Ageing Research Reviews 108 (2025) 102743

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Review article

# Interoception and aging

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ARTICLE INFO

*Keywords:*
Interoception
Homeostasis
NTS
Aging
Arachidonic acid
PGE2

ABSTRACT

Interoception refers to the body's perception and regulation of internal physiological states and involves complex neural mechanisms and sensory systems. The current definition of interoception falls short of capturing the breadth of related research; here, we propose an updated definition. Homeostasis, a foundational principle of integrated physiology, is the process by which organisms dynamically maintain optimal balance across all conditions through neural, endocrine, and behavioral functions. This review examines the role of interoception in body homeostasis. Aging is a complex process influenced by multiple factors and involving multiple levels, including physical, psychological, and cognitive. However, interoceptive and aging interoceptive interactions are lacking. A new perspective on interoception and aging holds significant implications for understanding how aging regulates interoception and how interoception affects the aging process. Finally, we summarize that arachidonic acid metabolites show promise as biomarkers of interoception-aging. The aim of this study is to comprehensively analyze interoceptive-aging interactions, understand the aging mechanism from a novel perspective, and provide a theoretical basis for exploring anti-aging strategies.

## 1. Introduction

Interoception emerges as a bidirectional interaction between the brain and body, allowing the nervous system to sense, interpret, integrate, and modulate internal bodily states (Berntson and Khalsa, 2021). Interoception involves complex sub-systems that perceive multisource signals. Its physiological roles depend on integrating physical patterns and spatial positioning (Zhao et al., 2022). Afferent neurons monitor the changes in the internal environment through the receptors and transmit the information to the central nervous system (CNS), which triggers adaptive responses. The endocrine system regulates the metabolism, body temperature, and other physiological functions through the secretion of hormones, while the immune system maintains the health of the body through inflammation and immune surveillance (Berntson and Khalsa, 2021; Craig, 2002; Quadt et al., 2018). The Visceral Nervous System controls visceral motor function, neuroendocrine regulation, pain perception, and survival behaviors (Benarroch, 1993). The role of interoception in brain-body interactions is central to somatic diseases, including chronic pain and comorbid conditions (Bonaz et al., 2021). As previous study believed that the appropriate stimuli for interoception were chemical in nature, chemical receptors are just one of many types of interoceptive sensory transducers. These include chemical receptors, neural receptors, glucose receptors, mechanoreceptors, and fluid receptors, as well as a range of other signaling transducers, such as free nerve endings that mediate visceral pain and temperature sensation (Berntson and Khalsa, 2021). Interoceptive impairments are increasingly recognized as an important component of neuropsychiatric disorders (Khalsa et al., 2018; Nord and Garfinkel, 2022; Tsakiris and Critchley, 2016). Dysfunctional interoception is part of the etiology of anxiety disorders (Paulus and Stein, 2010). Therefore, it is particularly important to better understand the definition of interoception and its loops in opening new horizons for disease research.

Aging is a complex biological process involving multiple physiological and psychological changes. Aging can significantly affect the function of the interoceptive system (Dobrushina et al., 2024). With age, the interoceptive changes may lead to changes in emotion and cognitive function (Brennan et al., 2023). There is a significant correlation between the degeneration of interoception and cognitive decline,

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https://doi.org/10.1016/j.arr.2025.102743
Received 4 December 2024; Received in revised form 4 March 2025; Accepted 3 April 2025
Available online 4 April 2025

especially in emotion regulation and cognitive processes (Longarzo et al., 2020). For instance, older adults may have a more muted physiological response to emotional stimuli compared to younger adults, which may be due to a weakened interoceptive function (Failla et al., 2020). Interoception provides a mapping of the body's internal landscape at both conscious and unconscious levels of processing (Khalsa et al., 2018). Among the conscious levels, the most studied are interoceptive sensibility (IS), accuracy (IACC), and awareness (IA). IS is defined as the self-perceived dispositional tendency to be internally self-focused and interoceptively cognizant, IACC as objective accuracy in detecting internal bodily sensations, and IA as metacognitive awareness of IACC (Garfinkel et al., 2015). Compared to the subjective experience of IS, the essence of IACC is objective ability. The effects of aging on the interoceptive system are not limited to changes in neural anatomy and physiology, but also involve alterations in IS and IACC (Ueno et al., 2020). Interoception manifests in both IACC and IS, and these traits exhibit individual differences (Murphy et al., 2019). IACC decreases with age and IS increases with age (Nusser et al., 2020). It is therefore of great significance to understand the interaction between interoception and aging.

## 2. The definition of interoception and its loops

### 2.1. The definition of interoception

The term "Interoception" was previously defined as the processing of visceral sensory input (Strigo and Craig, 2016), which refers to sensory input from internal receptors and distinguishes it from exteroception, or sensory input from receptors activated by external stimuli (Sherrington C, 1900). The interoceptive system not only regulates pure physiological processes, but also controls the information source of body state and function, thereby influencing so-called higher mental functions and behavior (Cameron, 2001). Currently, the interoception is more representative of the bidirectional communication between the visceral organs and the CNS, which is essential for maintaining body homeostasis, providing motivational drive, and regulating autonomic nervous system, cognitive and behavioral functions (Wang and Chang, 2024). For example, thermal sensation may serve as a model for skin-mediated interoception (Crucianelli and Ehrsson, 2023). One distinction between interoception and exteroception is whether the brain has inferenced the information, and external stimuli triggering sensation-control loops may be interoceptive, while exteroceptive stimuli trigger inference-control loops. Perceptual processes (inference) and controlling behavior involve the external state of the world, such as the physical properties of external objects (Toussaint et al., 2024). However, it is necessary to rule out the inference of perceptual processes on the position of the body in space and its temporal derivatives because this belongs to proprioception. In summary, although the concept of interoception is constantly changing, these concepts have not incorporated the important distinction of inferring the information. Here, interoception can be defined as the real-time sensory feedback perception caused by stimulation that is not inferred by the body organs to maintain whole-body homeostasis.

A major challenge in adaptive control of body homeostasis is that the brain cannot directly access the physiological and biochemical states of the body, but must infer them from sensory signals. This separation of the brain from the body's real state presents little difficulty for simple, reflex-like homeostatic control movements, but is a fundamental impediment to more complex allogeneic behaviors. Therefore, it is useful to distinguish between sensation (input from sensory channels) and perception (inferred hidden state that produces sensation) (Petzschner et al., 2017). This is precisely what we propose in this study, that the interoception is not an inferred sensation.

### 2.2. The composition and loop of interoception

The interoceptive system can usually be divided into four main parts: 1) Receptor and effector elements; 2) Afferent pathway; 3) Center of signal integration; 4) Efferent pathway (Fig. 1).

Receptor and effector elements

Receptor and effector elements including carotid body glomus cell (Iturriaga et al., 2021), pulmonary neuroendocrine cell (Lembrechts et al., 2012), enteroendocrine cell (Gribble and Reimann, 2019; Sahasrabudhe et al., 2024), immune cell (Klein Wolterink et al., 2022), and sensory neurons in the organ-intrinsic nervous system (Armour, 2008; Li et al., 2019; Spencer and Hu, 2020), skeletal interoceptive cell (Brazill et al., 2019; Lv et al., 2022), dorsal root ganglia (DRG) neurons (Nguyen et al., 2021), and fascia and mechanoreceptors (Astin et al., 2003).

Carotid Body Glomus Cell

The carotid body, located at the bifurcation of the common carotid artery, senses information from arterial blood and regulates cardiopulmonary function. It contains two cell types: multimodality chemoreceptor cells (type I globular cells) and supportive glial cells (type II globular cells) (Iturriaga et al., 2021). Carotid body globular cells synapse with sensory fibers and act as neurosecretory cells, producing a variety of neurotransmitters and neuromodulators such as adenosine triphosphate, adenosine, dopamine, acetylcholine, and nitric oxide. These cells are called PHOX2B+ and nodose-petrosal-jugular (NPJ) neurons (Zeng et al., 2018), PIEZO2 + nodose neurons (Min et al., 2019).

