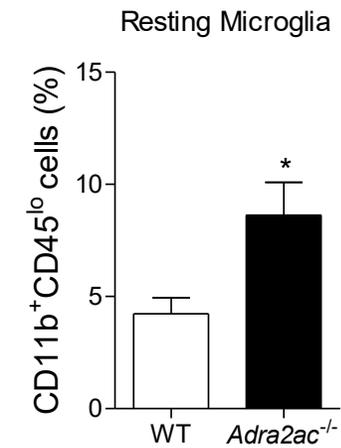
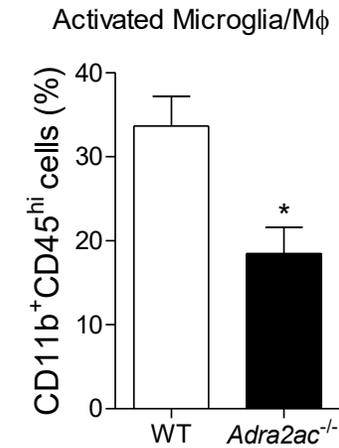
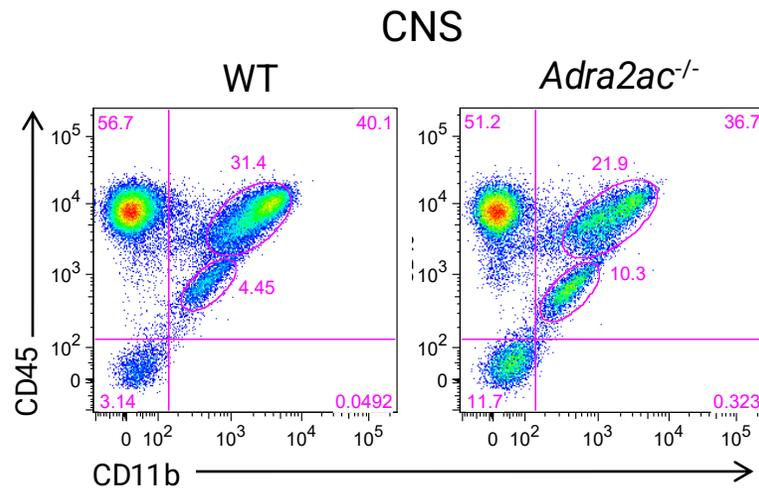


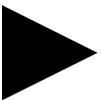


Sistema nervoso simpático modula a EAE



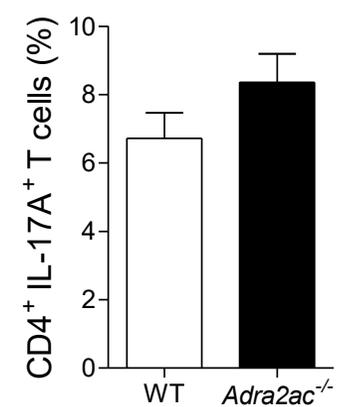
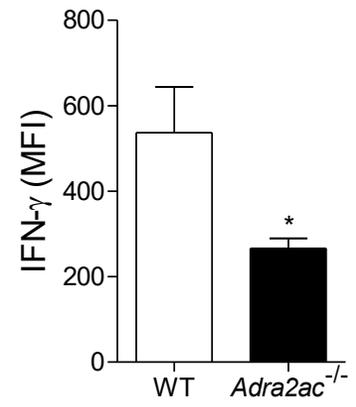
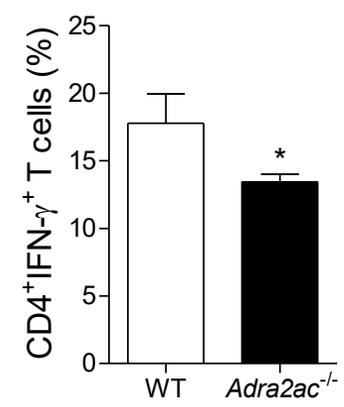
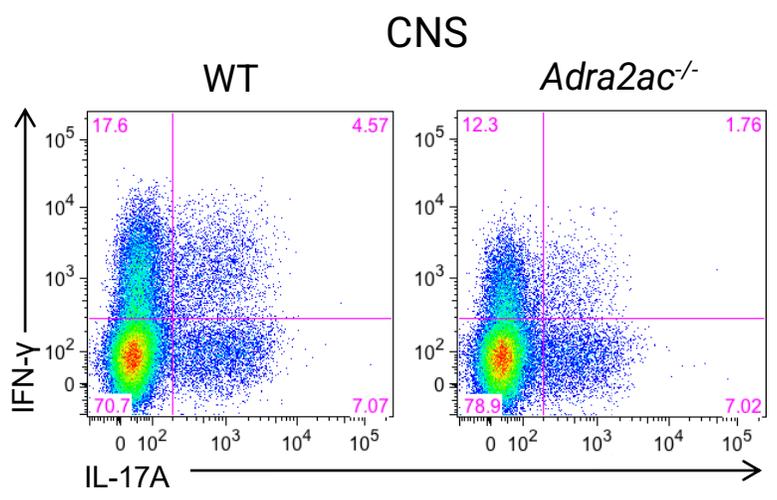
SNS reduz inflamação durante EAE



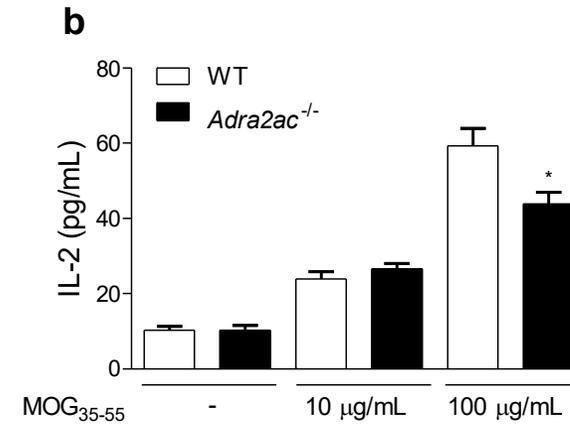
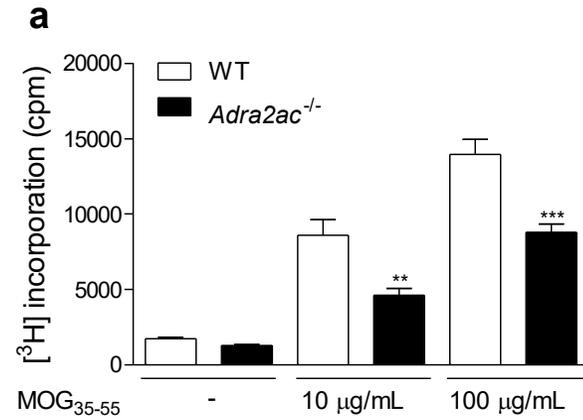


SNS diminui as células T CD4+ produtoras de IFN- γ

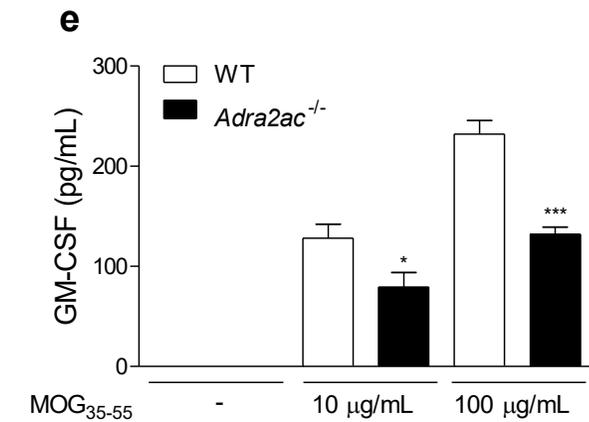
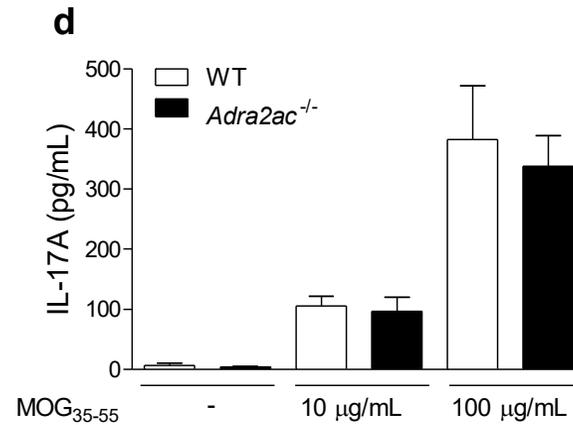
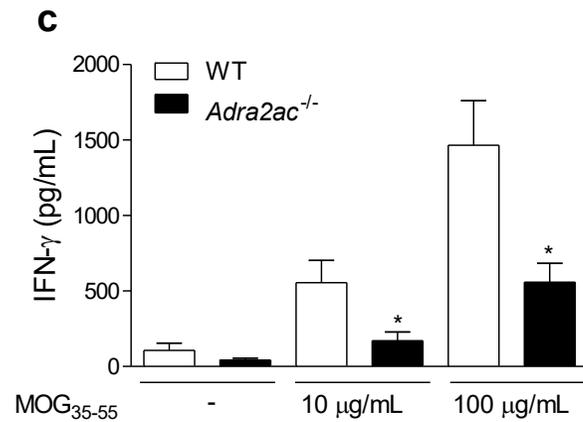
Gated CD3+CD4+



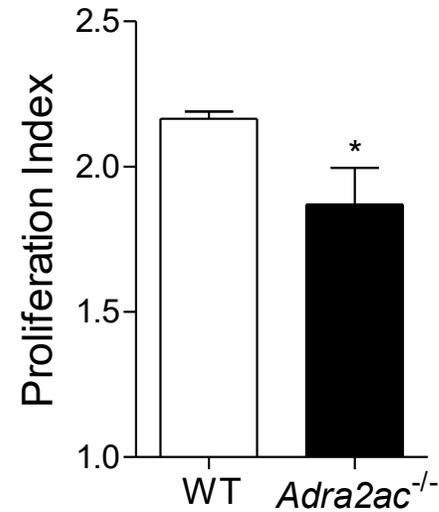
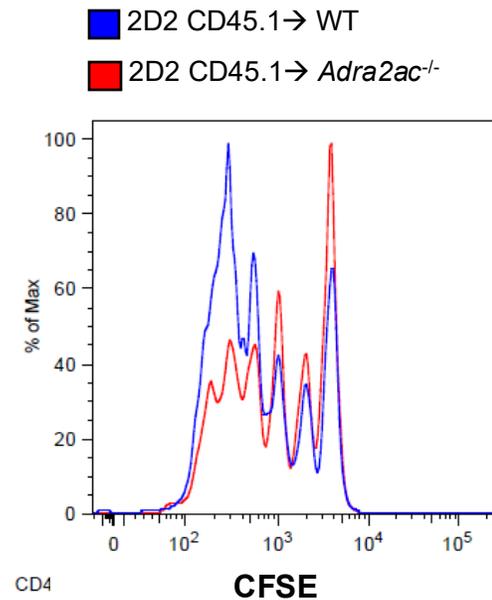
SNS diminui a proliferação e a produção de citocinas pelas células T CD4+



