Molecular Neurobiology (2019) 56:8035–8051
https://doi.org/10.1007/s12035-019-01655-0

Neurocognitive Disorders in Heart Failure: Novel Pathophysiological Mechanisms Underpinning Memory Loss and Learning Impairment

C. Toledo [1,2] · D. C. Andrade [1,3] · H. S. Díaz [1] · N. C. Inestrosa [2,4] · R. Del Rio [1,2,4]

Received: 6 December 2018 / Accepted: 20 May 2019 / Published online: 5 June 2019

Abstract
Heart failure (HF) is a major public health issue affecting more than 26 million people worldwide. HF is the most common cardiovascular disease in elder population; and it is associated with neurocognitive function decline, which represent underlying brain pathology diminishing learning and memory faculties. Both HF and neurocognitive impairment are associated with recurrent hospitalization episodes and increased mortality rate in older people, but particularly when they occur simultaneously. Overall, the published studies seem to confirm that HF patients display functional impairments relating to attention, memory, concentration, learning, and executive functioning compared with age-matched controls. However, little is known about the molecular mechanisms underpinning neurocognitive decline in HF. The present review round step recent evidence related to the possible molecular mechanism involved in the establishment of neurocognitive disorders during HF. We will make a special focus on cerebral ischemia, neuroinflammation and oxidative stress, Wnt signaling, and mitochondrial DNA alterations as possible mechanisms associated with cognitive decline in HF. Also, we provide an integrative mechanism linking pathophysiological hallmarks of altered cardiorespiratory control and the development of cognitive dysfunction in HF patients.

Keywords Heart failure · Cognitive impairment · Aging · Cardiorespiratory control · Signal pathway

Introduction

Chronic heart failure (HF) is a recognized health care problem affecting at least 26 million people worldwide with increasing incidence and prevalence [1, 2]. It has been reported that 14.9 million people across the EU [3] and 5.7 million in the USA [4] are HF afflicted. In the rest of the world, the numbers are not well documented; however, it has been estimated that HF prevalence would reach 1–2% of population, leading to increased mortality and morbidity, frequent hospital admissions, and reduced quality of life and functional status [5]. Notably, HF is the most prevalent cardiovascular disease in aging with a prevalence rising to ≥20% among men and women over 75 years of age [6]; this is no insignificant matter when one considers that HF prevalence will increase by 46% by the year 2030 [2, 7].

In HF, longer-term outcome, poor quality of life, and health care costs depend not only on cardiac function but also on the severity of secondary impairment of other organ systems, including the brain [8]. Given that cardiovascular diseases are the most common chronic condition in older adults, there is a high association between HF and cognitive impairments; a condition that represents underlying brain pathology that results in a decline in neurological faculties in aging [9–11]. In the last decades, an increasing body of evidence suggests that decreased cardiac function is independently associated with neurocognitive impairment, with HF proposed as the principal cause of cognitive dysfunction [12–14], a term known as "cardiogenic dementia". Findings of several surveys indicate that physical, social, work, and leisure activities are significantly impaired among HF patients [15]. These cognitive alterations are likely to result in forgetfulness and poor learning ability, which may impair treatment adherence and suboptimal self-care [14, 16, 17]. In addition, executive

C. Toledo and D. C. Andrade contributed equally to this work

✉ R. Del Rio
rdelrio@bio.puc.cl

1 Laboratory of Cardiorespiratory Control, Department of Physiology, Pontificia Universidad Católica de Chile, Santiago, Chile

2 Center for Aging and Regeneration (CARE-UC), Pontificia Universidad Católica de Chile, Santiago, Chile

3 Centro de investigación en fisiología del ejercicio, Universidad Mayor, Santiago, Chile

4 Centro de Excelencia en Biomedicina de Magallanes (CEBIMA), Universidad de Magallanes, Punta Arenas, Chile

dysfunctions impair patient ability to make decisions in critical situations, such as early recognition and interpretation of symptoms, increasing hospital admission and mortality rates [18]. Despite the presence of cognitive impairments in HF patients, very little is known about the molecular mechanism underpinning memory loss and learning impairment in cardiac failure patients.