### 2.3. Pulmonary neuroendocrine cell

The main part of the myelinated vagal airway afferents selectively contacts pulmonary Neuroendocrine cells (Lembrechts et al., 2012), which is located near the bifurcation of the airways and serves as a multimodal intrapulmonary sensor for inspired O2 and CO2 levels, volatile odors, mechanical stimuli, and respiratory status, such as capsaicin-sensitive TRPV1 + unmyelinated C fibers (Mazzone and Undem, 2016), MrgprC 11 receptor (Han et al., 2018), Na(V)1.8 nodose neurons (Talbot et al., 2015), TRPV1 −/GABRA1 + neurons (Bin et al., 2023), and P2RY1 $^{+}$ neurons (Bin et al., 2023; Chang et al., 2015).

### 2.4. Enteroendocrine cell

The sensory cell of the gut epithelium (also known as the neuropod cell) is the enteroendocrine cell (Sahasrabudhe et al., 2024), which have neurotransmission functions, hormone release elicited following nutrient stimulation, and synapse with the vagus nerve to transmit signals to the brain. Some gut epithelial enterochromaffin cells also express mechanosensitive PIEZO2 channels to sense intraluminal forces (Alcaino et al., 2018), intrinsic primary afferent neuron (IPAN) (Spencer and Hu, 2020), nodose neurons (Wang and Chang, 2024), GPR65 $^{+}$ neurons (Williams et al., 2016), Tachykinin 1–positive nodose neurons (Ichiki et al., 2022), and DRG neurons (Brookes et al., 2013).

### 2.5. Immune cell

The interaction between the nervous system and the immune system is well-established, and this interaction occurs mostly at sites where neurons and immune cells coexist(Klein Wolterink et al., 2022). Organ-resident immune cells, such as mast cells, macrophages, and dendritic cells, detect the presence of pathogens through different families of pattern recognition receptors. These are membrane receptors that recognize molecules from microorganisms. For example, TLR4 recognizes lipopolysaccharide, tumor necrosis factor α, and various inflammatory mediators. These are rapidly released upon TLR4 activation after LPS exposure, such as Na(V)1.8 DRG neurons (Huang et al., 2021).

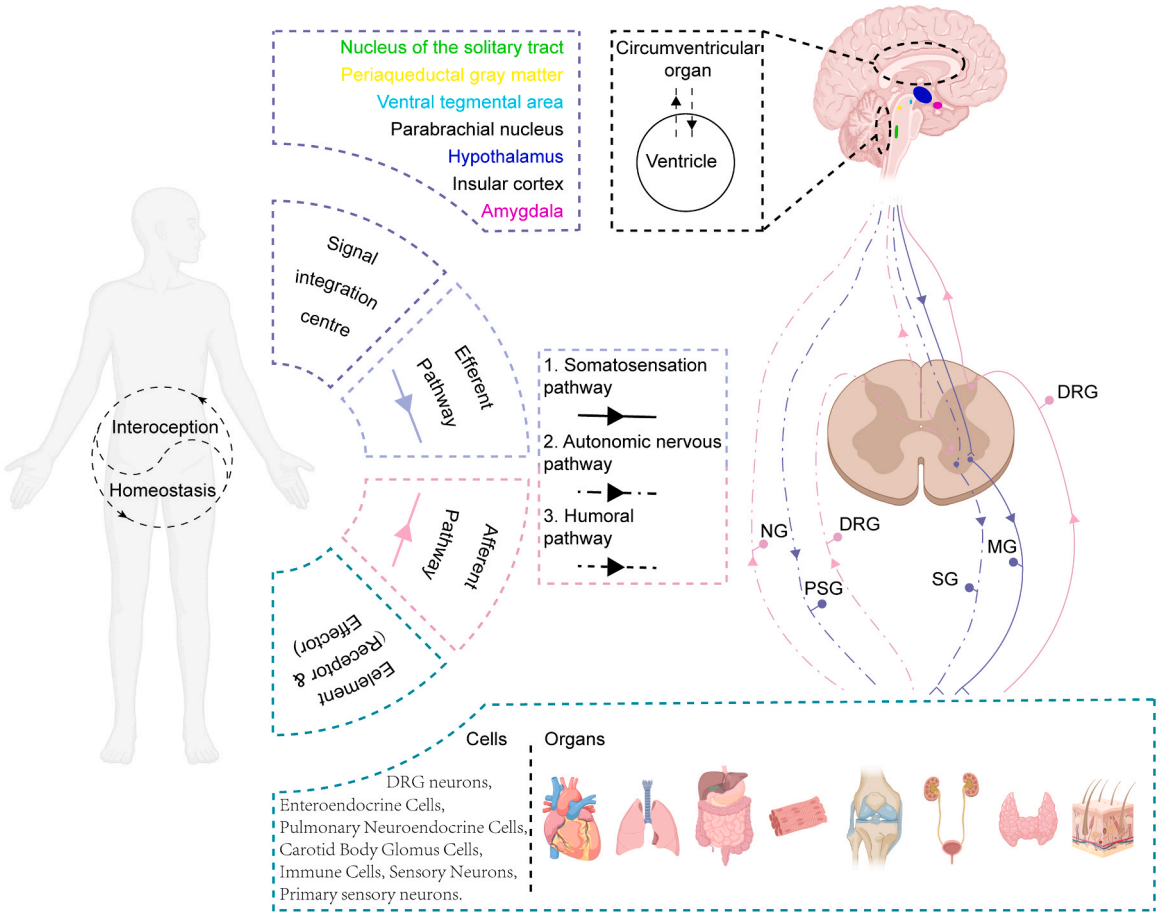


**Fig. 1.** The composition and loop of interoception.

### 2.6. DRG neurons

DRG neurons are present in multiple systems, such as the immune system contains Na(V)1.8 DRG neurons (Huang et al., 2021), expressing Calcitonin gene related peptide (CGRP), and substance P nerve fibers (Bellinger et al., 1992). Respiratory system contains PIEZO2$^{+}$ nodose neuron (Nonomura et al., 2017), TRPV1$^{+}$ neurons (Ruhl et al., 2020), Na (V)1.8 DRG nodose neurons (Talbot et al., 2015). Digestive system contains PIEZO2$^{+}$ enteroendocrine cells (Alcaino et al., 2018), the IPAN (Spencer and Hu, 2020), GPR65$^{+}$ neurons (Williams et al., 2016), Tachykinin 1–positive nodose neurons (Ichiki et al., 2022), sugar-specific nodose neurons (Li et al., 2022a). Cardiovascular system includes PIEZO2$^{+}$ nodose neurons (Min et al., 2019), PHOX2B$^{+}$ NPJ ganglion complex neurons (Zeng et al., 2018), circumventricular organ (CVO) sensory neurons, AGRP neurons (Xu et al., 2018), retrotrapezoid nucleus neurons (Mulkey et al., 2004), Pkd2l1$^{+}$ cerebrospinal fluid -contacting neurons (Huang et al., 2006). Somatosensory neurons with cell bodies in the DRG project to the skin, muscles, bones, and viscera to detect touch and temperature, as well as mediate proprioception and various types of interoception (Nguyen et al., 2021). In recent years, DRG neurons mediating skeletal interoception have received widespread attention. Bone metabolism is tightly regulated by the nervous system, and bone interoception regulates bone homeostasis (Lv et al., 2022). The cell bodies of bone-specific primary sensory neurons are in the DRG, along the spinal cord and cranial nerves. Their axons project to the target bone tissue (Brazill et al., 2019). Bone also acts as an endocrine organ and is used to regulate systemic metabolism (Lv et al., 2021). Somatosensory neuron (Brazill et al., 2019), L1 – L6 DRG send axons to bone (Tomlinson et al., 2016).