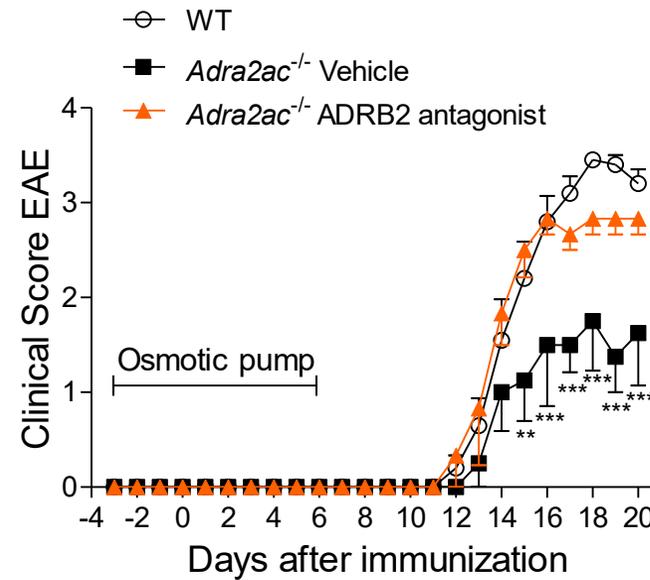
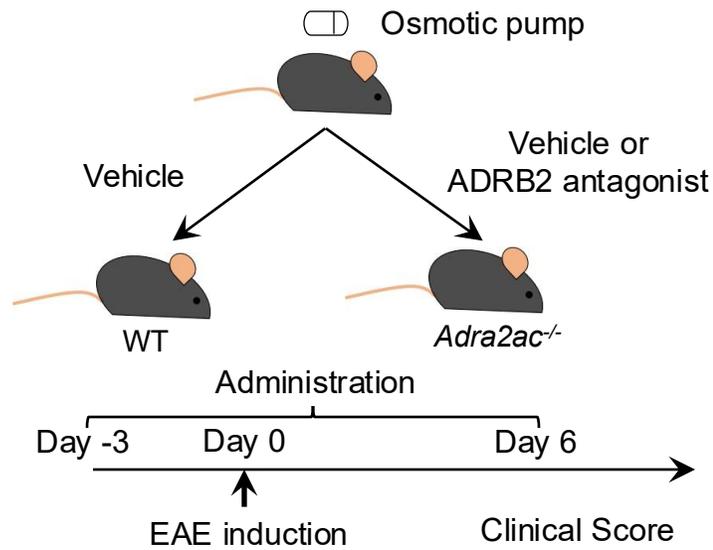
SNS diminui a proliferação e a produção de citocinas pelas células T CD4+



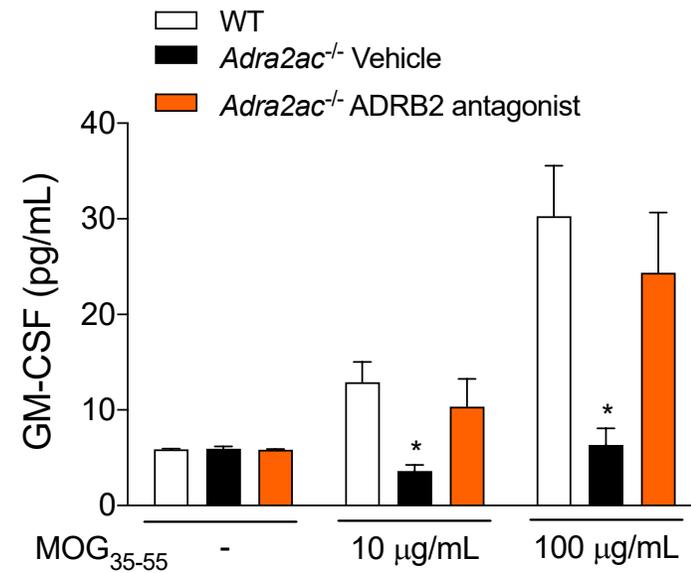
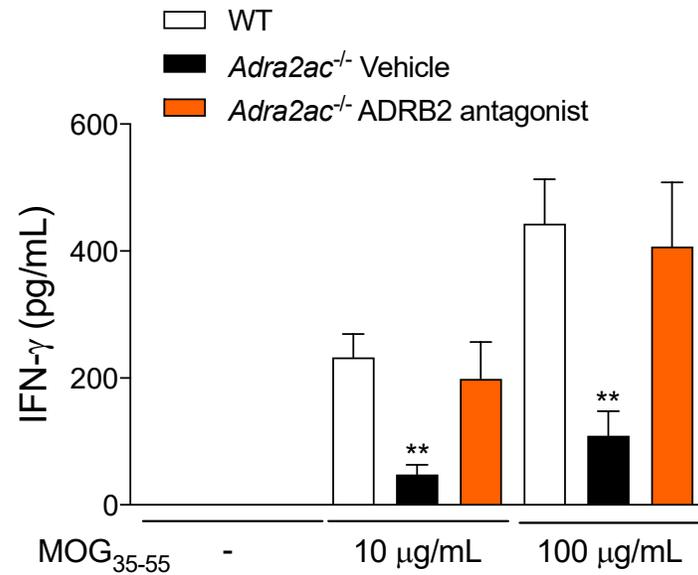
A hiperatividade do SNS reduz a proliferação *in vivo* das células T CD4+



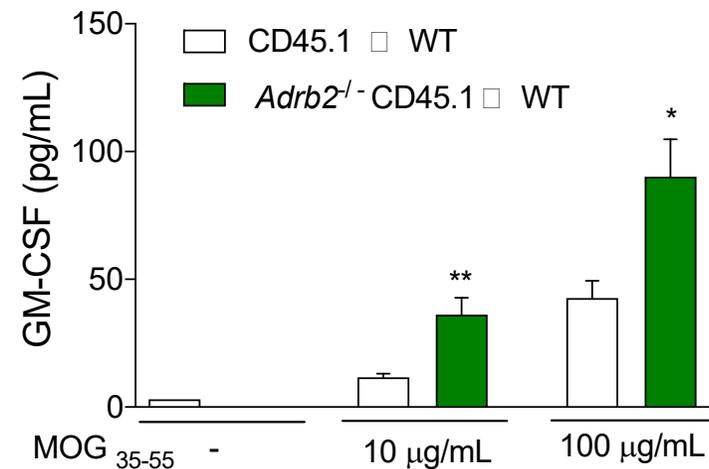
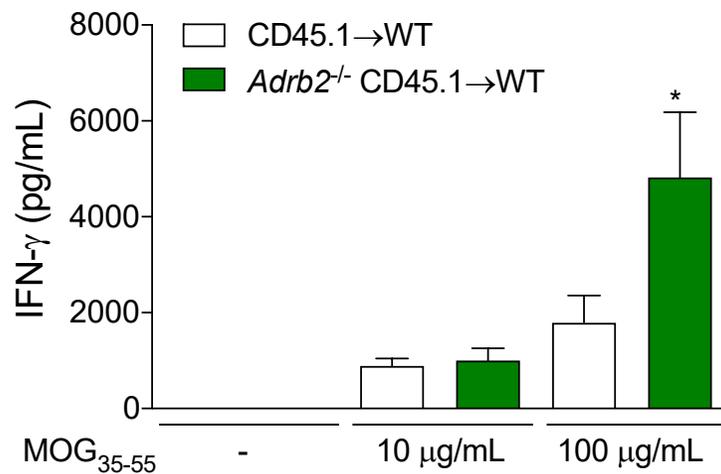
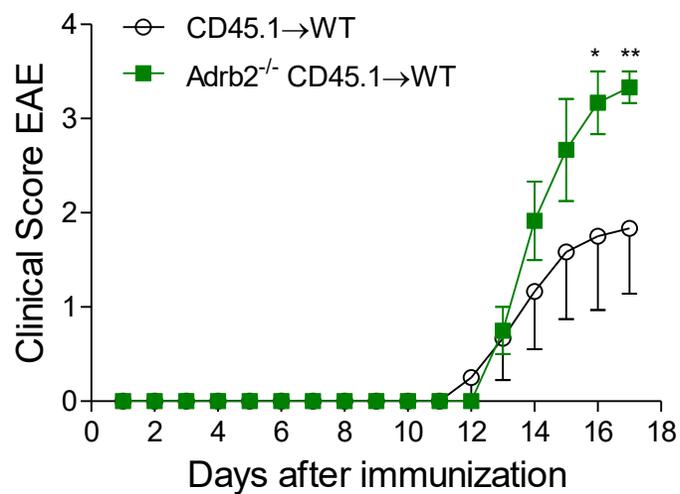
► Bloqueio da sinalização do ADRB2 restaura a EAE



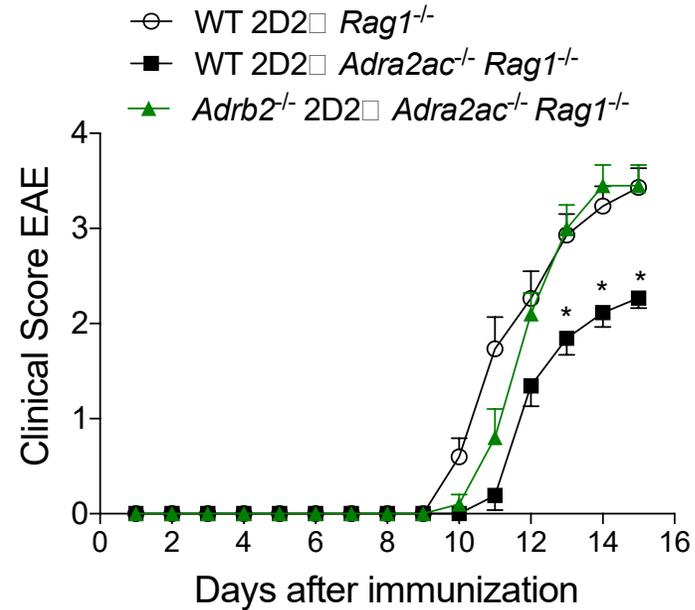
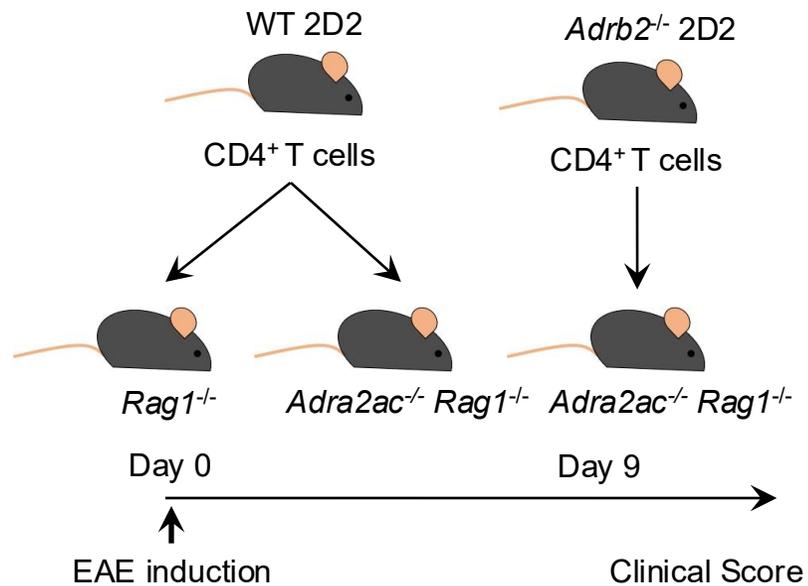
► Bloqueio da sinalização do ADRB2 restaura a produção de citocinas inflamatórias



