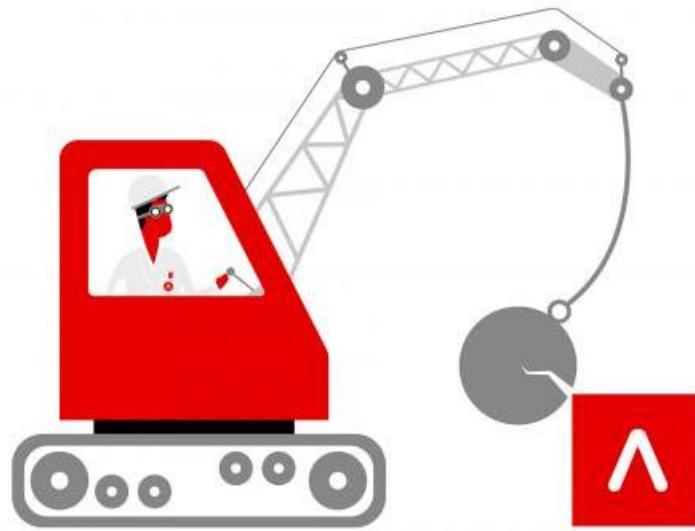


Central components of the systemic inflammatory response confer robustness to the infected host through functionally redundant regulatory processes



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Outline

- Some introductory remarks on biological robustness & function
- Robustness trade-offs related to the immune system
- Systemic inflammation, fever and reduced food intake as adaptive host responses to bacterial infection
- Functionally redundant pathways bring about fever and reduced food intake in response to detection of bacterial fragments by the host

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Biological robustness

- Robustness is a **property** that allows a system to maintain its **functions** despite external and internal **perturbation**.
- The robustness of a system can manifest itself in one of two ways: the system returns to its current attractor or moves to a new attractor that maintains the system's functions.
- Robustness is often **misunderstood** to mean staying **unchanged** regardless of stimuli or mutations, so that the structure and components of the system, and therefore the mode of operation, is unaffected.
- In fact, robustness is the **maintenance of specific functionalities** of the system against perturbations, and it often requires the system to change its mode of operation in a flexible way.

Robustness of cellular functions

- In general, robustness means the persistence of a system's characteristic behavior under perturbations or apparent complexity of cellular systems are intimately conditions of uncertainty.
- It is important to note that robustness (such as stability) encompasses a relative not an absolute property because no system can maintain stability for all its functions when encountering any kind of perturbation.
- ..., one has to take into account that robustness refers to the maintenance of specific functionalities of a system subjected to specific perturbations.

Robustness of cellular functions

- In biology, the concept of **robustness** closely relates to “stability,” “**homeostasis**,” and “canalization,” but it covers a broader class of phenomena (Kitano, 2002; Carlson and Doyle, 2002).
- For instance, **homeostasis** refers to maintaining a steady state, but **robustness** can also apply to dynamic processes in development.
- As integral feedback is necessary and sufficient for robust steady-state control, it explains **robustness** of phenomena such as perfect adaptation, **homeostasis**, and noise rejection (Csete and Doyle, 2002).

Towards a theory of biological robustness

- It important to realize that robustness is concerned with maintaining functions of a system rather than system states, which distinguishes robustness from stability or homeostasis.
- Homeostasis, stability, and robustness will be identical if the function to be preserved is the one that maintains the state of the system.
- In addition, the robustness of a subsystem often contributes to homeostasis of the system at the higher level.

Towards a theory of biological robustness

- Whereas **homeostasis** and stability are somewhat related concepts, **robustness** is a more general concept according to which a system is robust as long as it maintains functionality, even if it transits through a new steady state or if instability actually helps the system to cope with perturbation.
- Such **transition between states** is often observed in biological systems when facing **stress** conditions.
- ... examples of extreme robustness under harsh stress conditions show that organisms can attain an impressive degree of **robustness by switching from one steady state to the other**, rather than trying to maintain a given state.
- In summary, whereas robustness is a general concept, **homeostasis** or stability can be considered as **particular instances of robustness**.

The function debate in philosophy

- A theory of **function** is supposed to explain how such **biological norms** arise out of a physical world (i.e. why it is legitimate to expect from a heart that it pumps blood) (see especially Millikan, 1984: 17–19, 1989b; Neander, 1991a: 180–183).
- The **dominant theory of function** in naturalistic philosophy, the selected effects theory, defines the notion of **function** in terms of past selection and sees function attributions as a kind of historical selection explanations.
- However, biologists routinely **distinguish between functional explanations and evolutionary explanation** and important discussions of biological explanation by biologists tend to make an explicit distinction between the study of function and the study of evolution.

The function debate in philosophy

- According to the systemic approach the **function** of an item is the **role of that item in bringing about an activity or capacity of a complex system** of which that item is a part. For example, on this view it is the function of the heart to pump the blood because pumping the blood is how the heart contributes to the circulation of the blood.
- In [Craver's] view, **function** attributions describe **how an item participates in the activity of a mechanism**. Roughly speaking, mechanisms are complex systems that are organized in such way that they produce a regular activity.

Intermediate conclusion (1)

- Robustness in biology is a property that allows a system to maintain its functions despite external and internal perturbation and may involve transition through different state systems.
- Function in biology between
 - result of past selection
 - role item in bringing about a system's activity or capacity

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Robustness trade-offs and host–microbial symbiosis in the immune system

- Defense against pathogens is one of the most important issues for the survival of the organism. Such a function makes the organism more robust against external threats.
- As the immune system clearly provides robustness to the organism, interpretation of its molecular interactions and functions within the framework of biological robustness will help us to better understand the immune system within an integral framework of robust evolvable systems.

Biological robustness in complex host-pathogen systems

- Although the **immune system** evolved to be very robust to host organisms, there are **trade-offs** inherent in the system.
- ... the host immune system ... is fundamentally proinflammatory [58], and **requires active control** to reduce inflammatory reactions
- **Hyper-activation of a cytokine network**, ..., is one of the major factors that **aggravates patient health** and may results in death.

Biological robustness in complex host-pathogen systems

- ..., the **infection is generally localized** to epithelial cells yet extensive cytokine release often takes place **systemically**.
- This **systemic release of cytokines** particularly IL-1 α and IFN- γ aggravates inflammation leading to **fever** and lung inflammation, and sometimes **leads to fatality**.
- A series of experimental and clinical observations naturally leads to the conclusion that **control of cytokine production** may effectively **prevent** escalation of infection-triggered organ dysfunctions, and more generally **systemic inflammatory response syndrome (SIRS)**.

Pathobiology of Sepsis

Are We Still Asking the Same Questions?

Definitions: Consensus, 1992 (2)

Systemic Inflammatory Response (SIRS)

2 or more of following:

Temp $> 38^{\circ}\text{C}$ or $< 36^{\circ}\text{C}$

Heart Rate $> 90 \text{ bpm}$

RR > 20 or $\text{Pa}_{\text{CO}_2} < 32$

WBC $> 12\text{K}$, $< 4\text{K}$ or $> 10\%$ bandemia

Sepsis: SIRS + infection

Severe sepsis: sepsis with organ dysfunction,
hypoperfusion, or hypotension

Septic shock: sepsis with hypotension despite
fluid resuscitation

Multiple organ dysfunction syndrome

Altered organ function in an acutely ill patient;
intervention required for homeostasis

Biological Basis of the Behavior of Sick Animals

- Fever, as a primary marker of disease, is mentioned in both the Old and New Testaments and was considered as God's Punishment for human transgressions. In the Middle Ages fever was almost synonymous with the Black Death which killed one-fourth to one-third of the European population.
- Although elevated body temperature has long been viewed as a symptom of illness in both people and animals, until recently, fever has typically been thought of as an undesirable side effect of illness to be reduced by antipyretics such as aspirin.
- The behavioral mode, characterized by sleepiness, depression, loss of appetite, reduction of water intake, and cessation of grooming, are as common and ubiquitous among animal species when they are sick as is the occurrence of fever.