2) Afferent pathway

Previous studies have demonstrated that two major afferent pathways convey information and transmit it to the CNS (Ran et al., 2022). The first is the somatosensory nerve pathway, and the dorsal spinothalamic tract transmits temperature and pain sensations (Craig, 2002). It projects to the brain through the dorsal horn and mainly transmits signals related to temperature, pain, and tissue damage (Brazill et al., 2019), Normally, bone, skin (C-tactile afferents(Crucianelli and Ehrsson, 2023)) and muscle transmit interoceptive signals to the brain through this pathway (Ma, 2022). Signal transduction through the spinal cord is accomplished by the DRG afferent nerves, which innervate all organs as well as some spinal neurons in the enteric nervous system and projection neurons in the spinal dorsal horn. Most spinal afferent nerves (>95 %) innervate the skin and skeletal muscles, while only about 2 % innervate the viscera (visceral afferent neurons), such as the gastrointestinal tract, liver, and pancreas (Munzberg et al., 2023). Spinal neurons provide a direct internal sensory pathway to the thalamus and cerebral cortex, as well as a parallel pathway that conveys visceral and intracranial steady-state sensory activity and rises directly from the lower brainstem. The second is the autonomic pathway, which is dominated by parasympathetic afferent nerves, including the glossopharyngeal nerve and vagus nerve, and sympathetic afferent nerves that ascend through the dorsal column of the spinal cord (Chen et al., 2021b). For instance, the nodose ganglion or jugular ganglion, primarily sending axons to the brainstem to obtain visceral ascending signals (Holt et al., 2019), The ascending pathway of the vagus nerve mediates mechanical and chemical signals and is the primary ascending pathway for internal organs (Kupari et al., 2019). DRG neurons project to the spinal dorsal horn at corresponding levels through the vagus and glossopharyngeal nerves. Interoceptive signals are directly transmitted to the caudal brainstem, specifically the nucleus tractus solitarius (NTS), and bones, skin, and

muscles transmit interoceptive signals to the brain via somatosensory neurons of the DRG (Morrison and Scadden, 2014). It is generally believed that interoceptive signals within the physiological range are transmitted through the vagus nerve (Paciorek and Skora, 2020), Whereas signaling under more extreme pathological conditions is mediated by DRG (Wang and Chang, 2024). Sensory neurons innervating organs play an important role in providing spatial information for interoceptive signals. Neurons in the jugular ganglion, petrous ganglion, nodose ganglion, and dorsal root ganglion have spatially dedicated body goals in different spinal segments and transmit spatial information to the CNS (Livneh and Andermann, 2021; Ran et al., 2022). However, current studies have identified a third afferent pathway: the direct interaction pathway of body fluids. As CVOs lack an intact blood-brain barrier, they serve as a conduit for communication between the body's fluids and CVOs (Sisó et al., 2010), include the sub commissural organs, pituitary lobes, median eminence, pineal gland, end-organ vessels, subfornical organs, area postrema, and brain nuclei. The CVO is functionally divided into secretory and sensory types. Secretory types include the subcommissural apparatus, pituitary lobe, median eminence, and pineal gland, while sensory types comprise the endplate vascular apparatus, subfornical apparatus, and area postrema. These structures facilitate the sensing of circulating factors, which can detect hormones, cytokines, and pathogens, as well as changes in blood osmolality and sodium levels. Additionally, angiotensin is also sensed. The cerebrospinal fluid also contains molecules that mirror changes in the CNS internal environment (Rasmussen et al., 2022). TRPV1- and GABRA1 + neurons in the petrous region sense prostaglandin E2 (PGE2) released following influenza infection via the PGE2 receptor 3 and mediate systemic disease responses (Bin et al., 2023).

3) Center of signal integration

The processing of visceral signals is generally located in the central brain and is widely distributed in many brain regions, including the NTS (Abegg et al., 2017; Cutsforth-Gregory and Benarroch, 2017; Gamboa-Esteves et al., 2001; Neyens et al., 2020), hypothalamus (Critchley and Harrison, 2013; Xiao et al., 2023), ventral tegmental area (Goldstein, 2019), parabrachial nucleus (PBN), periaqueductal gray (PAG), amygdala, insular cortex (Azzalini et al., 2019; Dunn et al., 2010; Strigo and Craig, 2016), the rostral anterior cingulate cortex, orbitofrontal cortex, and medial prefrontal cortex (Fawley et al., 2021). The caudal NTS is one of the first brain centers to receive visceral information from the enteric nervous system, directly receiving both vagal and glossopharyngeal afferents (Cutsforth-Gregory and Benarroch, 2017) In addition to direct inputs from vagal sensory neurons, the NTS also receives spinal afferents conveying visceral information (Gamboa-Esteves et al., 2001), and humoral information from adjacent APs (Abegg et al., 2017), The NTS can also directly sense some circulating hormones, such as leptin. The NTS recruits the solitary nucleus to innervate the dorsal motor nucleus of the vagus and can directly activate the parasympathetic nervous system. In addition to direct autonomic outputs, the NTS also sends processed information to third-order brain areas including the paraventricular nucleus of the hypothalamus, PBN, central gray matter of the midbrain (Fawley et al., 2021), armoury nuclei, and midbrain PAG matter. These in turn connect to higher brain centers, including the amygdala, insular cortex, rostral and anteromedial cingulum, and medial orbitofrontal prefrontal region (Critchley and Harrison, 2013). The skeleton transmits to the NTS, and then interoceptive information is sent to the parabrachial nucleus, thalamus, hypothalamus, and hippocampus. Functional anatomical features of layer I neurons confirm that they are secondary steady-state sensory neurons, the hypothalamus is the main homeostatic integration region of the forebrain, and spinal cord (and trigeminal) layer I neurons provide direct interoceptive pathways to the thalamus and cortex (Craig, 2003; Ma, 2010). Interoceptive pathways also terminate in the cingulate motor cortex (Craig, 2004; Dum et al., 2009), and the insular cortex and cingulate cortex together constitute the homeostatic sensorimotor cortex (Craig, 2002; Heimer and Van Hoesen, 2006). Bilateral insular and cingulate cortex regions together act as homeostatic/emotional/limbic sensorimotor neocortex and provide adaptive (homeostatic) control of the body and brain (Strigo and Craig, 2016).

4) Efferent pathway

Although most current interoceptive research focuses on single organs, system-level interoception that spans organs would provide valuable information. Thyroid hormone and the neuropeptide Y neuron are co-expressed in the hypothalamus and are enhanced during PGE2-mediated skeletal interoception (Guo et al., 2023). The NTS directly conveys excitatory signals to the autonomic output centers to achieve fast reflexes. Organs located in the lower body such as the bladder, rectum, and reproductive organs are only innervated by spinal sensory neurons (Merrill et al., 2016). The spinal cord is responsible for relaying temperature and pain sensations to the thalamus via the spinothalamic tract, which is considered the pathway for interoceptive information (Craig, 2002). The fibers from the spinal cord project to various brainstem autonomic output nuclei (Craig, 2002). The PBN in the lateral hypothalamus receives both interoceptive and exteroceptive inputs from the spinal cord and NTS (Campos et al., 2018). The interoceptive information may be encoded by different sub-regions of the PBN (Pauli et al., 2022). The dorsal-ventral gradient of the PBN sends projections to various brain regions including the ventral tegmental area through the medial forebrain bundle, while the most lateral region of the PBN sends projections to the amygdala and insular cortex (Pauli et al., 2022). The insular cortex integrates both interoceptive and exteroceptive information, and the pattern of integration is dorsal to medial to ventral (Craig, 2009). The sympathetic and parasympathetic nervous systems innervate the skeleton (Hanoun et al., 2015), release neuropeptides from the synapses, and these neuropeptides diffuse to cells within the skeletal system to exert their effects.