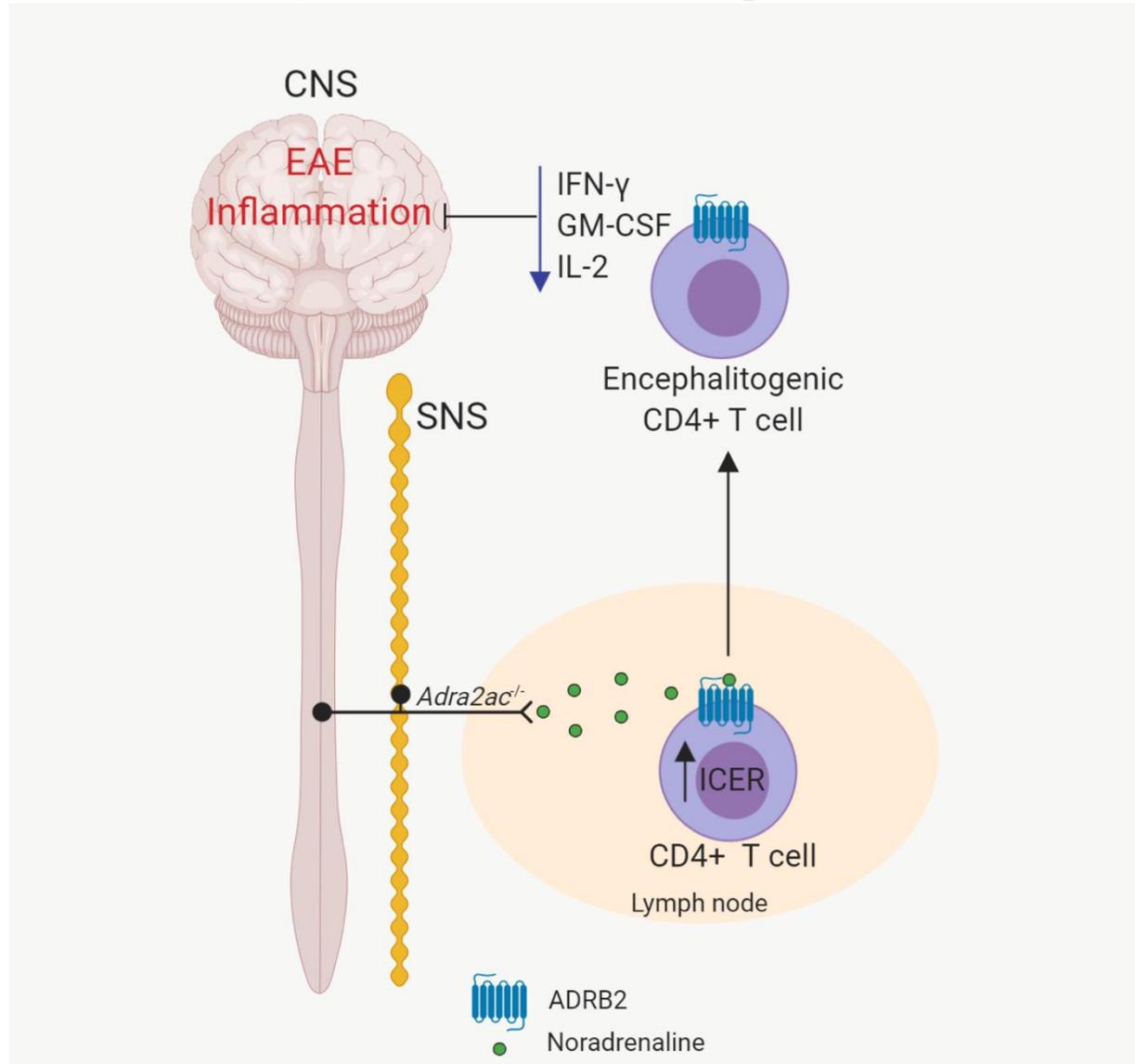
► Ausência do ADRB2 nas células imunes agrava a EAE



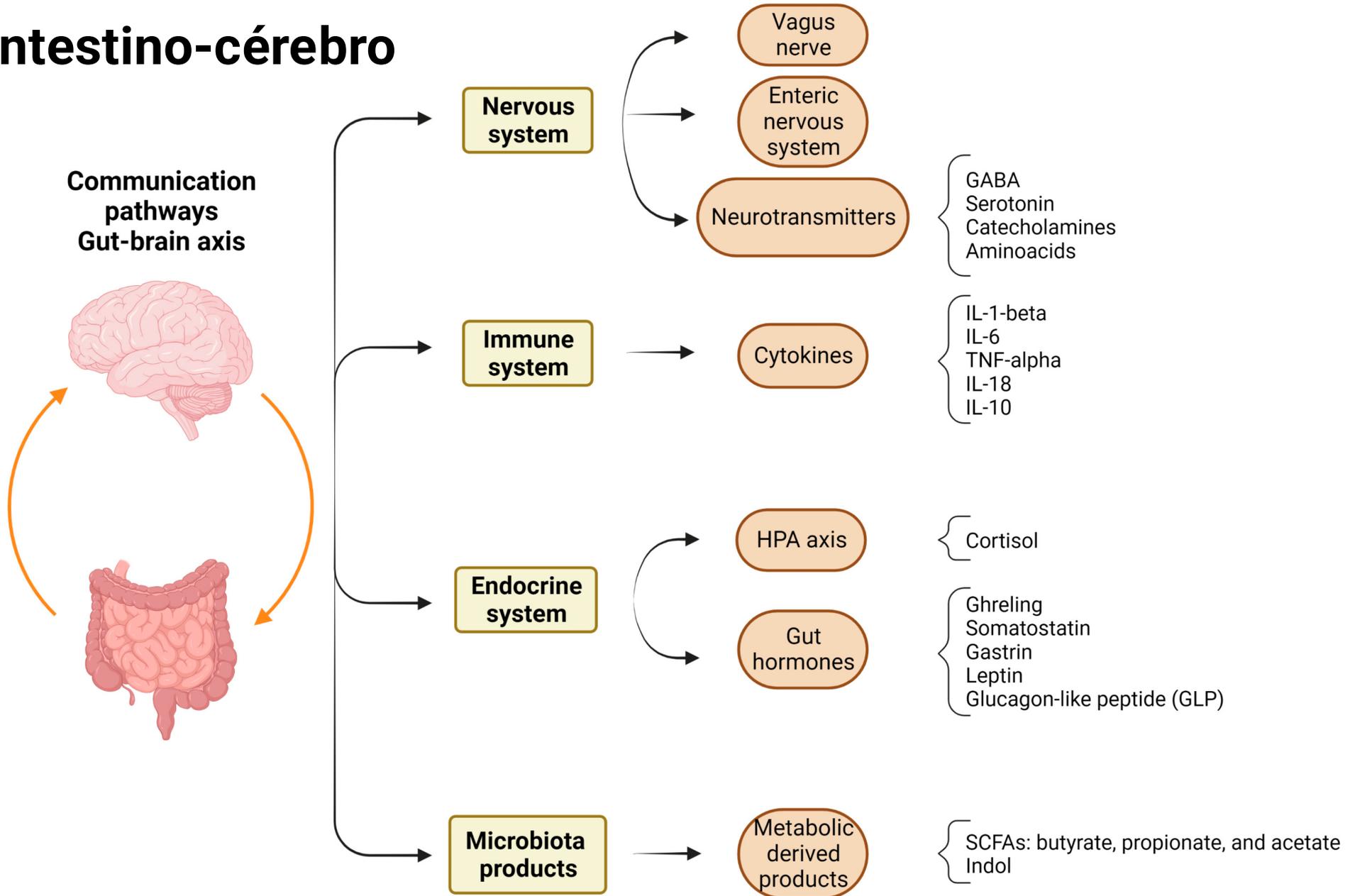
Ausência do ADRB2 nas células T CD4+ reverte a modulação da EAE pela hiperatividade do SNS