Deconstructing mammalian thermoregulation

- Thermoregulation is essential in all organisms, an evolutionary condition *sine qua non*. In mammals and other warm-blooded animals, homeothermy became an essential physiologic feature during evolution.
- Homeothermy, the physiologic capability to maintain a constant core body temperature with minimal deviation from the set point, provided a critical survival advantage to mammalian and avian phyla because it brought about a thermally equilibrated internal environment for cells and organs.
- This in turn rendered nutrition, metabolism, and excretion more robust and efficient, and permitted more precise and powerful functioning of excitable cells in the nervous system, as well as for contractile cells in heart, muscle, and smooth muscle, and evolutionary honing of an immune-defense and wound-healing system.

The evolution of the control of food intake

- The ultimate goal of an organism is to maximise its inclusive fitness, and an important **sub-goal must be the optimisation of the lifetime pattern of food intake**, in order to meet the nutrient demands of survival, growth and reproduction.
- The **fitness benefits of food intake are a function of its contribution to survival**, growth (including necessary body reserves) and reproduction.
- Against these benefits must be set costs. These **costs** include not only extrinsic foraging costs and risks, such as those due to **predation**, but also intrinsic costs associated with food intake, such as **obesity and oxidative metabolism** that may reduce vitality and lifespan.

Intermediate conclusion (2)

- Systemic inflammation as a trade-off of immune system-conferred robustness?
- Inflammation-associated fever and reduced food intake have long been considered undesirable and to reflect loss of function given the biological functions of constant body temperature and food intake.

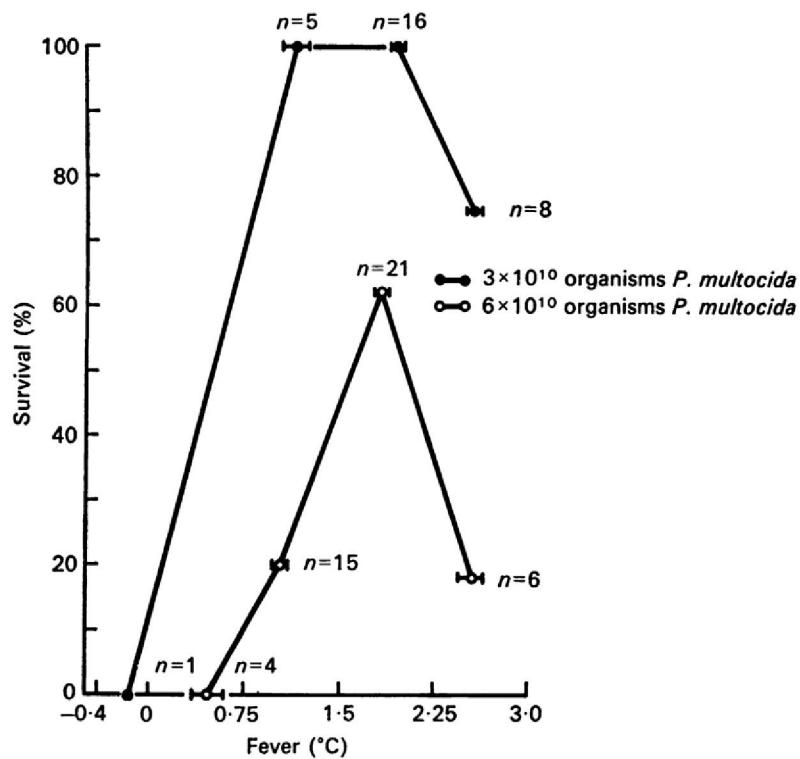
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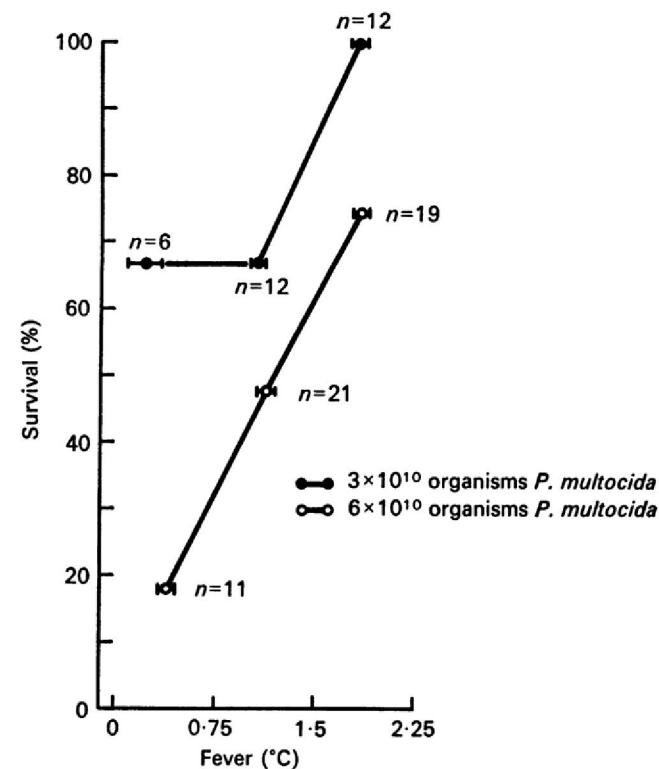
Biological Basis of the Behavior of Sick Animals

- The widespread occurrence of a physiological mechanism by which the body's cells produce a factor to cause a regulated elevated body temperature was recognized by Kluger [92,94] as an evolved mechanism going far back in vertebrate evolutionary time and which probably had some adaptive value in combating disease.
- However, the conceptual building blocks for understanding the physiological regulation of fever, sleep, and appetite have only recently been elucidated to the point that one can argue that the behavior of sick animals and people is not the result of debilitation but an adaptive strategy with survival implications.