Here, we need to focus on the NTS, a key structure in the interoceptive pathway, which has long been considered the anatomical basis for interoception (Craig, 2002). The NTS is involved in both somatic and autonomic interoceptive pathways and in integrating some of the signals. Mu-opioid receptor ligands can modulate many functions of vagal afferents innervating the NTS (Aicher et al., 2000).

Recent advances in interoceptive research increasingly recognize the importance of considering both afferent pathways and efferent pathways as functionally integrated loops (Berntson and Khalsa, 2021; Chen et al., 2021b). These loops mediate interactions between the brain and body (Petzschner et al., 2021, 2017). and provide a theoretical foundation for how interoception influences organ function and affects homeostasis (Berntson and Khalsa, 2021).

### 2.7. *Interoception and homeostasis*

Homeostasis is a fundamental principle of integrative physiology (Goldstein, 2019), and is a dynamic process that maintains an organism's optimal balance through neuroendocrine and behavioral functions under all conditions. Homeostatic control is a form of reactive, reflex-like control that is triggered by interoception and aims to maintain physiological variables within ranges compatible with life (Toussaint et al., 2024). The relationship between interoception and homeostasis is bidirectional. Interoception can affect the maintenance of homeostasis, and defects in interoception may be accompanied by disturbances in physiological homeostasis (Sedley et al., 2024). The interoceptive system plays a critical role in maintaining homeostasis by monitoring changes in the internal environment, such as temperature, nutrient levels, and oxygen concentration, and ensuring the normal functioning of physiological processes (Craig, 2002). Interoception provides real-time information on body homeostasis and may be involved in the regulation of homeostasis (Carvalho and Damasio, 2021). The brain senses the physiological and metabolic states of visceral organs, such as changes in blood pressure, gut motility, energy storage, and visceral pain, and integrates these states to maintain homeostasis throughout the body (Lv et al., 2022). Interoception is

essential for maintaining appropriate physiological states and coordinating metabolism by regulating eating behaviors, sugar balance, and lipid metabolism (Lv et al., 2022). It is not only critical for maintaining intrahost balance and homeostasis (acute changes that maintain intrahost balance) (Fotopoulou and Tsakiris, 2017), but also plays a pivotal role in a range of cognitive and affective processes (Barrett and Bliss-Moreau, 2009), including memory, decision-making, emotion processing, social interaction, and even consciousness, body ownership, and self-awareness (Paciorek and Skora, 2020). Mechanical signals are considered an important interoceptive signal for vascular tension and gut tension that helps maintain organ homeostasis (Bian et al., 2017). They perceive the bone PGE2 concentration's response to mechanical loading and regulate bone remodeling and structure, playing a critical role in processing interoceptive signals and regulating bone homeostasis (Gao et al., 2023). The maintenance of bone homeostasis depends on a dynamic, bidirectional dialogue between the brain, nervous system, and bone (Tozzi, 2015). In this process, the nervous system regulates bone remodeling by sensing mechanosensitive signals released from bone tissue, such as PGE2 (Gao et al., 2024), and integrating these peripheral signals through the hypothalamus. This mechanism is referred to as skeletal interoception (Xiao et al., 2023). Enhancing endogenous neuromodulatory repair signaling has been shown to promote functional bone regeneration (Sun et al., 2023). A low dose of celecoxib may aid in maintaining osteoceptive function, reducing the rate of vertebral endplate porosity and thereby decreasing sensory nerve innervation and spinal pain (Xue et al., 2021).

Homeostasis also impacts interoceptive function. An individual's interoceptive ability may decline with age, which is associated with a reduced capacity for homeostatic regulation, particularly manifested in degenerative diseases in the elderly (McDougall et al., 2014). Aging are often accompanied by impaired sensory nerve function and elevated PGE2 levels (Xiao et al., 2023). Aging can lead to homeostatic disorders, the ability to maintain homeostasis within the body declines with age (Bernard, 1974), and the body's ongoing attempts to achieve homeostasis may result in damage, which in turn accelerates the aging process (Moldakozhayev and Gladyshev, 2023). This seems to be a vicious cycle. To provide a new theoretical basis for resolve this cyclical impasse, we therefore focus subsequent discussions on elucidating the interconnections between interoception and aging.

### 2.8. Interoception and aging

Interoception is crucial for adaptability and emotion regulation and declines with age (Dobrushina et al., 2022; Khalsa et al., 2009; Mikkelsen et al., 2019). This makes it important to investigate Interoception and aging. Interoception can affect aging. Aging is known to be associated with declines in age-related sensory processing, including interoception (Weiner, 2015). Decreased Interoception and alexithymia in the elderly may share a common neural basis. Increasing age is associated with decreased activation during Interoception tasks, including the right operculum and supplementary motor area (SMA), and the effect of age is mediated by functional activation of the insular cortex and SMA as well as connectivity between these regions, and age also affects task-based functional connectivity, and the two major effects are decreased connectivity of the SMA insular network and increased connectivity of the prefrontal – lateral occipital network The effect of age is mediated by the decline of Interoception (Dobrushina et al., 2024). The content of CGRP, a neurotransmitter in sensory nerves, in aged animals shows a significant decreasing trend compared with young animals, which may also be one of the causes of senile osteoporosis (Zhang et al., 2016). Interoception decline and affective dysregulation may share a common neural basis, as aging is associated with reduced activation during interoceptive tasks, mediated by interoception decline (Dobrushina et al., 2024). A group of age-related diseases involves degeneration of noradrenergic neurons, and individuals with relatively effective central and autonomic noradrenergic systems may have survival advantage during reproductive years, as they can rapidly and massively increase delivery of catecholamines to receptors (Aston-Jones et al., 1991), participate in memory (Borodovitsyna et al., 2018), sense pain (Drummond et al., 2001), and obtain behaviors (Albares et al., 2015; Campese et al., 2017; Groessl et al., 2018; Mizunami et al., 2018). Recurrent stress may cause neurotoxicity through the release of catecholamines, with greater catecholamine release associated with greater self-toxicity and more prominent age-related catecholaminergic neurodegeneration (Goldstein, 2019).

Aging also impacts interoceptive. Accumulation of senescent cells, which secrete pro-inflammatory factors, disrupts homeostasis and immune system function with aging, leading to age-related diseases (Borghesan et al., 2020). The beneficial and harmful roles of cell aging and tissue repair are linked. Senescent cells promote tissue repair early on but cause chronic inflammation and age-related diseases when they accumulate and persist (Di Micco et al., 2021). Metabolic changes in senescent cells affect interoception and distort the brain's processing of hunger and satiety signals, disrupting homeostasis and whole-body energy balance (Ma et al., 2022). Aging-induced metabolic reprogramming impacts interoception by causing imbalances in the body's perception of energy demands, leading to stress responses and changes in energy balance (Gorgoulis et al., 2019). Metabolic changes in senescent cells affect interoception and distort the brain's processing of hunger and satiety signals, disrupting homeostasis and whole-body energy balance (Ma et al., 2022). Accumulation of senescent cells causes chronic inflammation associated with dysfunction of multiple interoceptive pathways (Ma et al., 2020a). The chronic inflammation from the senescence-associated secretory phenotype interferes with interoception (Watanabe et al., 2017), and disrupts feedback loops maintaining internal awareness and function (Birch and Gil, 2020), thereby accelerating systemic aging (Karpova et al., 2013; López-Otín et al., 2023). The destructive changes in autophagy in senescent cells alter interoception and disrupt the brain's perception of hunger and energy status (Kastenhuber and Lowe, 2017). The connection between cell aging and metabolism is through changes in hormone levels and nutritional sensing that affect interoceptive processes (Kumari and Jat, 2021).

This has been reported twelve hallmarks of aging (López-Otín et al., 2023), including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis. Here, we review the interactions between hallmarks biomarkers of aging and interoception (Fig. 2).