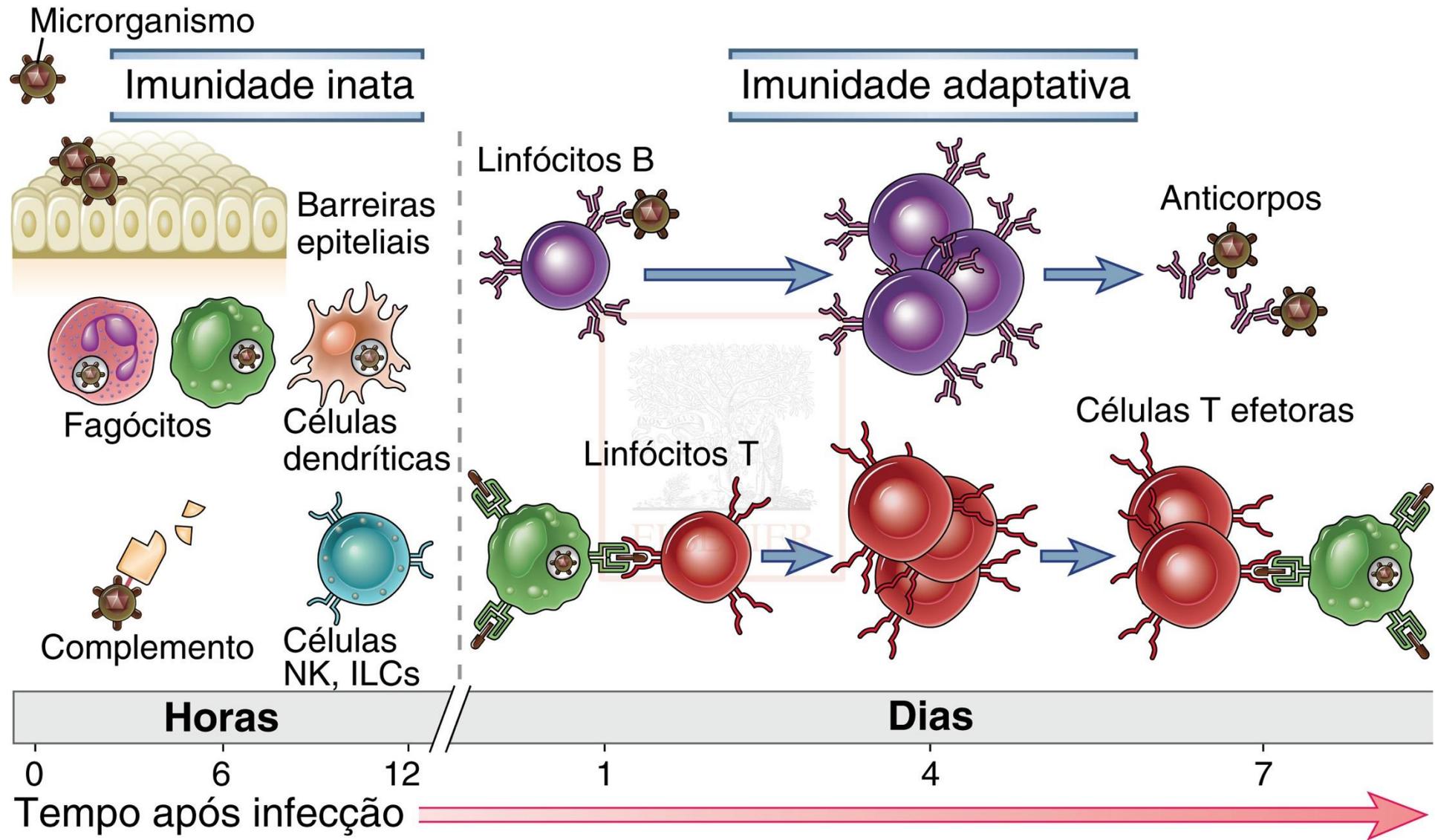
Modelo de modulação da EAE pelo SNS



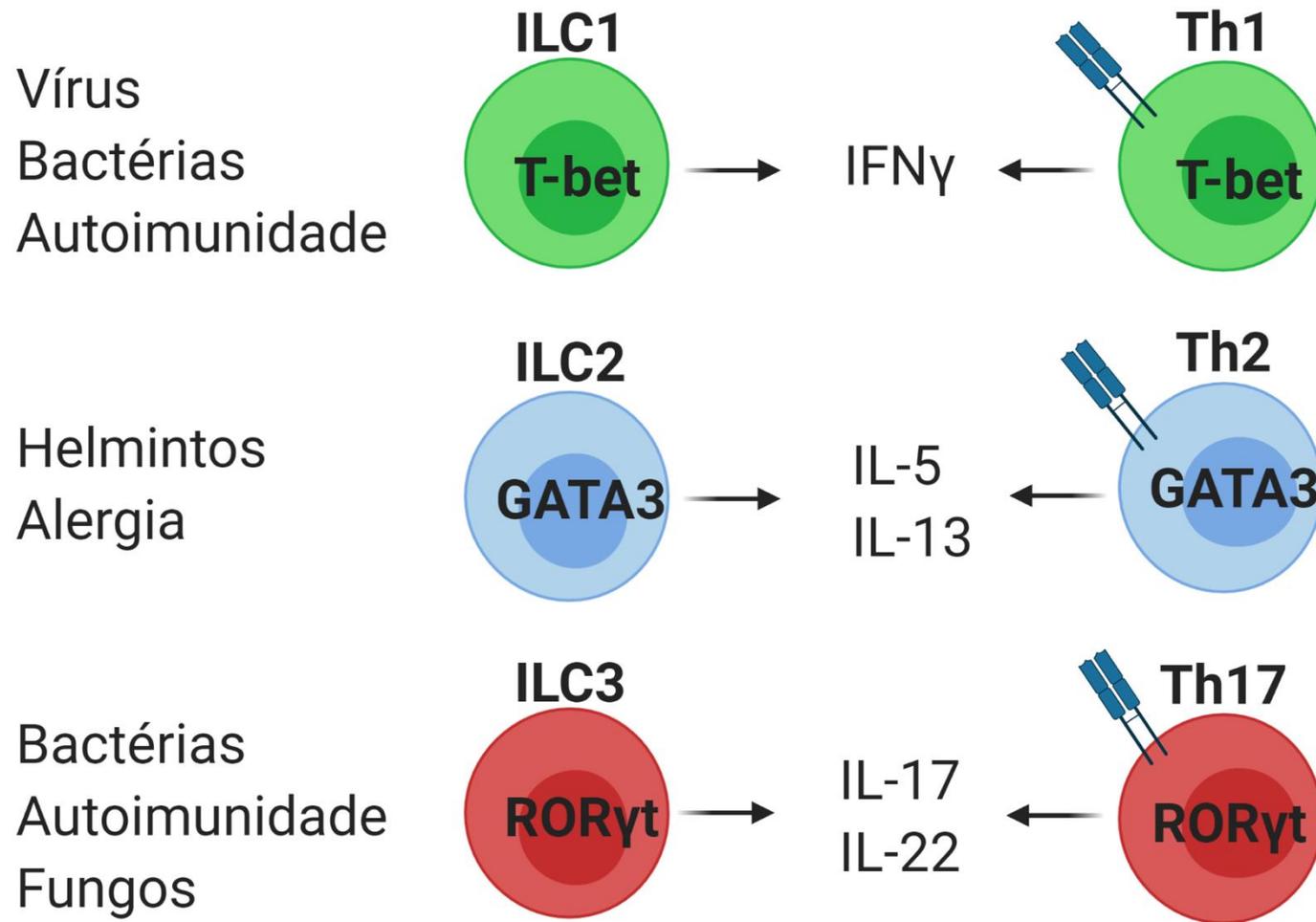
Eixo intestino-cérebro



Paradigma da imunidade inata e adaptativa

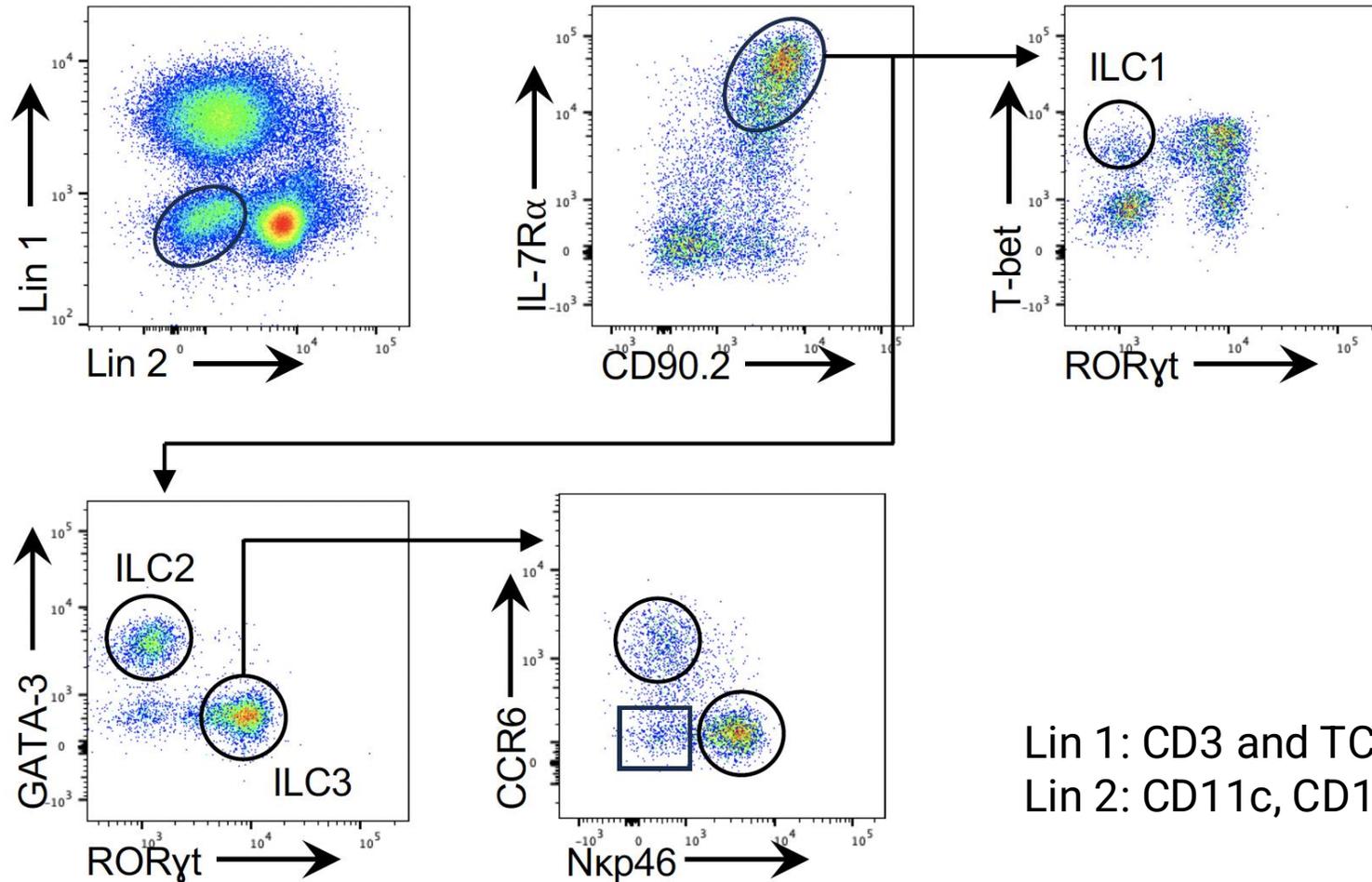


Células linfoides inatas espelham as células T auxiliares



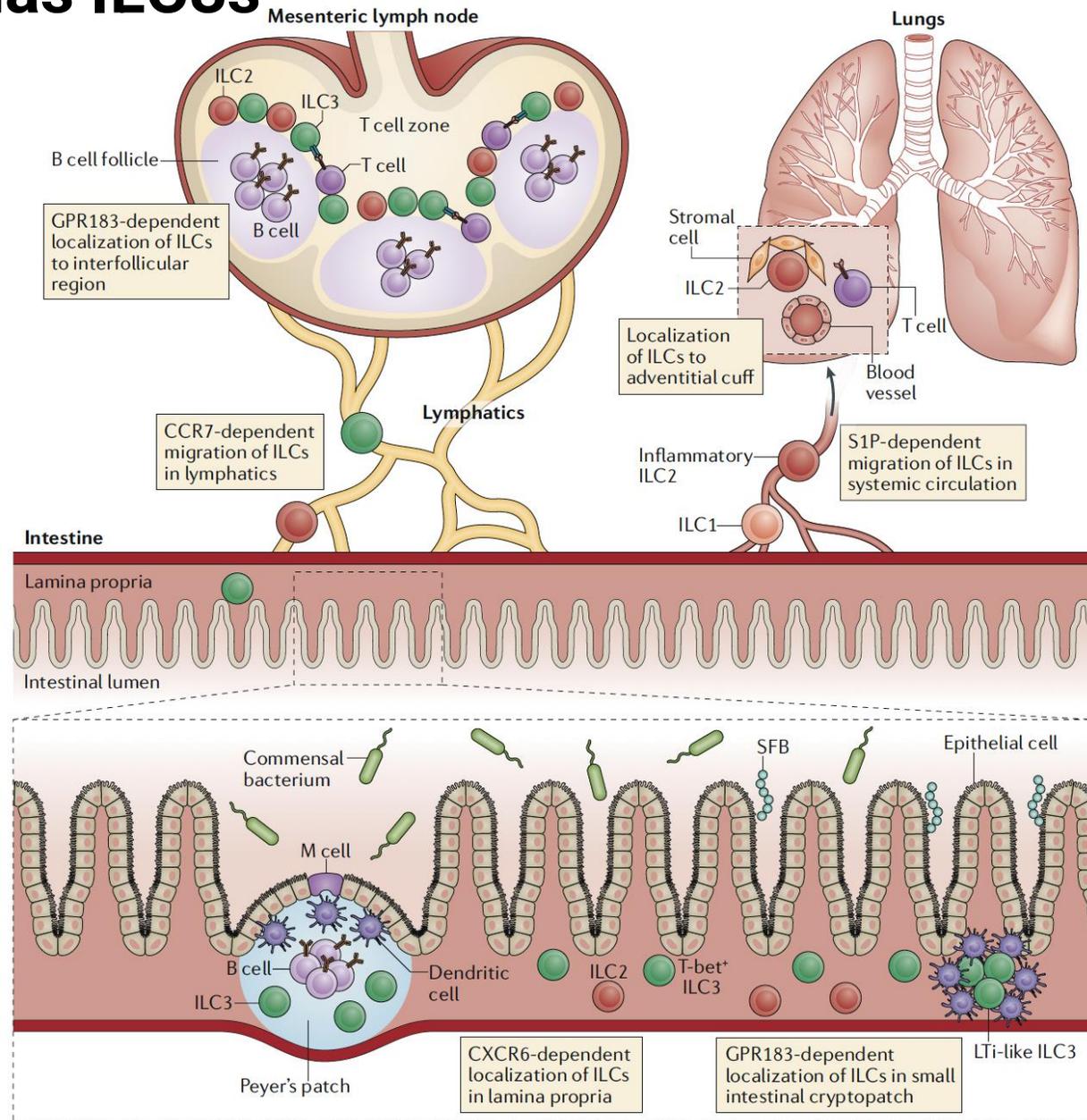
Caracterização fenotípica das células linfoides do grupo 3 (ILC3s)

Gated on live lymphocytes

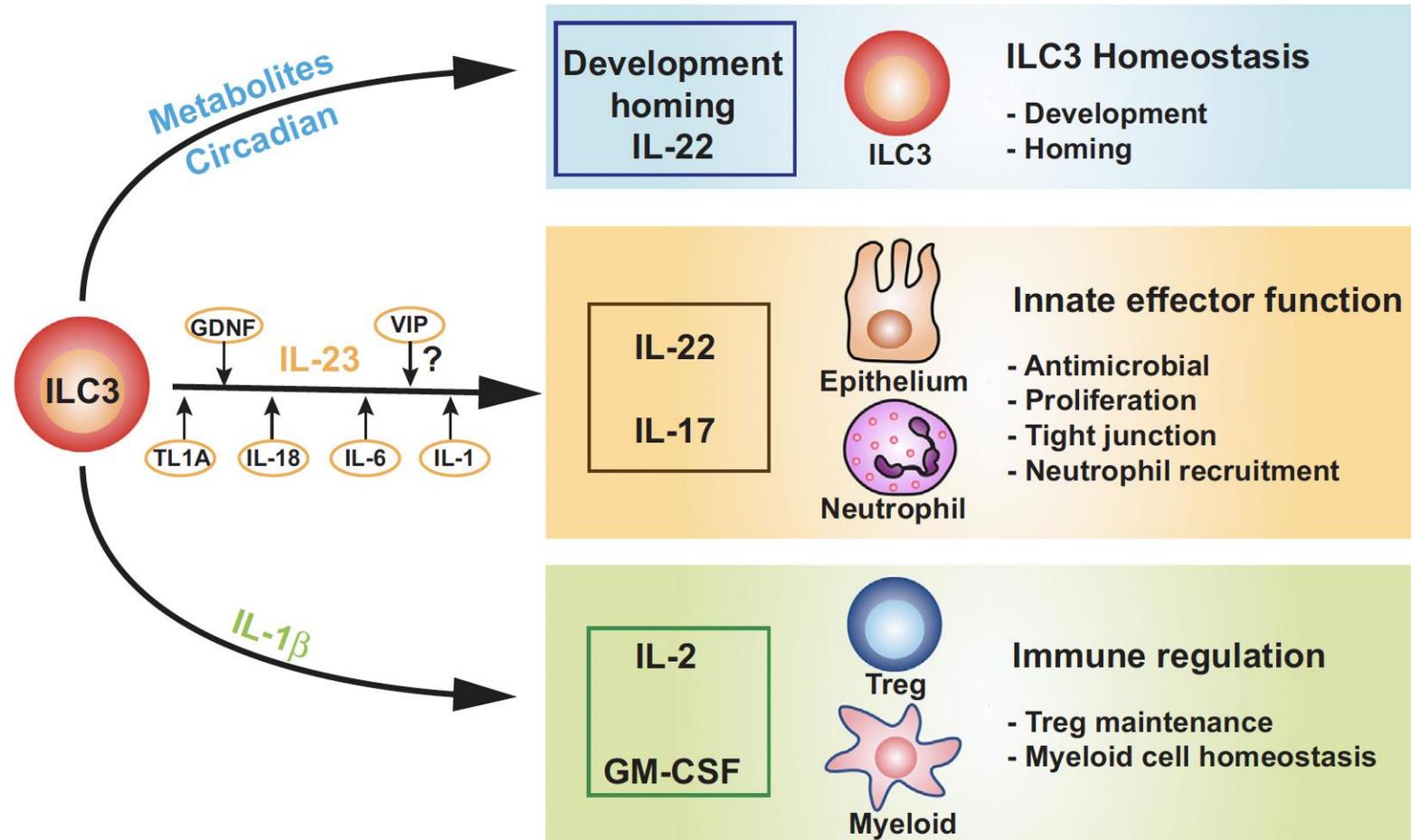


Lin 1: CD3 and TCR β .
Lin 2: CD11c, CD11b, B220.