Fever and survival in rabbits infected with *Pasteurella multocida*



Vehicle

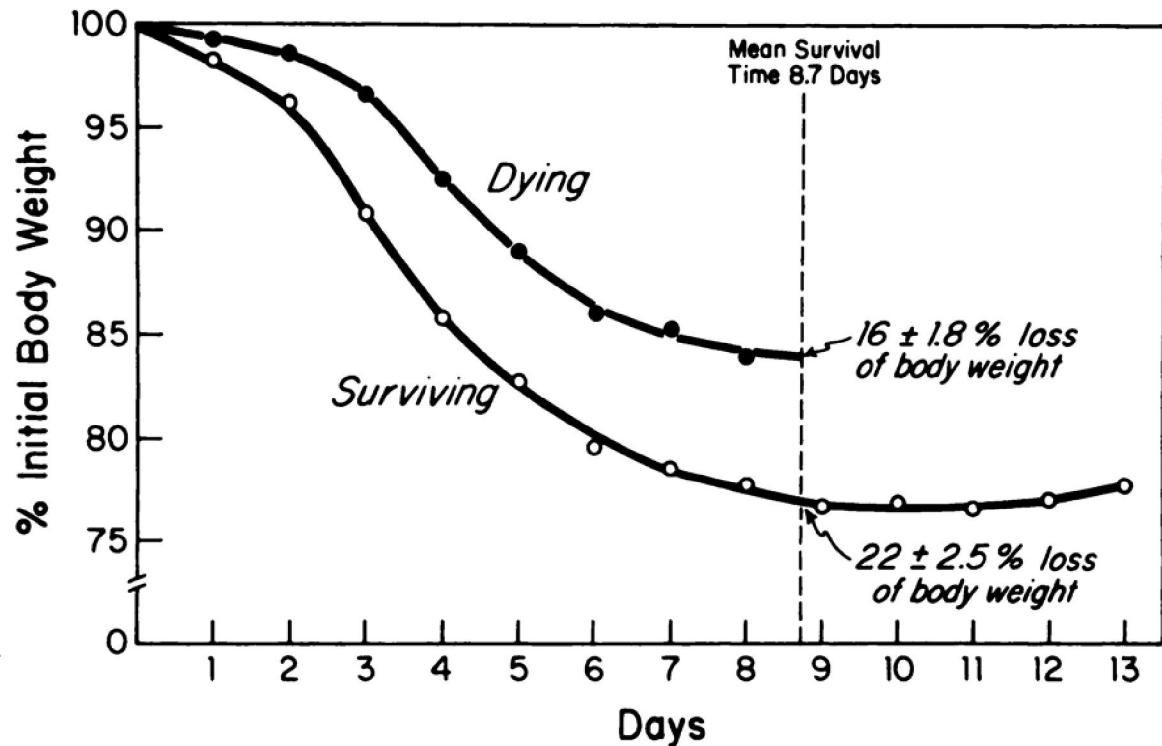


Antipyretics

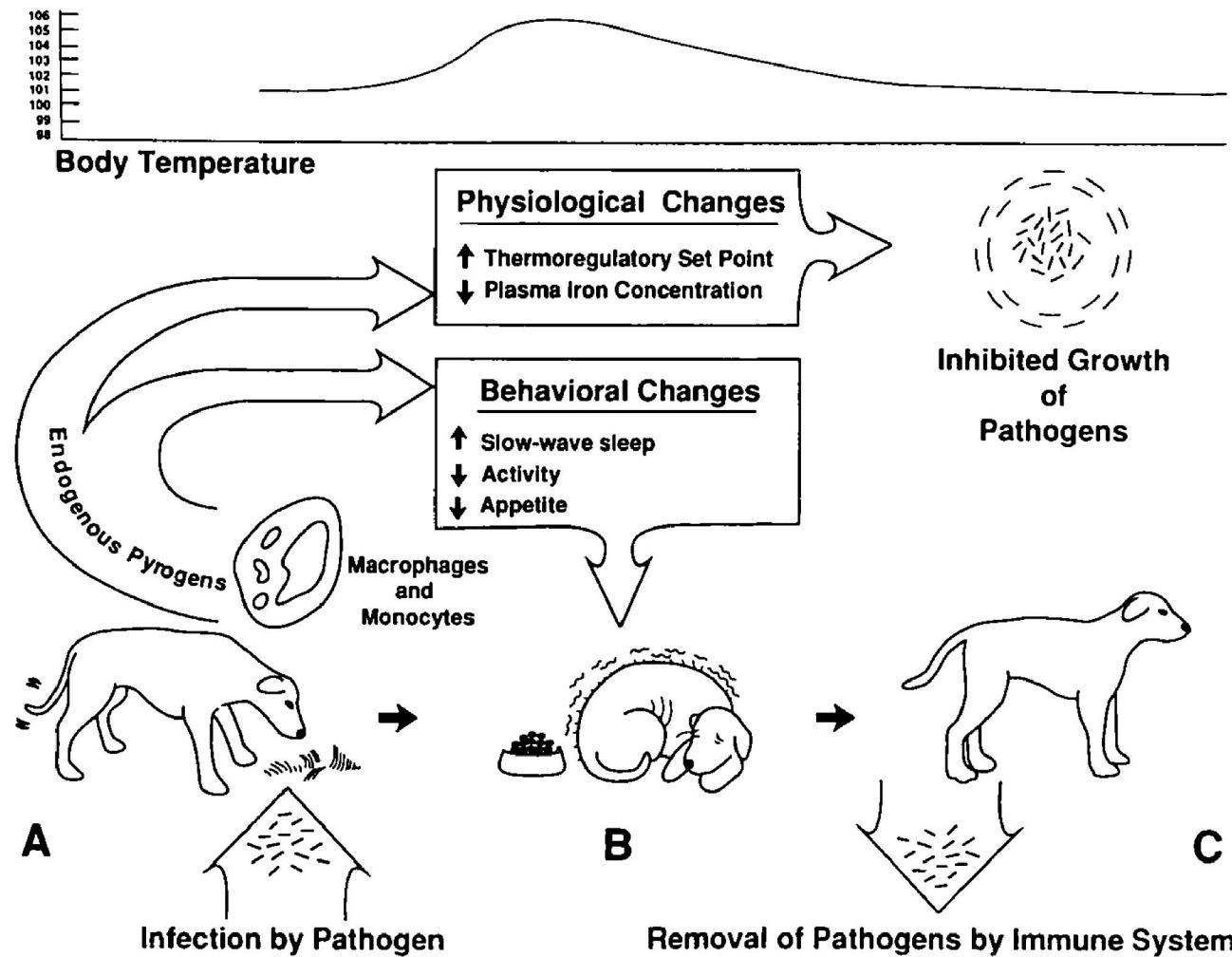
Anorexia of infection as a mechanism of host defense

	N	% Mortality	Mean survival time
Group 1 No infection, daily tube feeding followed by ad libitum feeding	10	0	
Group 2 Controls no infection, ad libitum feeding, daily tube passage ^a	30	0	
Group 3 Infection, ad libitum feeding, daily tube passage ^a	30	43	8.7 ± 1.5
Group 4 Infection, ad libitum feeding, plus tube feeding	30	93	3.9 ± 0.9

^a Without tube feeding.



Biological Basis of the Behavior of Sick Animals



Intermediate conclusion (3)

- Fever and reduced food intake are central nervous system components of the systemic inflammatory response and contribute to host survival after bacterial infection.