### 2.9. Genomic instability

Genomic instability refers to changes in the structure and number of cells in the genome, leading to mutations, chromosome abnormalities, and genome rearrangements. Microsatellite instability and chromosomal instability are major components of genome stability (Yang et al., 2019). Changes in interoception may affect an individual's response to bodily signals and could impact cell metabolism and growth, potentially contributing to genomic instability (Smith et al., 2020). Disruptions in interoception could affect cell stress responses and could lead to genomic instability. For instance, abnormal interoception has been linked to dysregulation of the cell cycle, which can result in DNA damage and failed repair mechanisms (Raina et al., 2021). Disrupted interoception may also contribute to abnormal DNA damage responses, increasing microsatellite instability (Requena and Garcia-Buitrago, 2020). Interoception is also closely tied to changes in the tumor microenvironment, where signals from the microenvironment can impact interoception and exacerbate chromosome instability (Livingston et al., 2023). Understanding the relationship between interoception and genomic instability holds promise for advancing both our understanding of disease mechanisms and the development of new therapeutic strategies.


**Fig. 2.** Interoception and aging.

### 2.10. Telomere attrition

Interoception may influence telomere length by impacting individual physiological states. Studies have suggested that interoception deficiency could result in dysregulation of physiological responses to stress, which may exacerbate oxidative stress and promote telomere shortening (MacCormack et al., 2024). Moreover, enhanced interoception may help individuals better regulate emotions and cope with stress, thereby slowing down the telomere shortening process (Ridout et al., 2019). People with lower interoceptive tend to exhibit greater psychological stress, which can negatively impact physical health and promote telomere shortening (Gillooly and Khazan, 2024). Furthermore, interoception is closely related to emotion regulation, and mood fluctuations may indirectly affect telomere length by influencing the endocrine system (such as cortisol levels). Research has found a significant association between long-term psychological stress and negative emotions with telomere shortening (Lemaître et al., 2021). suggesting a potential role of interoception in emotion management. For instance, individuals with stronger interoception can better identify and regulate their emotions, thus reducing stress levels and slowing down telomere shortening (Sudyka, 2019). Additionally, Additionally, enhanced interoception may indirectly protect telomeres by promoting healthy behaviors such as exercise and balanced diets, providing a new perspective on the relationship between interoception and telomere shortening (Rai et al., 2022). Telomere shortening is associated with interoceptive dysfunction in various physiological and pathological states, especially aging-related diseases (Schroder et al., 2022; Yang et al., 2024). Therefore, understanding the impact of telomeric degradation on interoceptive function may offer new intervention strategies to improve health outcomes in aging and disease.

### 2.11. Epigenetic alterations

Epigenetic changes are critical for numerous bodily functions, and epigenetic alterations may further disrupt neural function by impacting neurotransmitter synthesis and metabolism (Wani and Shadab, 2019). Enhanced interoception has been proposed to improve cardiovascular health, a process that may involve epigenetic regulation of genes associated with cardiovascular function (Bijsterbosch et al., 2023; Leganes-Fonteneau et al., 2021). In children and adolescents, interoceptive development is also closely linked to epigenetic changes (Finnerup et al., 2021). Stimulation-induced ectopic activity in the DRG and the thalamus is involved in the regulation of epigenetics (Finnerup et al., 2021). Studies have demonstrated a significant association between teenagers' body image and interoceptive ability, which may be influenced by epigenetic factors (Locatelli et al., 2023; Todd et al., 2019). In the context of interoception, understanding the interaction with epigenetics is crucial for investigating childhood trauma (Cross et al., 2017). By exploring the interaction between interoception and epigenetics, researchers can better understand individual differences in physical and mental health and how these differences can be improved through intervention measures.

### 2.12. Loss of proteostasis

The relationship between interoception and protein homeostasis has

not been well explored, but it can be speculated that they may influence each other through shared physiological mechanisms. For example, changes in interoception may alter an individual's stress response, which in turn can affect protein synthesis and degradation processes in cells. Studies have found that interoception training can improve an individual's decision-making ability and reduce anxiety levels, possibly by enhancing their ability to perceive their physiological state (Sugawara et al., 2020). Interoceptive changes may also be associated with disruptions in protein homeostasis, providing a new perspective on the mechanisms of both mental and physical diseases (Aman et al., 2022). For instance, a reduced sensitivity to interoception may lead to misunderstandings of the body's state, thereby affecting an individual's response to health signals and exacerbating disruptions in protein homeostasis (Pereira et al., 2024). Meanwhile, the maintenance of protein homeostasis may also support the normal functions of interoception, suggesting that exploring their interactions provides a new perspective on understanding psychological and physiological well-being.

### 2.13. Disabled macroautophagy

The relationship between interoception and macroautophagy is an emerging research area. Current studies suggest that changes in interoceptive ability may affect the activity of macroautophagy. For instance, interoceptive defects may result in weakened cellular responses to endogenous stress, thereby impacting the initiation and regulation of macroautophagy (Chamoun-Emanuelli et al., 2019). Moreover, the interaction between interoception and emotional states may further impact health states by affecting the function of macroautophagy. Research shows that the activity of macroautophagy may be inhibited in patients with emotional disorders, which is associated with decreased interoceptive ability (Lyvers and Thorberg, 2023). Therefore, future research can focus on elucidating the specific mechanisms underlying the relationship between interoception and macroautophagy, which may provide new targets and strategies for the treatment of related diseases.

### 2.14. Deregulated nutrient-sensing

Multidimensional assessment of interoception is gradually emerging to help understand its role in disordered eating. For instance, classification of individual interoceptive abilities can reveal differences in perception of physiological status among individuals, which may impact their food choices and metabolic responses (Suksasilp and Garfinkel, 2022). Moreover, interoceptive training is thought to improve decision-making, anxiety levels, and somatic symptoms (Sugawara et al., 2020), suggesting that enhancing interoception may benefit individuals with disordered eating. Mechanisms underlying disordered eating are closely related to multiple physiological signaling pathways. Studies show that nutrient intake can modulate metabolic states and energy balance through activation of the mTORC1 signaling pathway, among others(Fernandes and Demetriades, 2021). Furthermore, dietary components (such as high-fat diets and non-caloric sweeteners) can regulate taste receptors, potentially leading to metabolic imbalances and further complicated the relationship between interoception and nutrition(Zhang et al., 2023b). Delving into the interaction between interoception and disordered eating has the potential to offer new insights and treatment approaches for these disorders.

### 2.15. Mitochondrial dysfunction

Mitochondria are the energy factories of cells, and their dysfunction not only affects cellular energy metabolism but has also been implicated as a key mechanism underlying neuronal damage (Rahman et al., 2020). Mitochondrial dysfunction may lead to declines in interoception, and is closely associated with neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease, which are often accompanied by deficits in interoception (Mani et al., 2021; Rahman et al., 2020). Mitochondrial dysfunction may impact interoception through multiple mechanisms. First, mitochondria serve as the center for energy metabolism in cells, and energy deficiency may impair the function of brain regions critical for interoception, such as the prefrontal cortex and insula (Hubens et al., 2022; Putilina, 2022). Second, mitochondrial dysfunction can trigger oxidative stress and neuroinflammation, both of which have been implicated in changes to interoception (Jubaidi et al., 2020; Zhang et al., 2024). For instance, oxidative stress can damage neurons and impair their ability to process interoceptive signals. Moreover, research has suggested that interoceptive deficits may be closely related to individual psychological well-being. Many studies have demonstrated a significant association between decreased interoception and anxiety, depression, and other emotional disorders (Loureiro et al., 2024; MacCormack et al., 2024). Therefore, understanding how mitochondrial dysfunction affects interoception is crucial for developing new therapeutic strategies. For instance, certain plant compounds have been proposed to improve mitochondrial function and may potentially help restore interoception, improving mental health outcomes (Jubaidi et al., 2020; Qi et al., 2022). Individuals with lower interoception may exhibit heightened physiological responses to stress, which may exacerbate the oxidative stress state of the mitochondria and further impair their function (Burrows et al., 2022). Interoception has also been implicated in neurobiological mechanisms, involving the modulation of various neurotransmitters and neural pathways (Park et al., 2022). Depression is often associated with reduced interoception, which may be linked to mitochondrial dysfunction. Furthermore, interoceptive deficits may impair self-regulation, leading individuals to adopt inappropriate coping strategies when facing physical or psychological stress, which may further aggravate mitochondrial damage (Mani et al., 2021). Restoring interoception could thus represent a potential intervention to improve mitochondrial function. Mindfulness interventions, for example, have been shown to effectively enhance interoception and positively impact mental health (Molteni et al., 2024). These interventions may indirectly improve mitochondrial function by reducing stress levels and improving emotional states (Lovelock et al., 2021), For instance, mindfulness training can help individuals become more aware of their internal physiological states, enabling better emotion regulation and reduced oxidative stress responses in the mitochondria.