Distribuição anatômica das ILC3s



Funções das células linfoides inatas do grupo 3 (ILC3s)



Trends in Immunology

Neurônios entéricos peptídeo intestinal vasoativo (VIP) estão próximos com ILC3

Article

Feeding-dependent VIP neuron–ILC3 circuit regulates the intestinal barrier

<https://doi.org/10.1038/s41586-020-2039-9>

Jhimmy Talbot¹, Paul Hahn¹, Lina Kroehling¹, Henry Nguyen¹, Dayi Li¹ & Dan R. Littman^{1,2}✉

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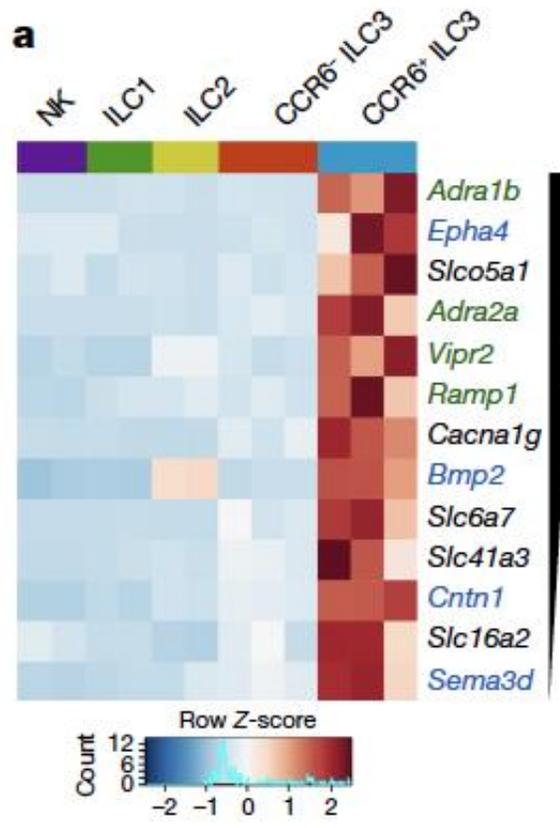
Published online: 12 February 2020



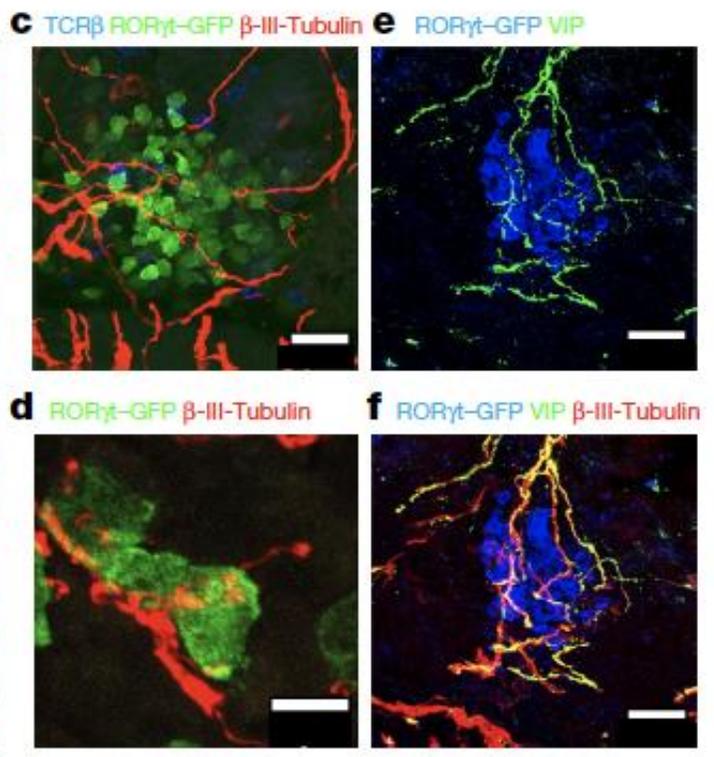
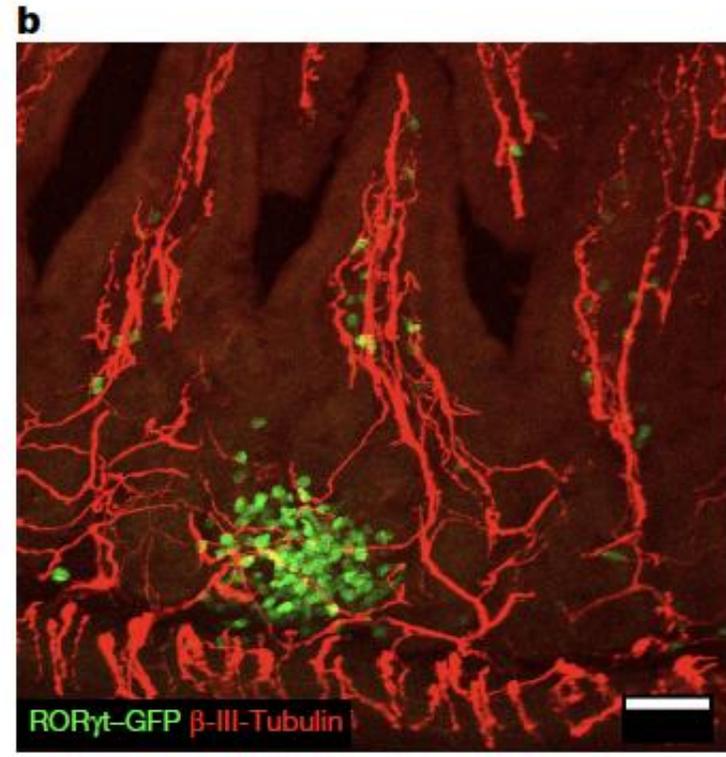
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The intestinal mucosa serves both as a conduit for the uptake of food-derived nutrients and microbiome-derived metabolites, and as a barrier that prevents tissue invasion by microorganisms and tempers inflammatory responses to the myriad contents of the lumen. How the intestine coordinates physiological and immune responses to food consumption to optimize nutrient uptake while maintaining barrier functions remains unclear. Here we show in mice how a gut neuronal signal triggered by food intake is integrated with intestinal antimicrobial and metabolic responses that are controlled by type-3 innate lymphoid cells (ILC3)^{1–3}. Food consumption rapidly activates a population of

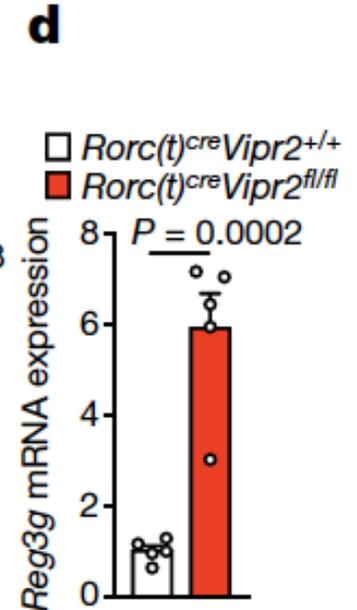
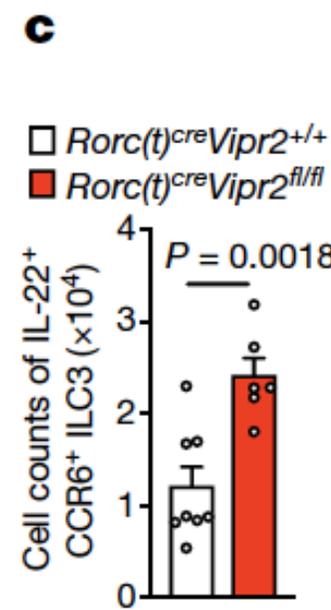
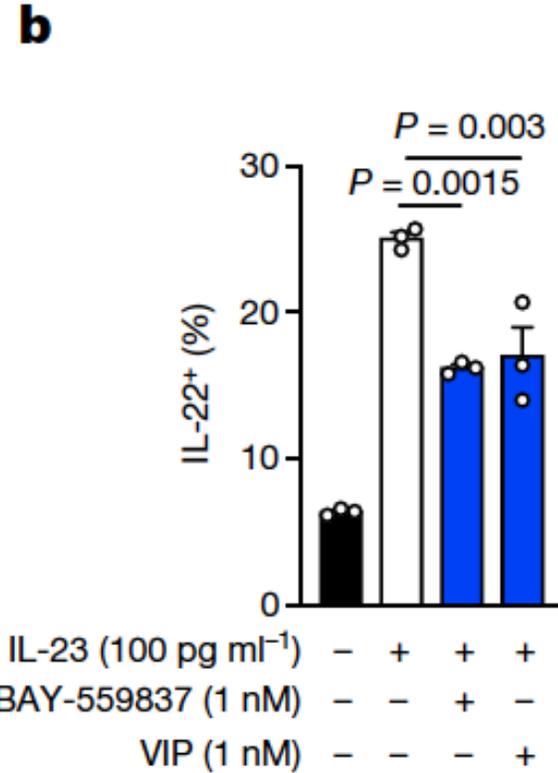
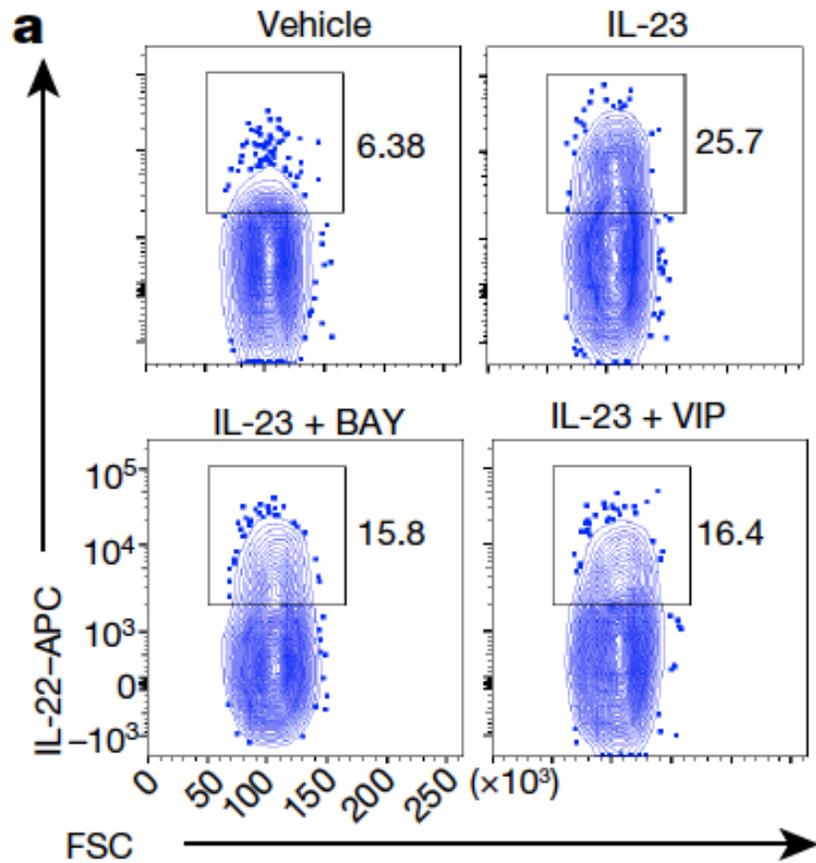
▶ Neurônios entéricos - peptídeo intestinal vasoativo (VIP) estão próximos com ILC3