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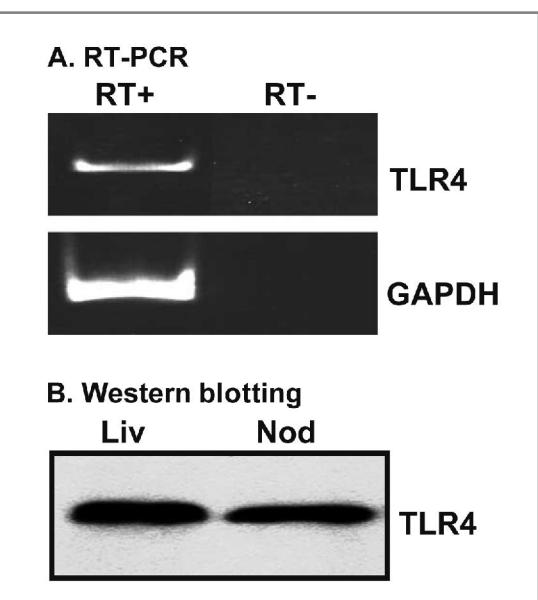
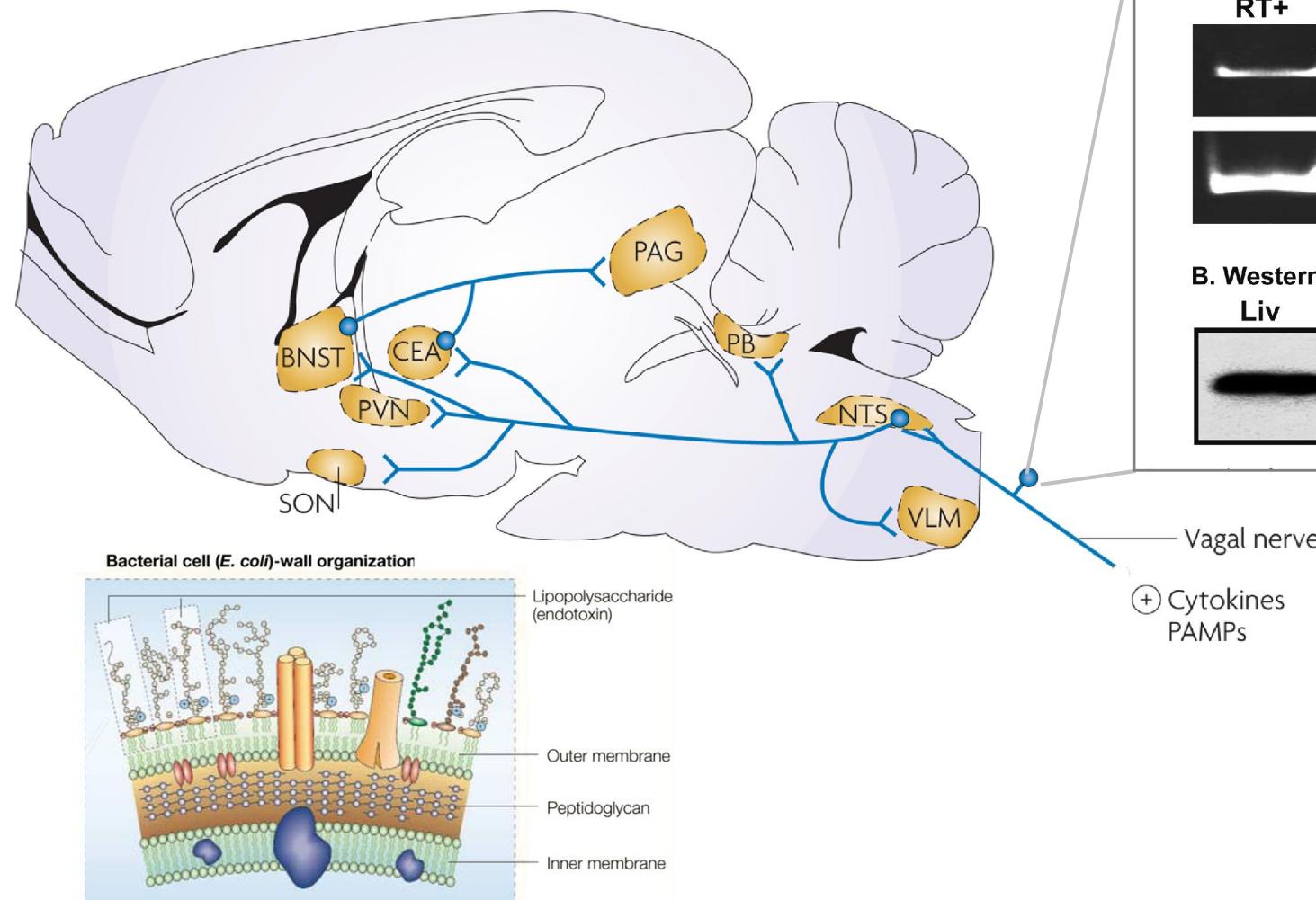
Mechanisms of CNS response to systemic immune challenge: the febrile response

- The acute-phase reaction is a multisystem response to inflammatory stimuli that is mediated in part by leukocyte-derived hormones known as cytokines.
- Increasing evidence indicates that cytokines can engage the central nervous system (CNS), which coordinates several components of the acute phase reaction^{1–5}.
- These CNS-mediated responses include fever, headache, alterations in the secretion of adrenal and pituitary hormones, changes in the sleep-wake cycle, anorexia, inactivity, nausea and emesis.

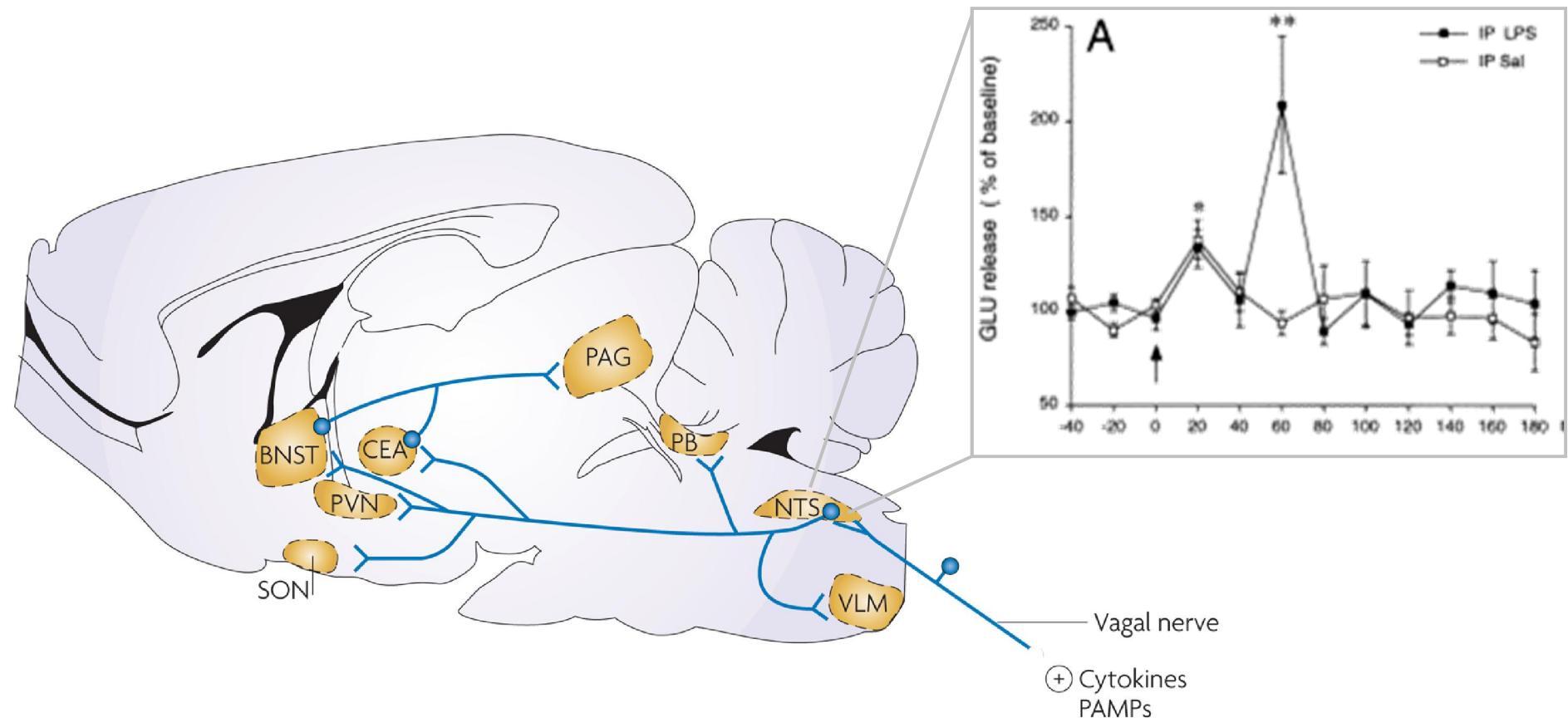
Mechanisms of CNS response to systemic immune challenge: the febrile response

- The organismal benefit of these responses is indicated by the fact that they are widespread among vertebrates with components even seen in some invertebrates².
- For example, increases in body temperature might improve the ability of white blood cells to fight infection by certain microorganisms while simultaneously inhibiting the growth of some microbes.
- In addition, sleepiness, malaise and inactivity enable energy conservation during periods of decreased caloric intake^{4,6}.