### 2.16. Cellular senescence

The role of cellular senescence in multiple diseases also suggests a potential link with interoception (Anaraki et al., 2024; Wan et al., 2023). Accumulated cellular senescence can impair an organism's interoceptive ability, leading to metabolic disorders and functional decline (Dolati et al., 2021). The molecular changes associated with cellular senescence may affect the neurobiology of interoception, resulting in emotional and behavioral alterations (Princilly et al., 2023). Interoceptive training has been shown to improve decision-making, reduce anxiety, and alleviate somatic symptoms, suggesting that interoceptive enhancement may help mitigate the psychological and physiological issues related to cellular senescence (Sugawara et al., 2020). IACC is closely related to emotional states and decision-making abilities, which in turn may influence the cellular senescence process (Suksasilp and Garfinkel, 2022). In cellular senescence research, it is found that cellular senescence is closely related to the occurrence of multiple diseases, especially in the aging process, and the interoceptive ability of cells may be affected, thereby affecting the physiological functions of cells (Anaraki et al., 2024; Princilly et al., 2023). People with poorer interoception are more anxious and emotionally unstable when facing physiological stress, which may accelerate the aging process of cells (MacCormack et al., 2024). Interoceptive training is considered to improve an individual's decision-making ability and emotion regulation, which may counteract the impact of cellular senescence through the regulation of physiological states (Sugawara et al., 2020). The enhancement of interoception may

have a positive role in delaying cellular senescence. Recent studies show that interoceptive training can improve decision-making, reduce anxiety, and improve somatic symptoms, which may be related to a better understanding of physiological states(Sugawara et al., 2020).

### 2.17. Stem cell exhaustion

Interoceptive deficits may affect an individual's feedback on bodily states, thereby influencing the function and self-renewal capacity of stem cells. Research has shown that subjective difficulties in interoceptive processing in individuals with autism are associated with accuracy in heart rate perception, which may suggest that interoceptive deficits could lead to decreased stem cell function (Itoi et al., 2024). In stem cell research, stem cell exhaustion is an important biological phenomenon, typically characterized by declined proliferation and self-renewal capacities. Multiple studies have shown that stem cell exhaustion is closely associated with its microenvironment, metabolic status, and intracellular signaling pathways. Interoception may regulate these signaling pathways to influence stem cell function. Interoception may regulate the state of stem cells through metabolic pathways (Ando et al., 2023). Moreover, training in interoception has been found to improve decision-making ability, anxiety levels, and somatic symptoms (Sugawara et al., 2020), which may provide new insights into intervention strategies for stem cell exhaustion. The mechanism of stem cell exhaustion is complex and involves multiple biological processes, including cell competition and regulation of gene expression. Recent research has shown that the absence of Hes1 leads to exhaustion of hematopoietic stem cells, suggesting that interoception may be related to the determination of stem cell fate (Ma et al., 2020b). In addition, when stem cells respond to changes in the microenvironment, their interoceptive ability may affect their survival and proliferation. For example, stem cells in the tumor microenvironment may exhibit exhaustion characteristics due to deficient interoception, providing a new perspective on tumor biology (Li et al., 2024). As research progresses, the multi-dimensional evaluation framework of interoception will provide us with a more comprehensive perspective to help us understand the complex mechanisms of stem cell exhaustion (Suksasilp and Garfinkel, 2022).

### 2.18. Altered intercellular communication

Cellular communication plays a critical role in maintaining physiological homeostasis and regulating the internal environment of an organism. Through single-cell transcriptomics, scientists can uncover changes in cell-to-cell signaling under different conditions and how these changes affect intracellular signaling responses. Alterations in intercellular signaling pathways may be closely associated with the occurrence and development of various diseases, including cardiovascular and neurological disorders (Hao et al., 2021). Studies have shown that cell interactions not only affect the development and function of neurons, but may also impact individual emotions and behaviors. For instance, research has found that cellular communication is significantly altered in patients with autism, which might be a major factor contributing to their decreased interoceptive abilities (Astorkia et al., 2022). Moreover, changes in cellular communication can, in turn, affect the neural mechanisms underlying interoception by influencing the plasticity of neurons (Engelen et al., 2023). The physiological basis of interoception is also linked to changes in cellular communication. For example, cardiac interoception, which regulates the function of cardiac muscle cells, influences an individual's emotional state and interoceptive ability. Studies have shown that cardiac cellular communication is crucial for coping with physiological stress and maintaining cardiovascular health (Segers et al., 2019). Therefore, understanding the mechanisms of cellular communication holds promise not only for revealing the biology of interoception but also for developing new therapeutic strategies to improve the various psychological and physiological issues arising from interoceptive disorders.

### 2.19. Chronic inflammation

Interoceptive deficits may lead to inaccurate interpretation of internal body states, exacerbating symptoms of chronic inflammation (Haruki and Ogawa, 2024). Chronic inflammation is associated with a range of diseases, including autoimmune and cancer, which share the common feature of prolonged immune activation and tissue injury (Rogovskii, 2024). In this context, interoceptive deficits may increase patients' sensitivity to pain and discomfort, thereby affecting their quality of life. For instance, chronic inflammation patients often exhibit higher emotional distress and poorer interoception while assessing pain (Seifert and Baerwald, 2021). This phenomenon not only impacts physical health, but can also result in mental health problems such as anxiety and depression (Smith et al., 2022). Notably, enhancing interoception may improve mood and cognitive functions in chronic inflammation patients. Some studies apply high-frequency transcranial direct current stimulation to effectively improve individuals' interoception and bodily awareness (Schultze et al., 2024), suggesting a potential novel intervention for chronic inflammation and related diseases, highlighting the potential value of interoception in disease management.

### 2.20. Dysbiosis

The gut microbiota is established early in development, and early exposure to stress and adversity can promote interoceptive dysfunction (Elwyn et al., 2023). Disruption of the microbiota not only impacts the host's physiology but can also affect interoception through multiple mechanisms (Kang et al., 2024). Variations in interoception have been implicated in the pathogenesis of multiple psychiatric disorders, such as autism, anxiety, and schizophrenia (Itoi et al., 2024; Torregrossa et al., 2022). The composition and function of the gut microbiota have been implicated in the pathogenesis of these diseases, and dysbiosis of the gut microbiota may impact interoception and thereby influence an individual's emotions and behaviors. The gut microbiota plays a critical role in maintaining host health, especially through the regulation of immune responses and metabolic processes. Dysbiosis of the microbiota may result in increased inflammation, which can in turn affect the function of the CNS and interfere with interoception. For instance, studies have found significant associations between gut dysbiosis and the development of depression and anxiety, which may be due to the microbiota's impact on neurotransmitter synthesis and metabolism via the gut-brain axis (Gabriele et al., 2022; Luo et al., 2023). Furthermore, interoceptive dysfunction may lead to misinterpretation of physiological signals and exacerbation of psychological symptoms, forming a vicious cycle (Loureiro et al., 2024; MacCormack et al., 2024). Clinically, assessment and training targeting interoception may offer a new therapeutic approach for improving emotional and behavioral problems arising from gut microbiome dysbiosis. By enhancing individuals' awareness of interoception, it may help improve their understanding of physiological states and promote healthy behaviors, which can in turn improve gut microbiome composition and function (Poerio et al., 2024; Sugawara et al., 2020). With further investigations into the relationship between interoception and gut microbiome dysbiosis, more effective interventions can be developed to improve both mental and physical health in the future.