Fold change between CCR6⁺ ILC3 and CCR6⁻ ILC3

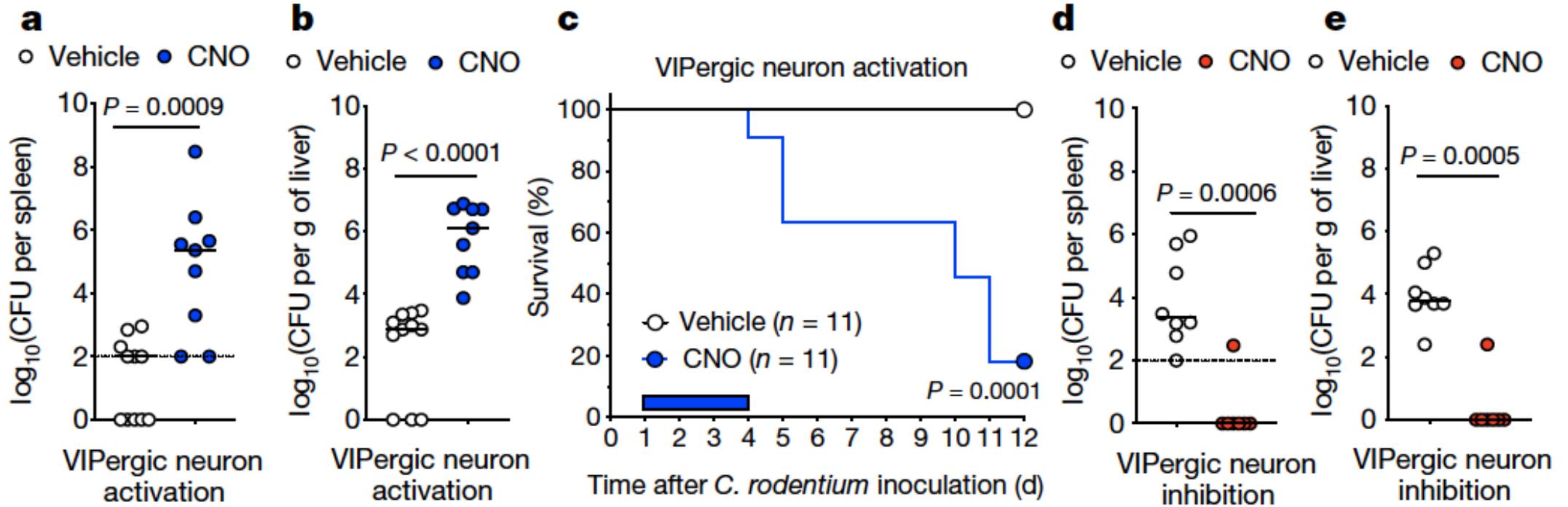


Inibição dependente de VIPR2 das ILC3 CCR6⁺ e da resposta antimicrobiana

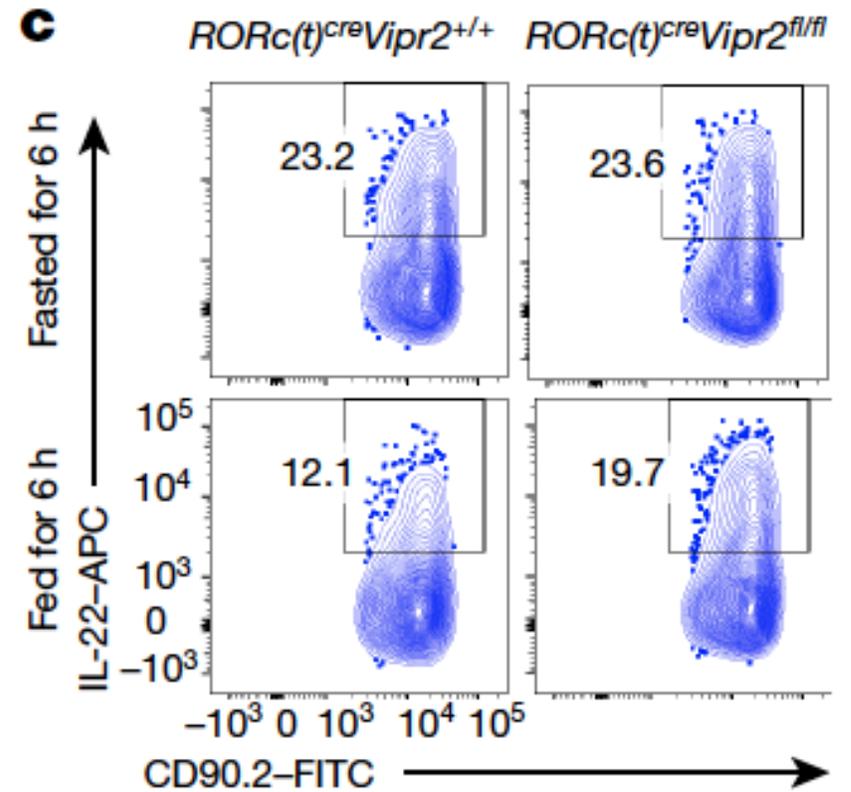
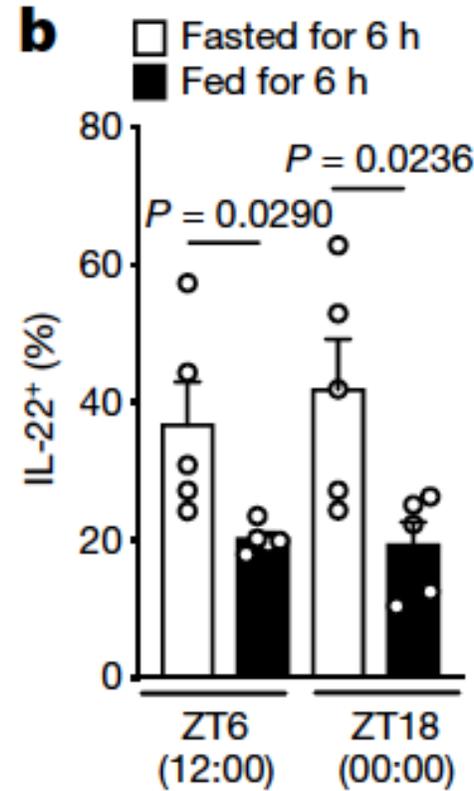
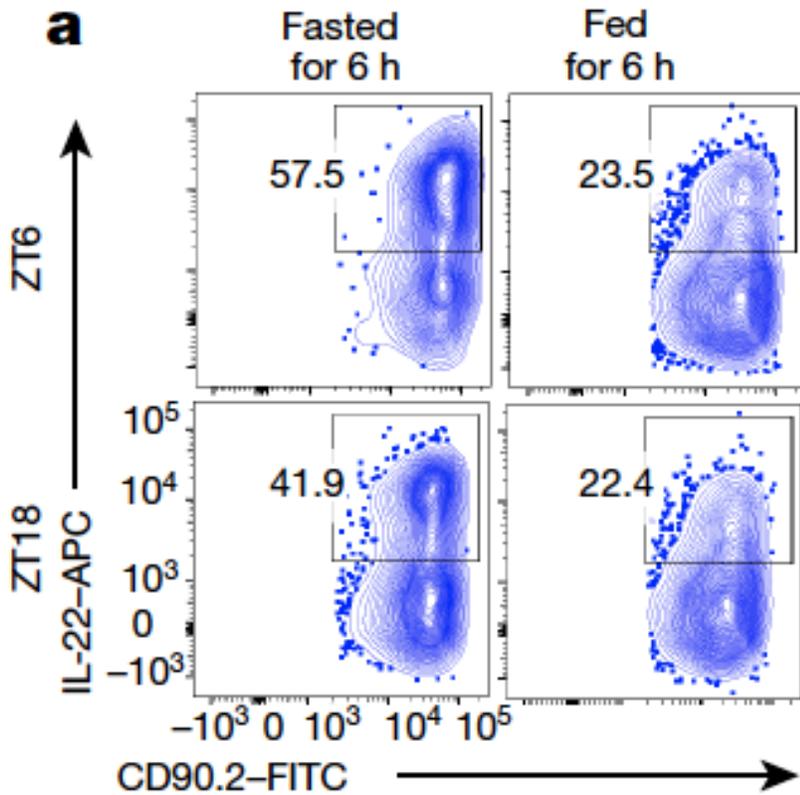


BAY: VIP receptor agonist

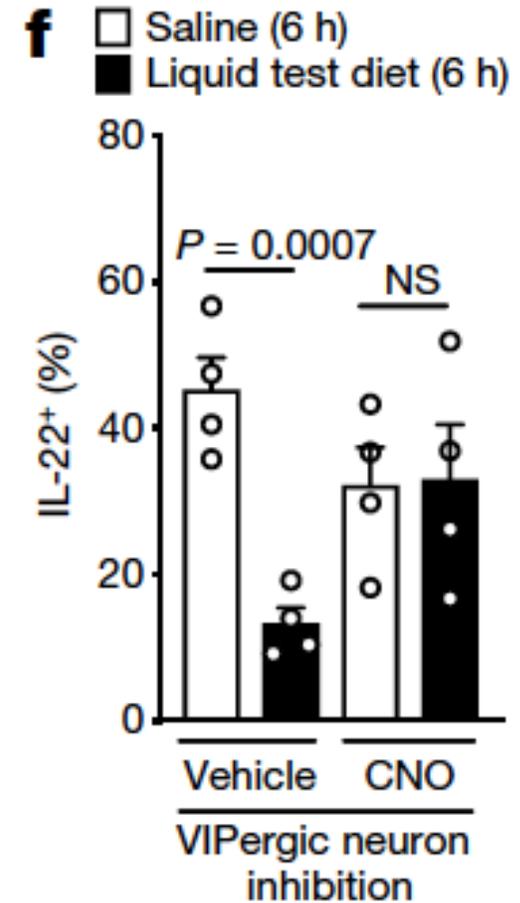
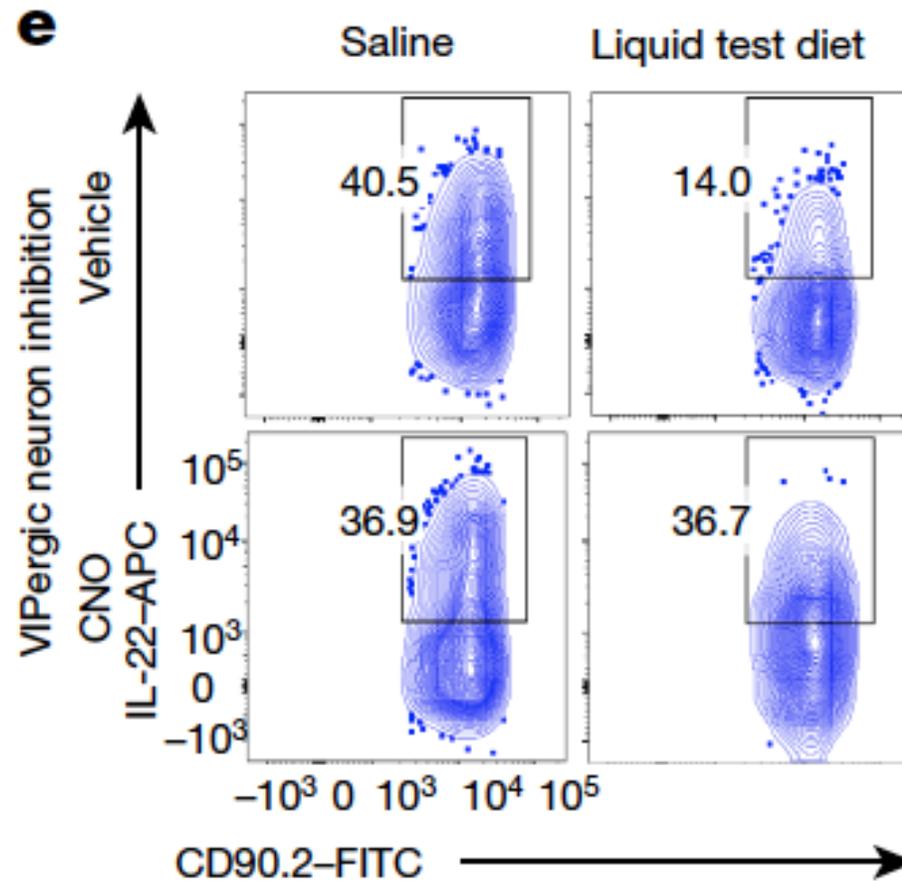
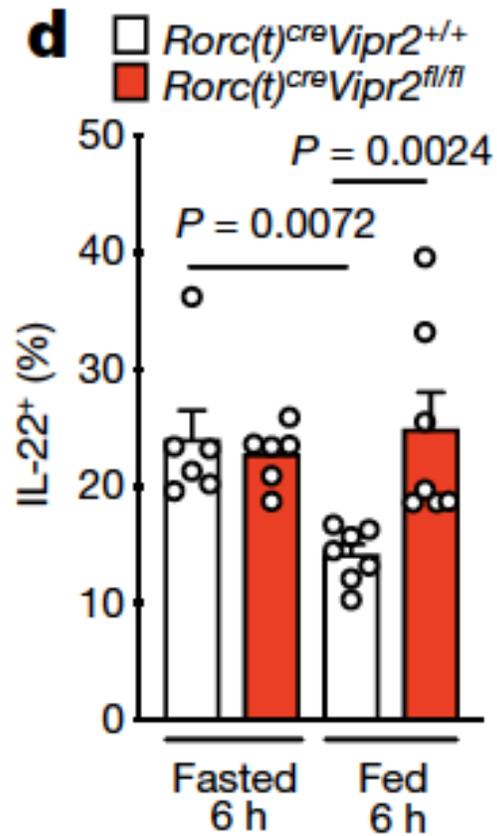
A sinalização VIPérgica reduz a função da barreira mucosa