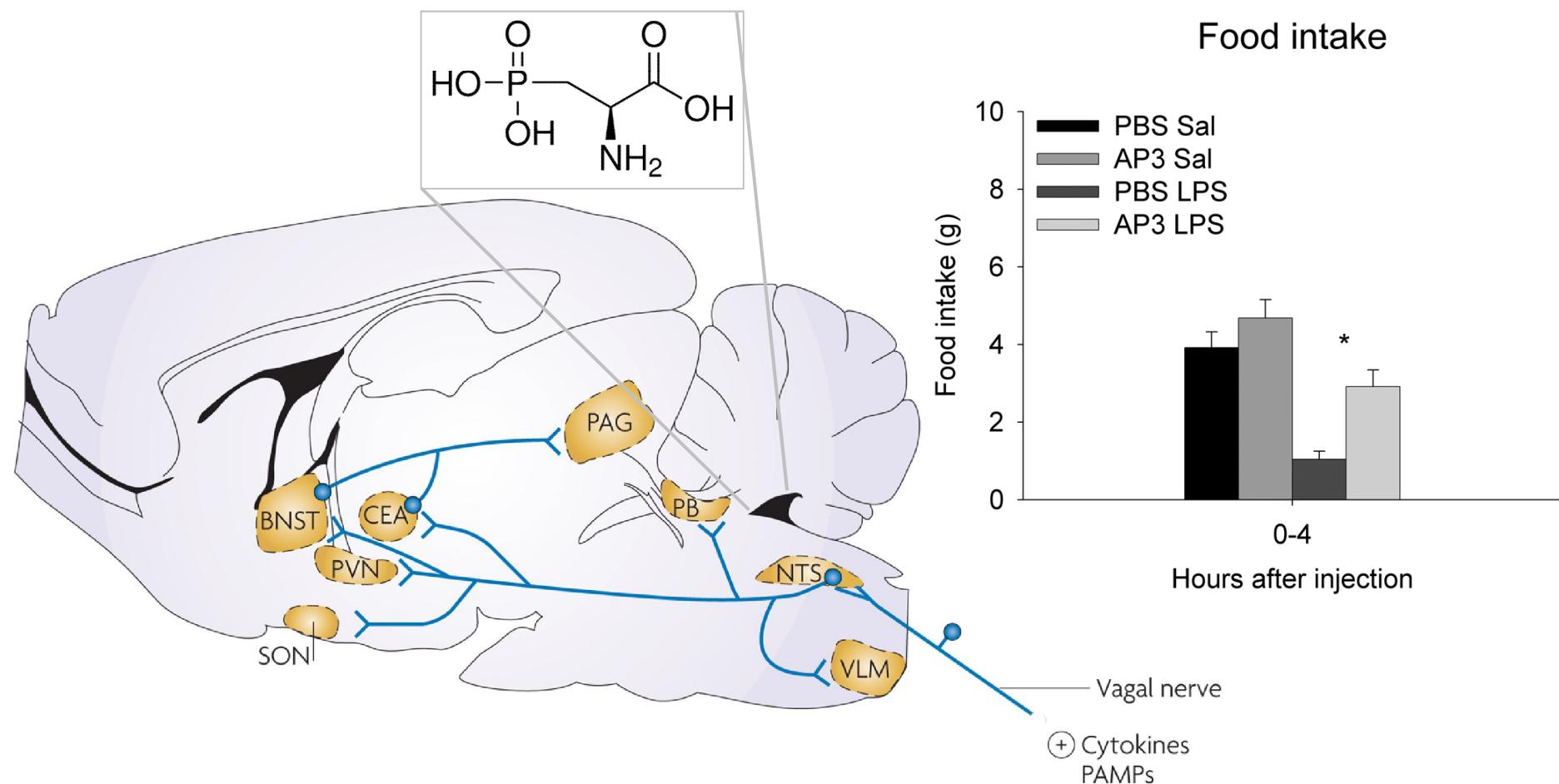
Vagus nerve nodose ganglion expresses bacterial LPS-recognizing Toll-Like Receptor



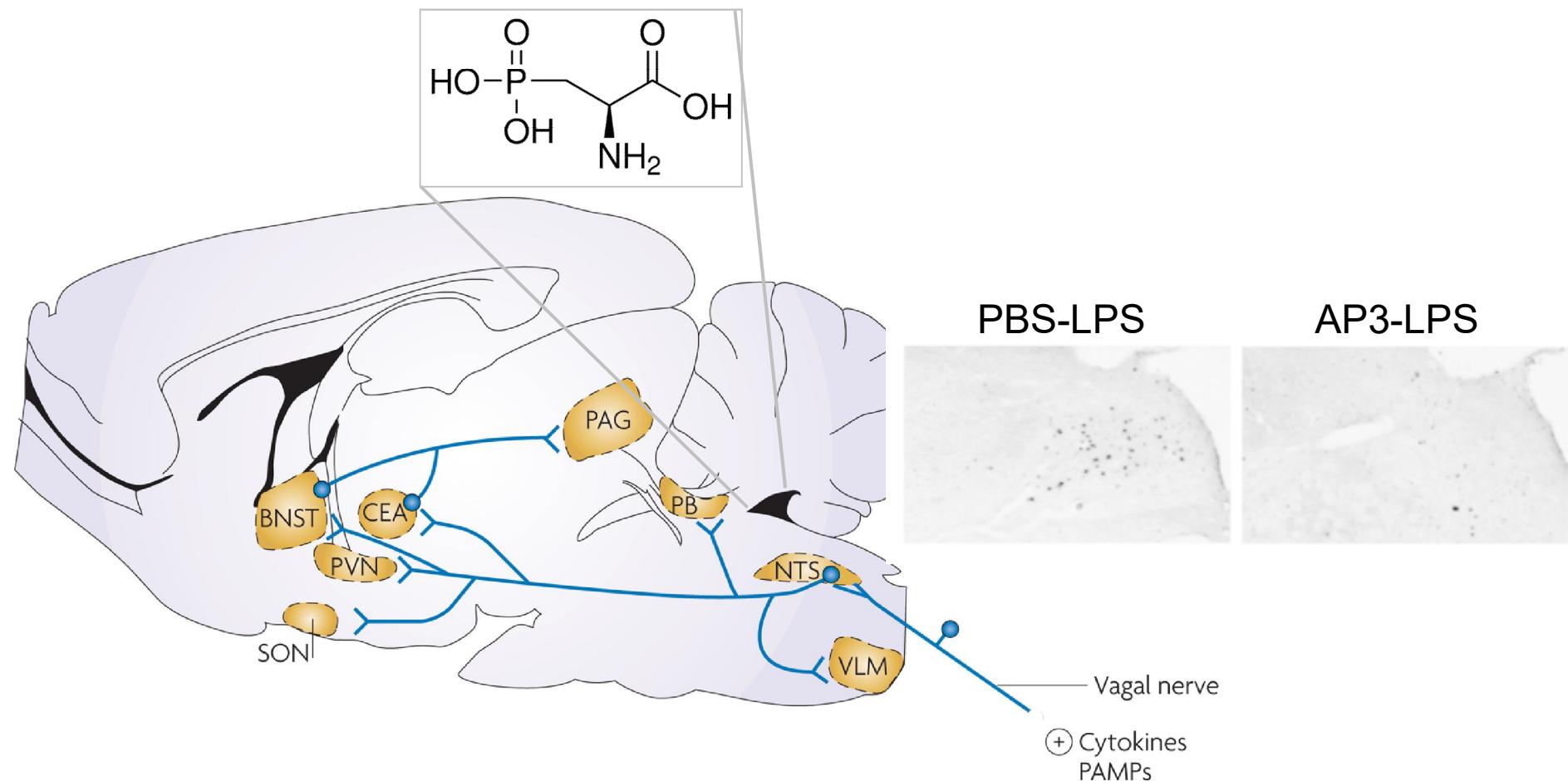
Increased glutamate release in nucleus of the solitary tract after ip administration of bacterial LPS