Here, we propose two concepts: Interoceptive aging and interoception of aging (Supplemental table 1). Interoceptive aging refers to cellular/tissue aging resulting from interoceptive dysregulation. Conversely, Interoception of aging refers to interoceptive dysregulation resulting from aged cells/tissues (Fig. 3). Based on the current evidence, there is an indirect causal relationship between interoception and aging, indicating that the two are interactive. Regarding the direct causal relationship between interoception and aging, we propose the following

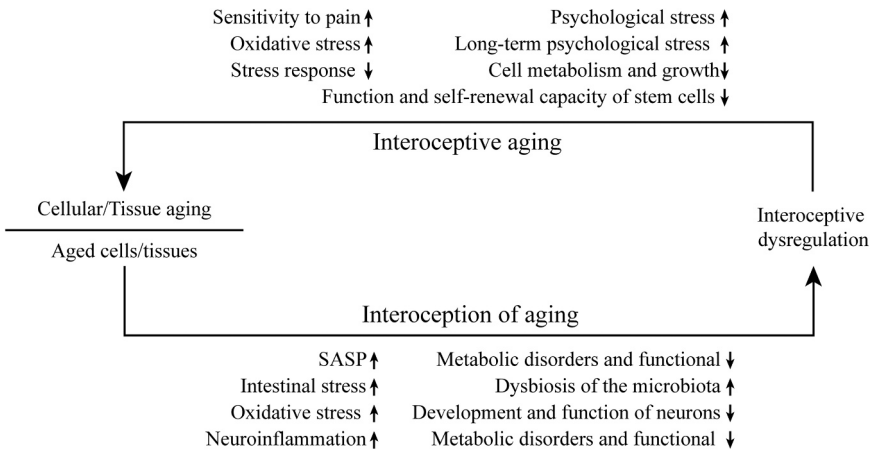


**Fig. 3.** The description of interoceptive aging and interoception of aging.

research ideas: 1. Validate using Mendelian randomization analysis to select genetic instrumental variables related to aging (such as PGE2); 2. Verify the spatiotemporal regulation of key targets in the interoception and aging pathway through transgenic mouse models; 3. Test the effects of Senolytic drugs (Dasatinib + Quercetin) on improving heart rate variability in elderly subjects.

### 2.21. *The potential markers of Interoception-aging*

Arachidonic acid (AA), an omega-6 polyunsaturated fatty acid, is essential for maintaining cellular homeostasis (Bernard, 1974). AA is primarily obtained exogenously (Li et al., 2022b; Zhang et al., 2021) and endogenously synthesized (Conway et al., 2020). Studies have found that AA metabolism is significantly enhanced in aging individuals (Luo et al., 2020), and inhibition of AA synthesis can reduce the progression of age-related diseases (Xiao et al., 2024). AA may influence aging through shortened telomeres (Freitas-Simoes et al., 2019), induced cellular senescence (Naru et al., 2008), and production of reactive oxygen species (Pompeia et al., 2002). AA is a general marker of fibroblast aging (Lorenzini et al., 2001). Low levels of AA in the DRG, spinal cord, thalamus, and cortex of aged mice exacerbate neuropathic pain after nerve injury (Bishay et al., 2013). AA metabolism occurs via cyclooxygenase (COX) pathway, mainly producing prostaglandins (PGs) and thromboxanes (TXs) through COX-1 and COX-2 enzymes. Among these, PGE2 is a major product of this pathway, promoting inflammation and pain perception (Li et al., 2021). The lipoxygenase (LOX) pathway converts AA into leukotrienes (LTs) and lipoxins (LXs) through 5-LOX, 12-LOX, and 15-LOX enzymes (Tallima, 2021). The cytochrome P450

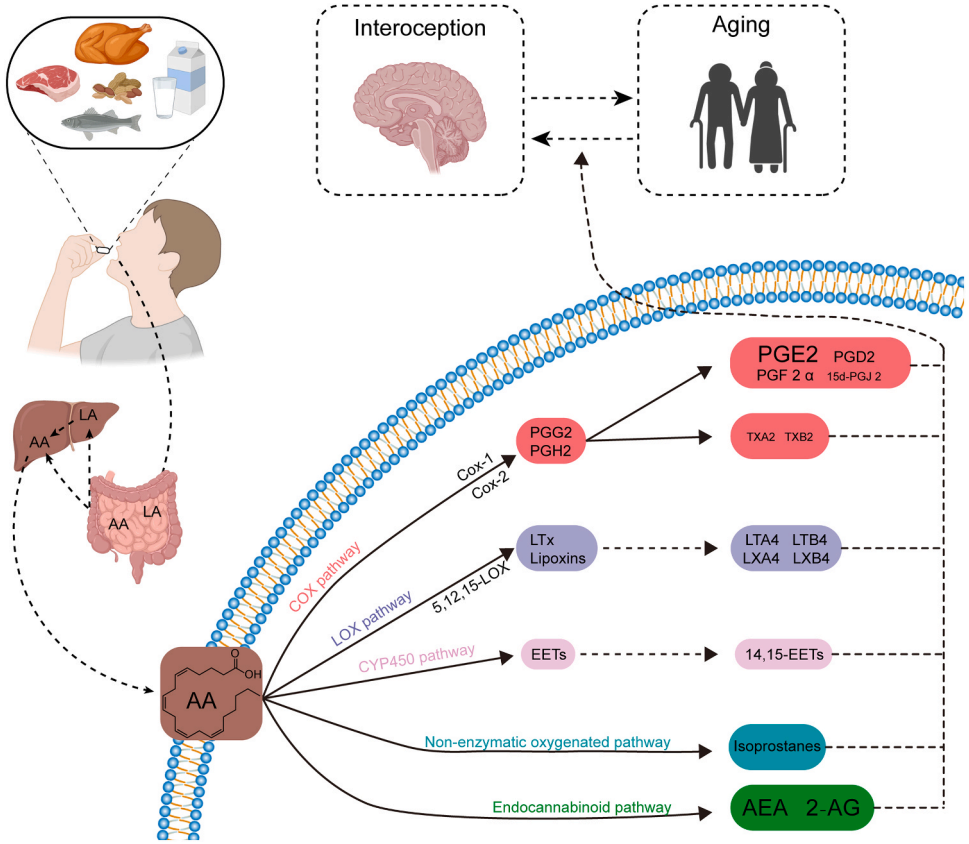


**Fig. 4.** The potential biomarkers of Interoception-aging.

(CYP450) pathway generates epoxyeicosatrienoic acids (EETs) via P450 enzymes(Wang et al., 2024). Non-enzymatic oxidation produces isoprostanes (Collodel et al., 2022). The endocannabinoid pathway (Rahaman and Ganguly, 2021) comprises key signaling molecules such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG) (Paradisi et al., 2006) (Fig. 4).

PG are lipid compounds involved in inflammatory signaling and regulating neuronal communication (Bourgognon et al., 2018). Four specific prostaglandins-PGD2, PGE2, PGF2α, and 15d-PGJ2 are considered "progerogenic" because they are elevated in aging cells (Wiley et al., 2021). These cells produce PGE2, which is a marker of tissue aging (Palla et al., 2021), and it drives brain aging through PGE2–EP2 signaling (Minhas et al., 2021). PGE2, as the most studied PG, has been implicated in multiple interoceptive circuits, including sodium homeostasis (Zhang et al., 2023c), bone loss, and fat metabolism (Guo et al., 2023), pain (Gao et al., 2024; Xue et al., 2021), and chronic inflammation (Oriolo et al., 2019). Elevated PGD2 levels may increase symptoms associated with the vagus nerve (Maher et al., 2015). PGD2 promotes sympathetic transmission in the tissue through both presynaptic and postsynaptic actions, whereas PGF2α appears to act primarily postsynaptic (Bedwani and Hill, 1980). Unfortunately, there are currently no studies investigating the relationship between 15d-PGJ2 and the interoceptive system.