► A alimentação reduz a produção de IL-22 por ILC3 CCR6⁺ por meio da ativação de neurônios VIPérgicos



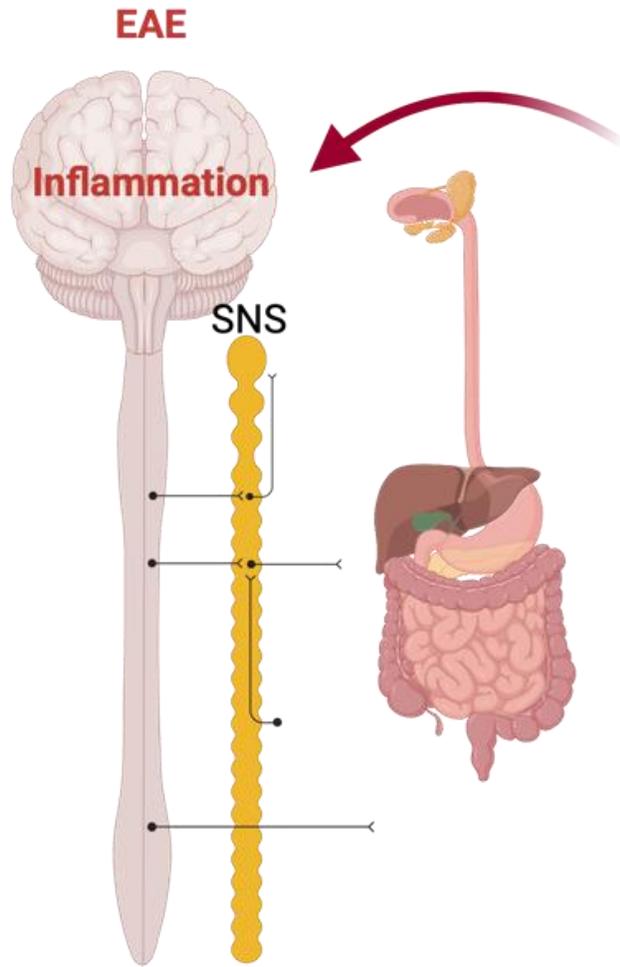
A alimentação reduz a produção de IL-22 por ILC3 CCR6⁺ por meio da ativação de neurônios VIPérgicos



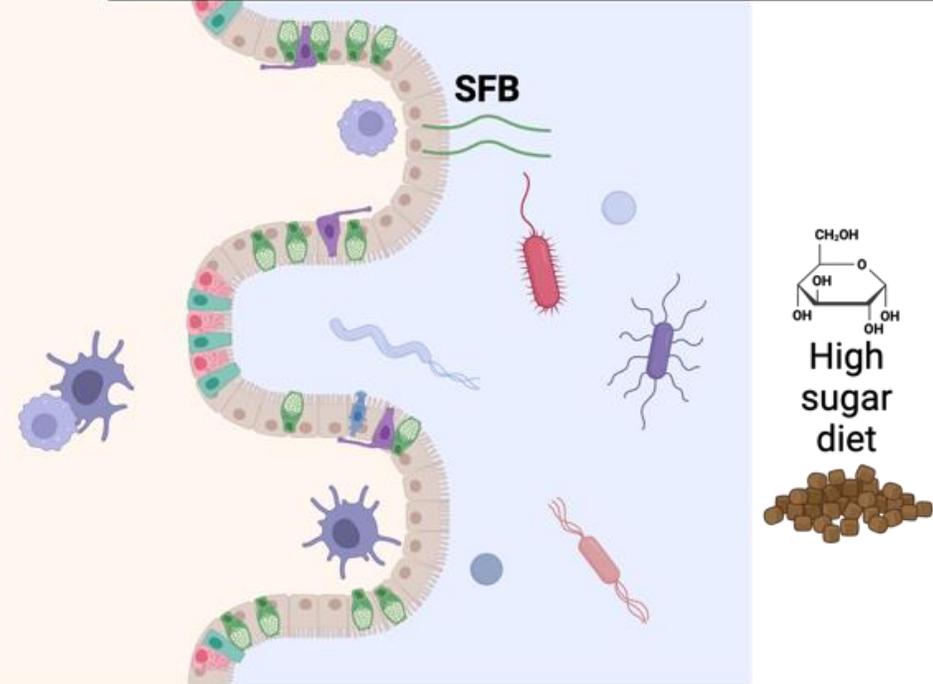
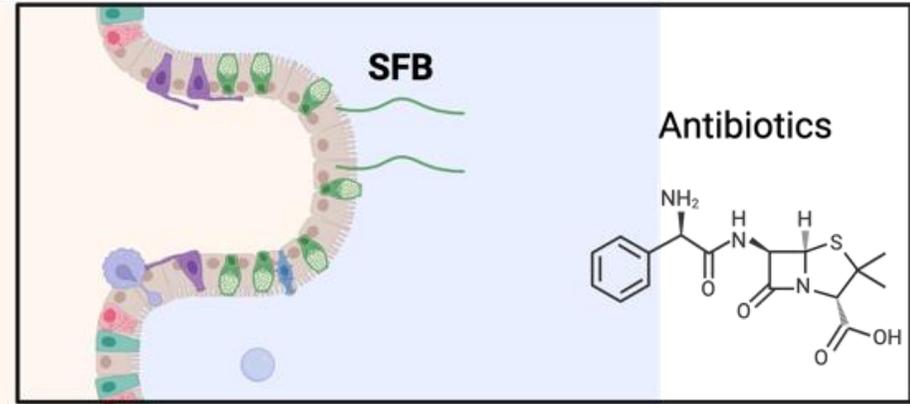
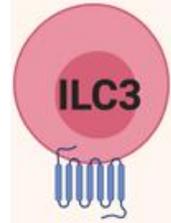
Brain