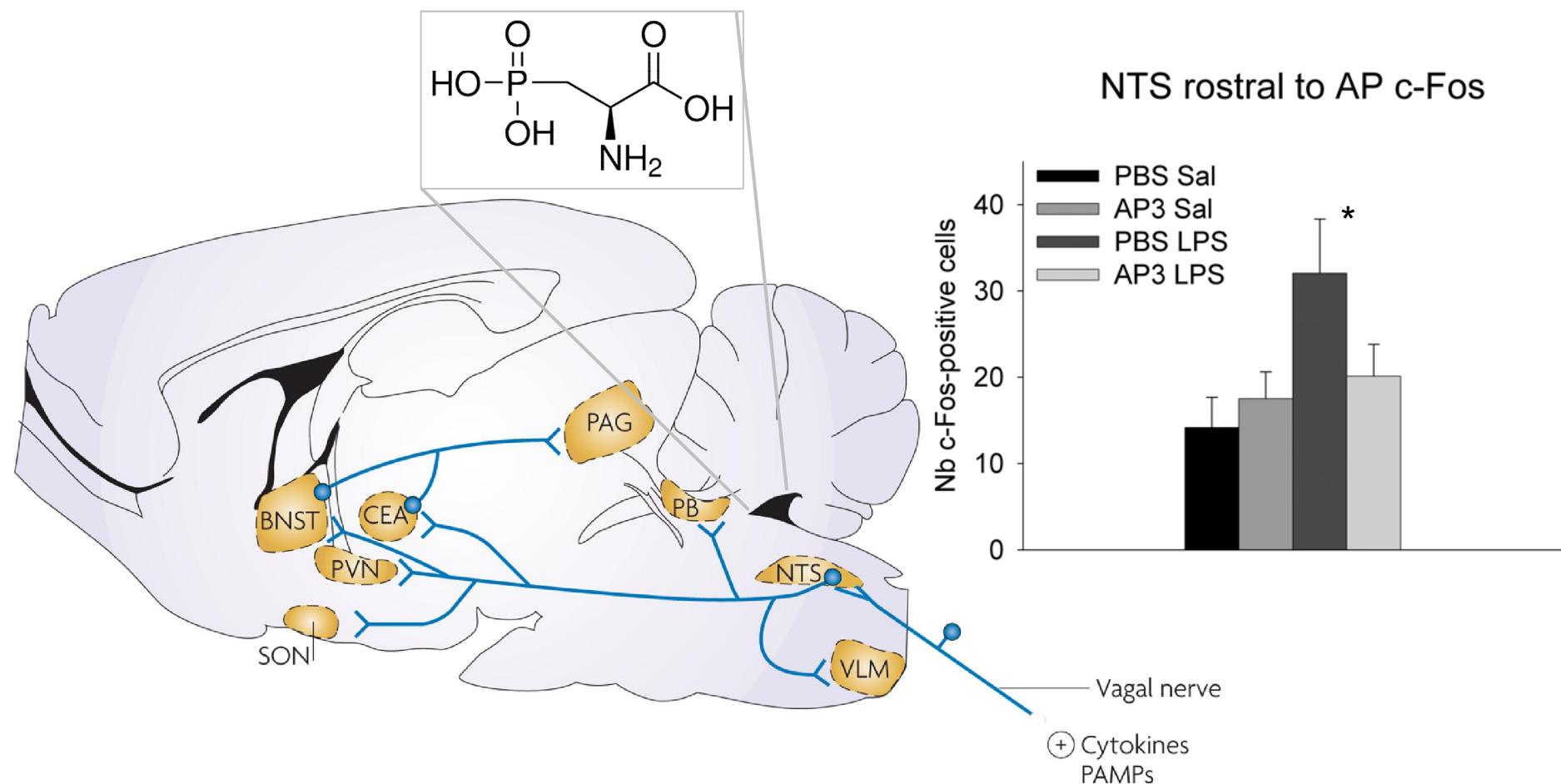
Brainstem glutamate receptor antagonism increases food intake after ip LPS administration