LTs are elevated in both aging and AD and are associated with cognitive impairment (Adams et al., 2023; Mrowetz et al., 2023). BLT 1 (LT receptor) is expressed on astrocytes in the NTS, and increasing the concentration of LTs in the NTS significantly increases blood pressure in rats, indicating that LTs may be involved in regulating the interoceptive system (Waki et al., 2013). LX content is significantly lower in aged mice than in young mice (Al Saedi et al., 2022). LXA4 administration inhibits renal inflammation and tubular epithelial cell senescence (Chen et al., 2021a). Vagus nerve transection reduces LX and delays chronic inflammation resolution (Serhan et al., 2019). LXA4 reduces vagally mediated airway smooth muscle contraction and inhibits acetylcholine release (Tamaoki et al., 1995).

AD is characterized by impaired performance and impaired consciousness on interoceptive tasks (Santamaría-García et al., 2024). 14, 15-EET crosses the blood-brain barrier and prevents brain amyloid-β deposition and prevents AD development (Wu et al., 2023). 14, 15-EET content is significantly decreased in aging cells (Zhang et al., 2023a).

Oxidative stress can inhibit β-adrenergic responses and/or regulate sympathetic nervous system activity (Bell et al., 2003). Emotional and mental health decline with increasing oxidative stress markers (Savage et al., 2022). Isoprostanes have become reliable biomarkers of oxidative stress within the body (Savage et al., 2022). They are also used as markers of muscle aging (Vinel et al., 2018). Free F2-isoprostanes plasma concentrations significantly increase in aged rats compared to young rats (Roberts and Reckelhoff, 2001). Both F2-isoprostanes and 8-iso-prostaglandin F2α rise markedly in AD, serving as potential biological markers (Trares et al., 2022).

The endocannabinoid system modulates interoception in the gut. During exercise, it increases dopamine levels in the ventral striatum during exercise, thereby driving hedonic, rewarding, anxiolytic, and analgesic effects (Dohnalová et al., 2022). Circulating endocannabinoids (eCBs) and their receptors in the nucleus accumbens show robust functional correlations and represent potential targets in anorexia nervosa (AN) (Miranda-Olivos et al., 2023). eCB signaling, as a molecular marker of aging (Paradisi et al., 2006), is significantly reduced in the hippocampus of aged mice. Cannabinoid receptor deficiency leads to cognitive decline and age-related histopathological changes in the brain (Nidadavolu et al., 2022). AEA and 2-AG are the only known neurotransmitters that function as retrograde synaptic messengers with neuroprotective properties (Paradisi et al., 2006). With age, AEA levels decrease significantly in the caudate putamen and medial prefrontal cortex along with the cingulate cortex. 2-AG shows a significant decrease in the hippocampus and caudate putamen (Nidadavolu et al., 2022). AEA and 2-AG participate in bone signaling, maintaining bone homeostasis (Bab et al., 2009).

Based on the above research findings, we propose that metabolites of AA could serve as the potential biomarkers for investigating the relationship between interoception and aging (Table 2). A limitation of this theoretical proposal is that the use of AA metabolites as biomarkers is based on previous research summaries rather than laboratory results. We hope that more researchers will join efforts to validate these proposed potential biomarkers to uncover the interaction mechanisms underlying interoception-aging.

## 3. Conclusions and future perspectives

In addition to presenting the latest concept of interoception, this study explores the role of interoception in homeostasis and its interaction with aging. It further reviews potential of AA metabolites as the biomarkers of interoception-aging. Based on the findings of this study, future research should focus on the following directions:

Transdisciplinary integration: combining neuroscience, molecular biology, and psychology to explore the relationship between interoception and aging from an integrative perspective, especially through multidimensional means (such as multimodal neural imaging and multi-omics research) to reveal the mutual interaction between interoception and the aging.

Multimodal detection and drug development: Multimodal biomarker analysis may reveal interoceptive modulation strategies for aging delay. Concurrently, drug development targeting validated biomarkers could advance precision medicine.

Preventive health management: Integrating interoceptive assessments into health monitoring systems enables early intervention against age-related functional decline, thereby enhancing seniors' quality of life.

Future research on interoception-aging interactions will not only unravel their biological mechanisms but also offer novel strategies to delay aging and promote healthy longevity.

**Table 1**
Different definitions of interoception, as initially proposed by (Khalsa and Lapidus, 2016) and further refined in the present manuscript.

| Reference | Definition |
|---|---|
| Sherrington (1906) | The sensory nerve receptors that react to stimuli originating within the body |
| Vaitl (1996) | A general concept, which includes two different forms of perception: proprioception and visceroception |
| Cameron (2001) | The afferent information that arises from anywhere and everywhere within the body – the skin and all that is underneath the skin, e.g., labyrinthine and proprioceptive functions – not just the visceral organs |
| Cameron (2002) | Perception of the functions and physiological activities of the interior of the body |
| Craig (2002) | The sense of the physiological condition of the entire body, not just the viscera |
| Khalsa (2009) | The perception of internal body states |
| Couto (2013) | A core aspect of motivational regulation of behavior and cognition |
| Critchley (2013) | The brain receives and responds to continuous dynamic feedback of afferent visceral signals |
| Paulus (2013) | A process that involves the integration of internal bodily information into the central nervous system. |
| Barrett (2015) | The perception and integration of autonomic, hormonal, visceral and immunological homeostatic signals |
| Khalsa and Lapidus (2016) | The process of how the brain senses and integrates signals originating from inside the body |
| Quadt et al. (2018) | A type of perception of the internal state of the body that is distinct from exteroceptive senses and proprioception. |
| Lv et al. (2022) | An organism's ability to sense its internal state to maintain homeostasis |
| Suksasilp and Garfinkel (2022) | The sensing, interpretation and integration of signals originating from within the body across both conscious and unconscious levels of processing |

**Table 2**
The potential biomarkers of interoception-aging.

| Range | Biomerkers | Interoceptive dysregulation | Aged cells/ tissues | Strength of recommendation |
|---|---|---|---|---|
| Ia | PGE2 | Positive | Positive | A |
| Ib | AEA | Negative | Negative | |
| | 2-AG | Negative | Negative | |
| II | PGD2 | Positive | Positive | B |
| | PGF2α | Positive | Positive | |
| | LTA4 | Positive | Positive | |
| | LTB4 | Positive | Positive | |
| | LXA4 | Negative | Negative | |
| | LXB4 | Negative | Negative | |
| | 14, 15-EET | Negative | Negative | |
| | Isoprostanes | Positive | Positive | |
| III | 15d-PGJ2 | Positive | - | C |

## Abbreviation

CNS, Central Nervous System; DRG, Dorsal Root Ganglia; CVO, circumventricular organ; CGRP, Calcitonin gene related peptide; NPJ, nodose-petrosal-jugular; NTS, nucleus tractus solitaries; PGE2, prostaglandin E2; AD, Alzheimer's disease; AA, Arachidonic acid; COX, cyclooxygenase; LOX, lipoxygenase; TX, thromboxane; PG, prostaglandin; LT, leukotriene; CYP, cytochrome; EETs, epoxyeicosatrienoic acids; LX, lipoxin; eCB, Circulating endocannabinoid; AEA, anandamide; 2-AG, 2-arachidonoylglycerol

## Funding

This study was supported by the Scientific Research And Innovation Platform For Intelligent and precise treatment of bone and joint diseases in Shaanxi Province (No. 2024PT-13) and the Discipline Capacity Building Program of Xi'an Science and Technology Bureau (No. 23YXYJ0003). The funding source had no influence on the study design, data collection, analysis, or interpretation of the findings.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.arr.2025.102743.

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