Gut



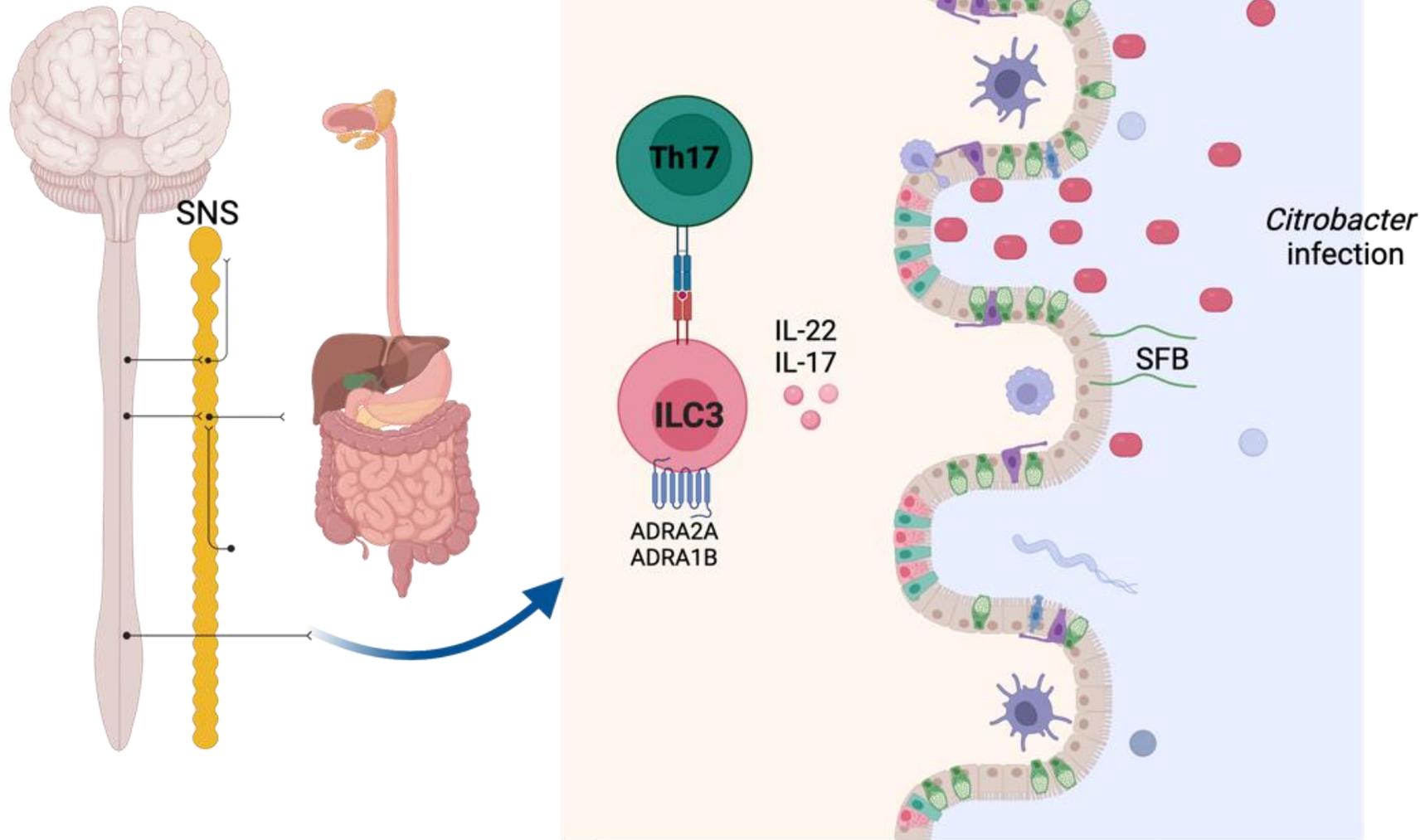
Δ MHC-II



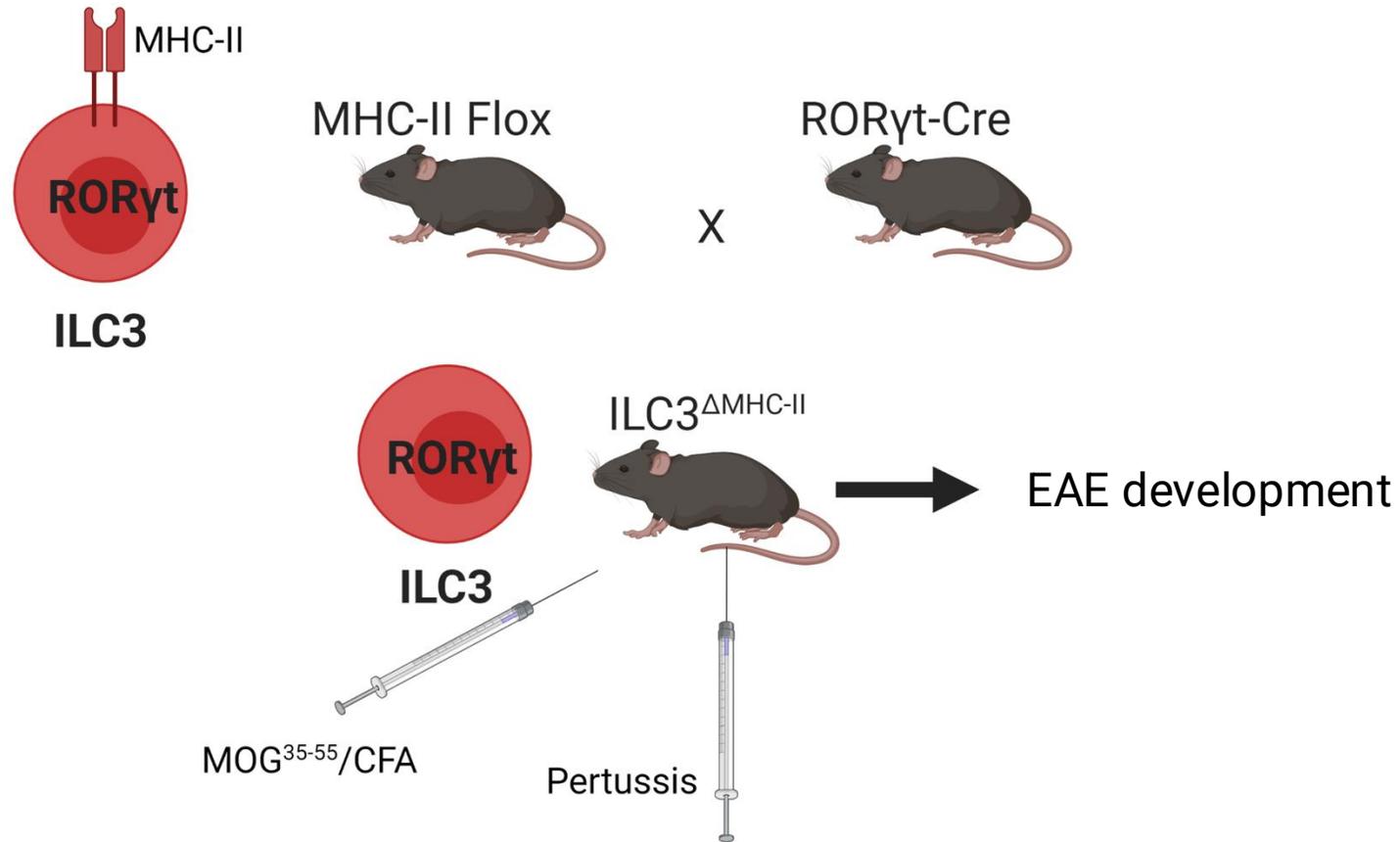
Brain



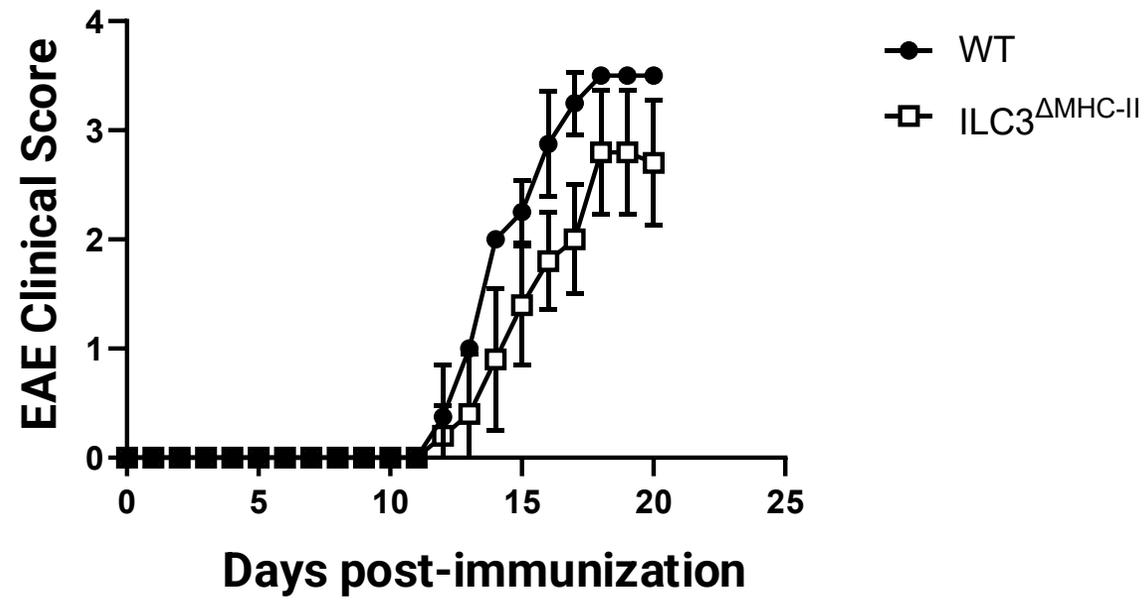
Gut



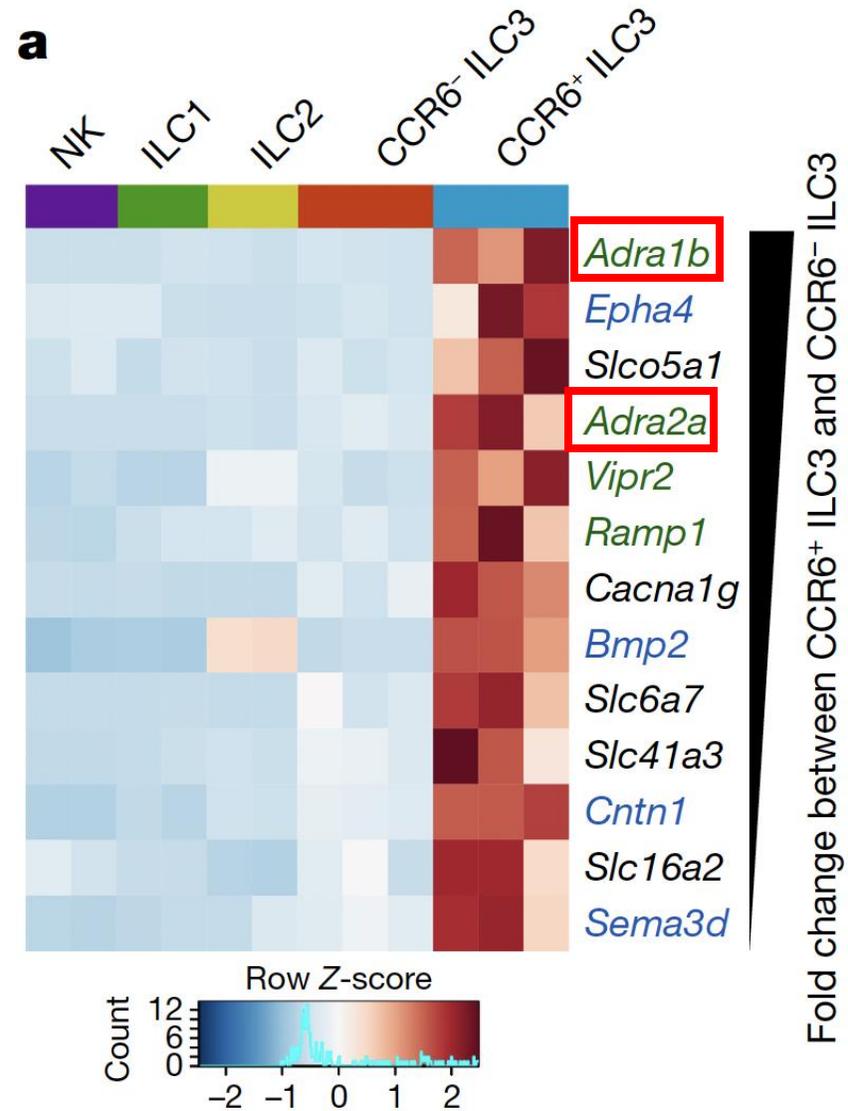
Papel das ILC3 na indução da EAE



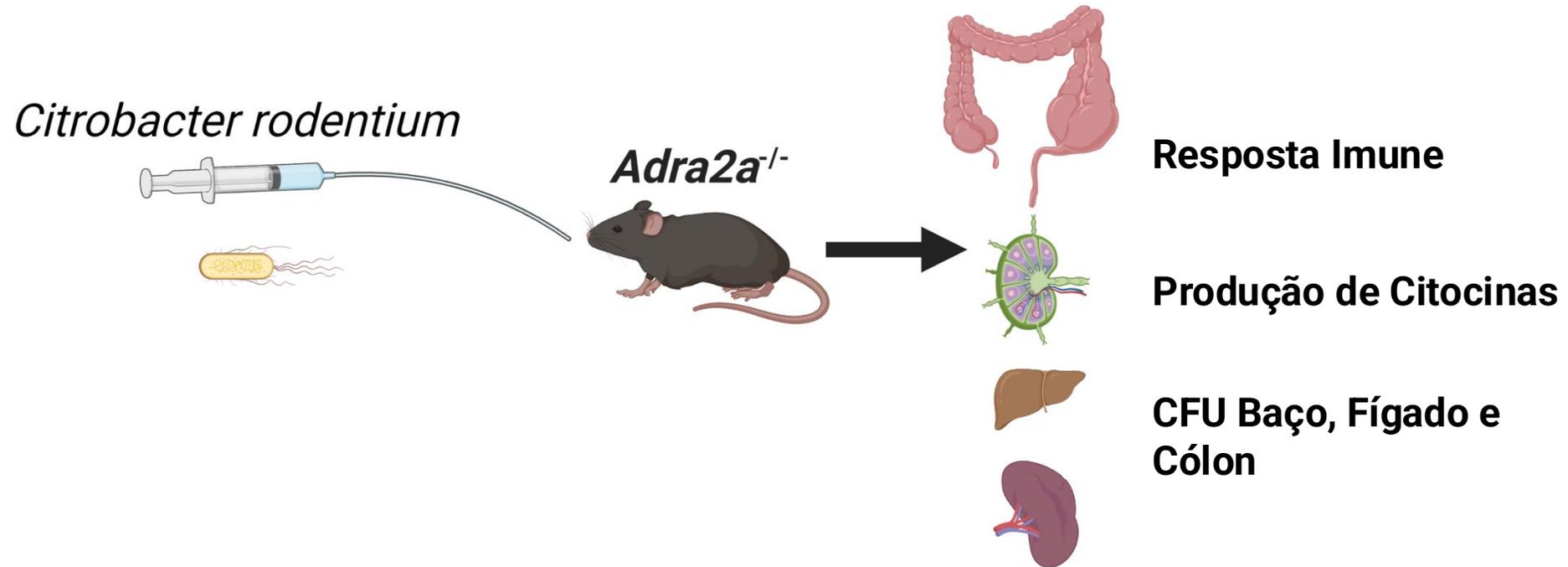
ILC3s são essenciais para a indução de EAE



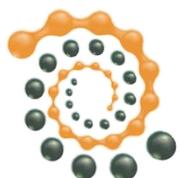
As ILC3s expressão receptores adrenérgicos



Infecção por *Citrobacter rodentium*



Recrutando alunos de graduação



Departamento de Imunologia



ICB-USP

Leandro Pires Araujo



Imunobiologia e Neuroimunologia
(Imune Lab) - Laboratório 213



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