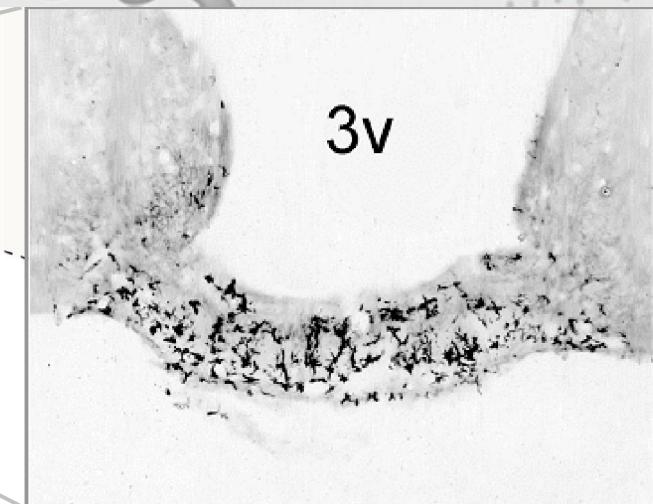
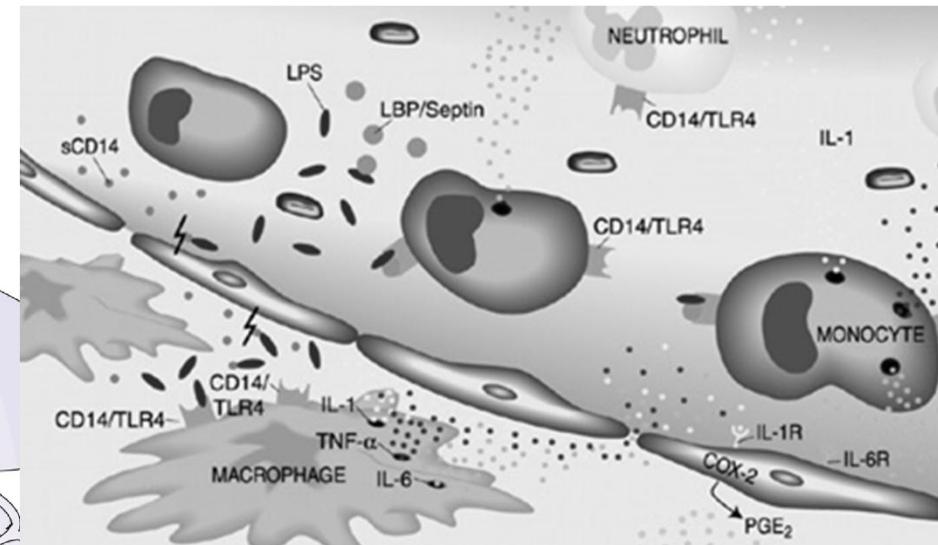
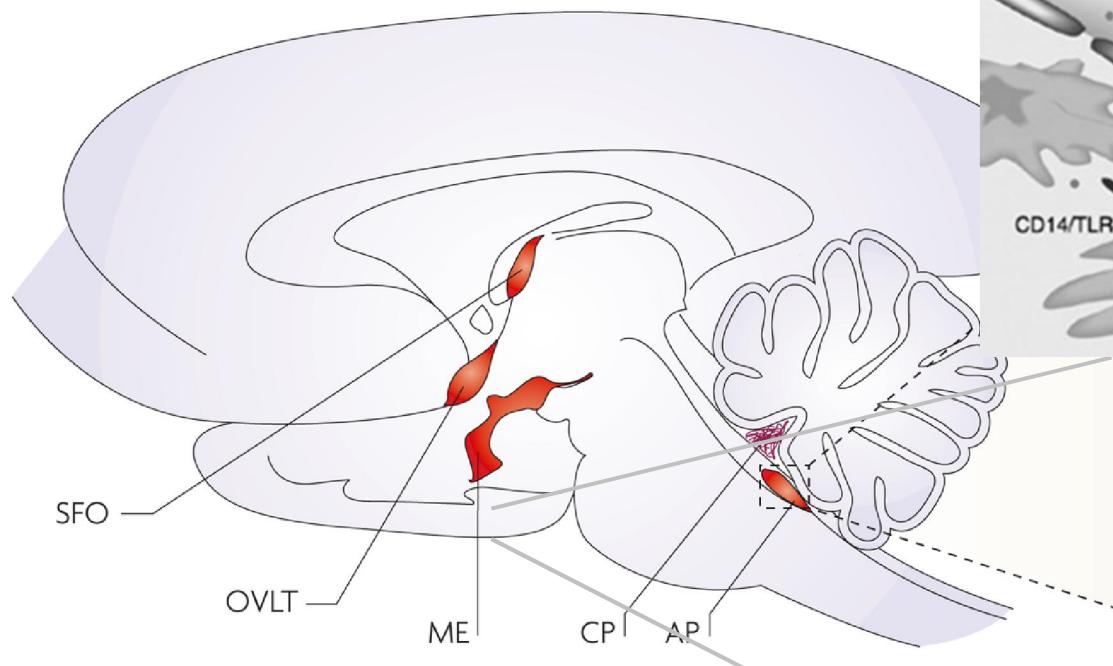
Brainstem glutamate receptor antagonism reduces ip LPS c-Fos in nucleus of the solitary tract



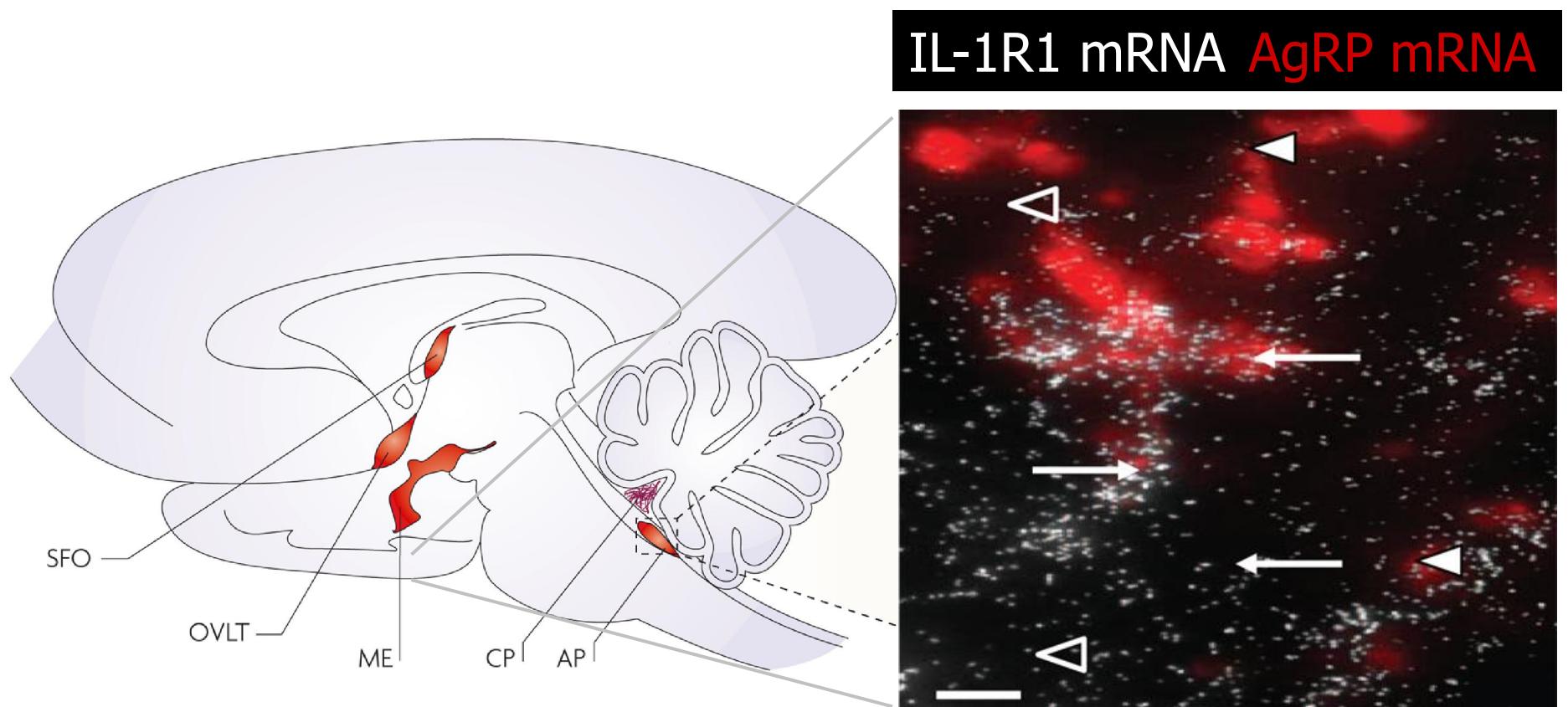
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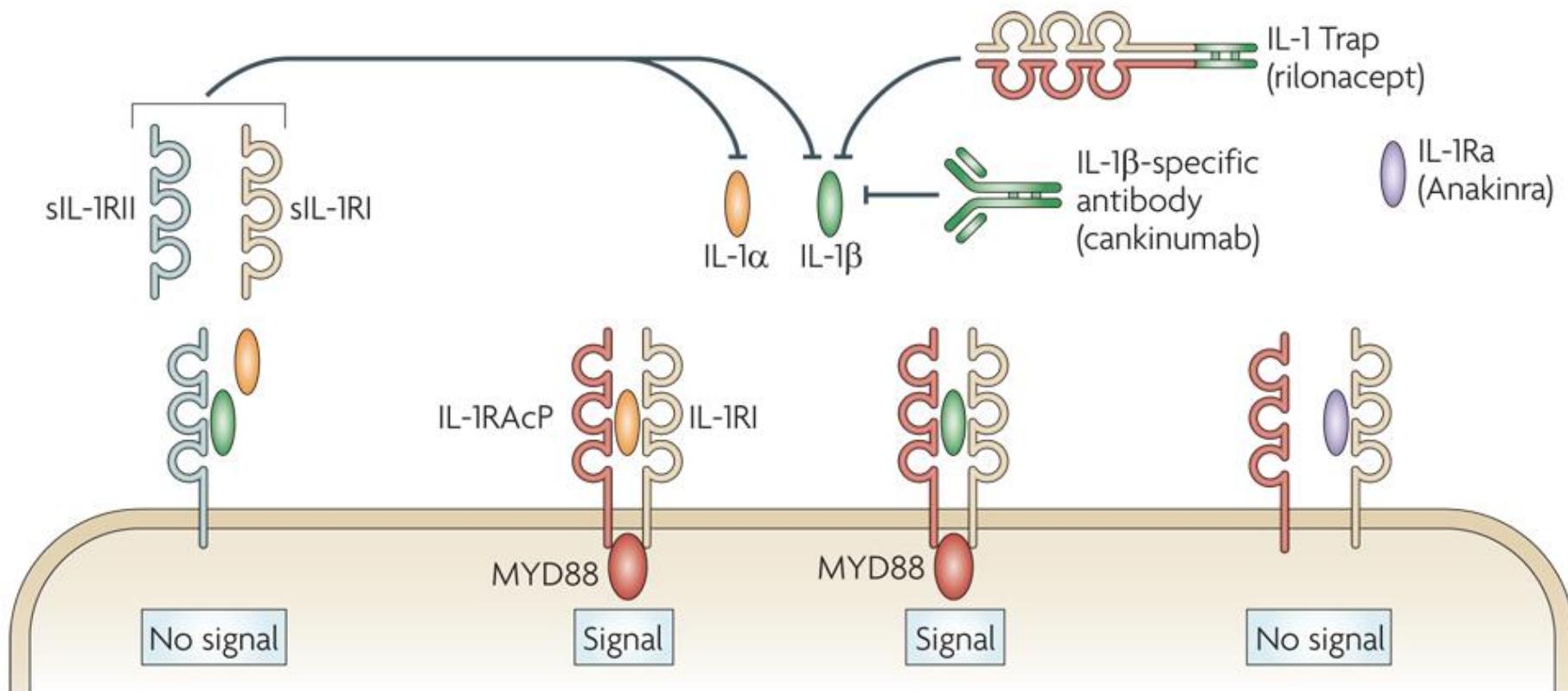
Interleukin-1 is produced in hypothalamus after ip LPS administration



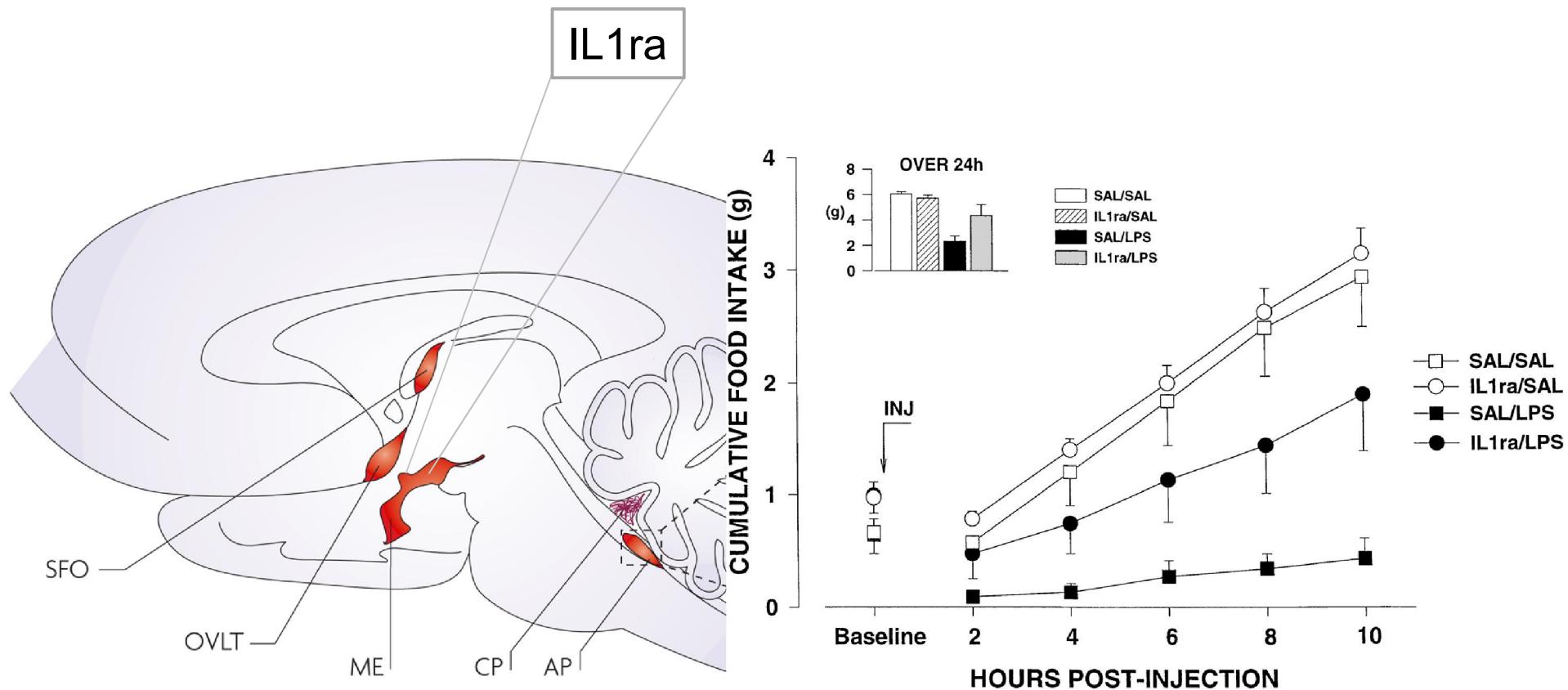
Interleukin-1 type 1 receptor mRNA in hypothalamic Agouti-Related Protein (AgRP)-expressing neurons



Does Interleukin-1 act in the forebrain to sustain ip LPS-induced sickness behavior?



Blocking Interleukin-1 receptors in forebrain attenuates ip LPS-induced hypophagia



Intermediate conclusion (4)

- Functionally redundant brainstem and hypothalamic pathways to bring about reduced food intake in response to detection of bacterial fragments by the host.

Overall conclusion

- Fever and reduced food intake are the consequence of temporary new 'homeostatic' set points during systemic inflammation and confer robustness to an animal host faced with bacterial infection.
- Functionally redundant immune-to-brain and nervous pathways bring about fever and reduced food intake in response to host detection of bacterial fragments.