Currently, cognitive impairment is one of the most common co-occurring chronic conditions among elderly people with HF [12–14]. Its incidence varies widely from 35 to about 80% depending on the studied population (age and diagnostic criteria of patients), features of disease (severity, stage, and subtypes of HF), instruments used to assess cognition and study design [8, 19]. Overall, published studies seem to confirm that HF is associated with cognitive impairment that includes primarily memory, attention, mental flexibility, and global cognitive deficits [14]. Importantly, the association between impairment cognitive function and HF in older persons is multifactorial and includes shared risk factors for chronic cognitive decline. Risk factors for HF, such as atherosclerosis, hypertension, obesity, and diabetes mellitus, can also lead to cognitive impairment [19]. Consequently, identifying the pathophysiological mechanisms that contribute to cognitive impairment in HF will help to develop future treatments intended to improve quality of life in these patients.

In the present review, we have tried to compile the update pathophysiological mechanism involved in the establishment of neurocognitive alterations in HF. Based on the available scientific literature, we will review the contribution of cardiovascular and respiratory alterations as a possible mechanism associated with neurocognitive alterations in HF. Accordingly, we will discuss the possible link between pathophysiological mechanisms associated with cardiorespiratory control and the mechanisms underlying cognitive impairment in HF patients, with a special emphasis in the most important processes associated with chronic disease in advanced age; brain hypoperfusion, oxidative stress, and neuroinflammation, Wnt signaling, and mitochondrial dysfunction [20, 21].

Heart Failure and Neurocognitive Function

Several studies published in the last years have sought to characterize the phenotype of HF associated with cognitive dysfunction and brain changes. However, the molecular mechanisms underlying pathophysiological alterations in neurocognitive impairment following HF have not been fully understood. Recent evidence shows that microRNA-1 (miR-1) is released in exosomes by the failing heart and transported to the brain where miR-1 downregulates SNAP-25 ultimately leading to a reduced synaptic vesicle secretion and impaired synaptic plasticity [22]. In addition, Li et al. [23] showed that knock-down of the presenilin gene in *Drosophila* increased IP3 receptor expression and reduced SERCA expression in the heart. Contrarily, overexpression of the presenilin gene reduced ryanodine receptor expression, suggesting that mutations in the presenilin gene which has been linked to the early-onset of familial Alzheimer's disease may also be involved in cardiac tissue alterations through the regulation of calcium dynamics. Mammalian studies are needed to validate this hypothesis. These studies contribute to the understanding of the relationship between cardiovascular damage and brain dysfunction.

HF is a chronic progressive disease that can be defined as both an abnormality of cardiac structure, and/or function, in which the heart muscle is unable to deliver enough blood to peripheral tissues for meet their oxygen needs, despite normal filling pressures [24]. HF is caused by cardiac dysfunction, as a result from impairment or loss of cardiac muscle, characterized by left ventricular dilatation, hypertrophy, or both [25, 26]. Generally, HF is recognized as a myocardial disease causing systolic ventricular dysfunction, where HF patients present a reduced ejection fraction (HFrEF) due to reduced contraction and emptying of the left ventricle [24]. However, abnormalities of ventricular diastolic function also cause HF and it is diagnosed when symptoms and signs of HF are presented with a preserved ejection fraction (HFpEF) at rest [27].

Alterations in neuronal structure, loss of synapses, and dysfunction of neuronal networks are processes related with normal aging [28]. However, age-related diseases accelerate the rate of neuronal dysfunction and late-life cognitive decline [29]. In HF patients, the occurrence of cognitive impairments has often been viewed as coincidental events, because the prevalence of both HF and cognitive impairments increases with age. However, results of population-based studies on elder patients have shown that HF patients show up to 2-fold increase risk of developing cognitive impairments compared with age-matched controls [30]. In fact, approximately 50% of HF patients who underwent brain imaging studies displayed global cortical thinning and hippocampal atrophy, suggesting alterations in memory and cognitive processes [31].

Cognition is a superior cortical function involving multiple brain processes that allows an individual to perform tasks that require quick processes to decide and to execute functions (i.e., perceiving, thinking, knowing, reasoning, remembering, analyzing, planning, paying attention, generating and synthesizing ideas, creating, judging, being aware, and having insight) [29, 32]. Thus, cognitive function is among the most pressing concerns of geriatric matters, as cognitive decline is the primary determinant of disability in late life. Even more, presence of cognitive impairment may interfere with self-care in chronic diseases because both treatment and monitoring require a high degree of comprehension, self-control, and adherence to treatment recommendations (Fig. 1).

The neuropsychological deficits in older HF patients are characterized by mild cognitive impairment, a general term used to describe a subtle but measurable deficit in one or

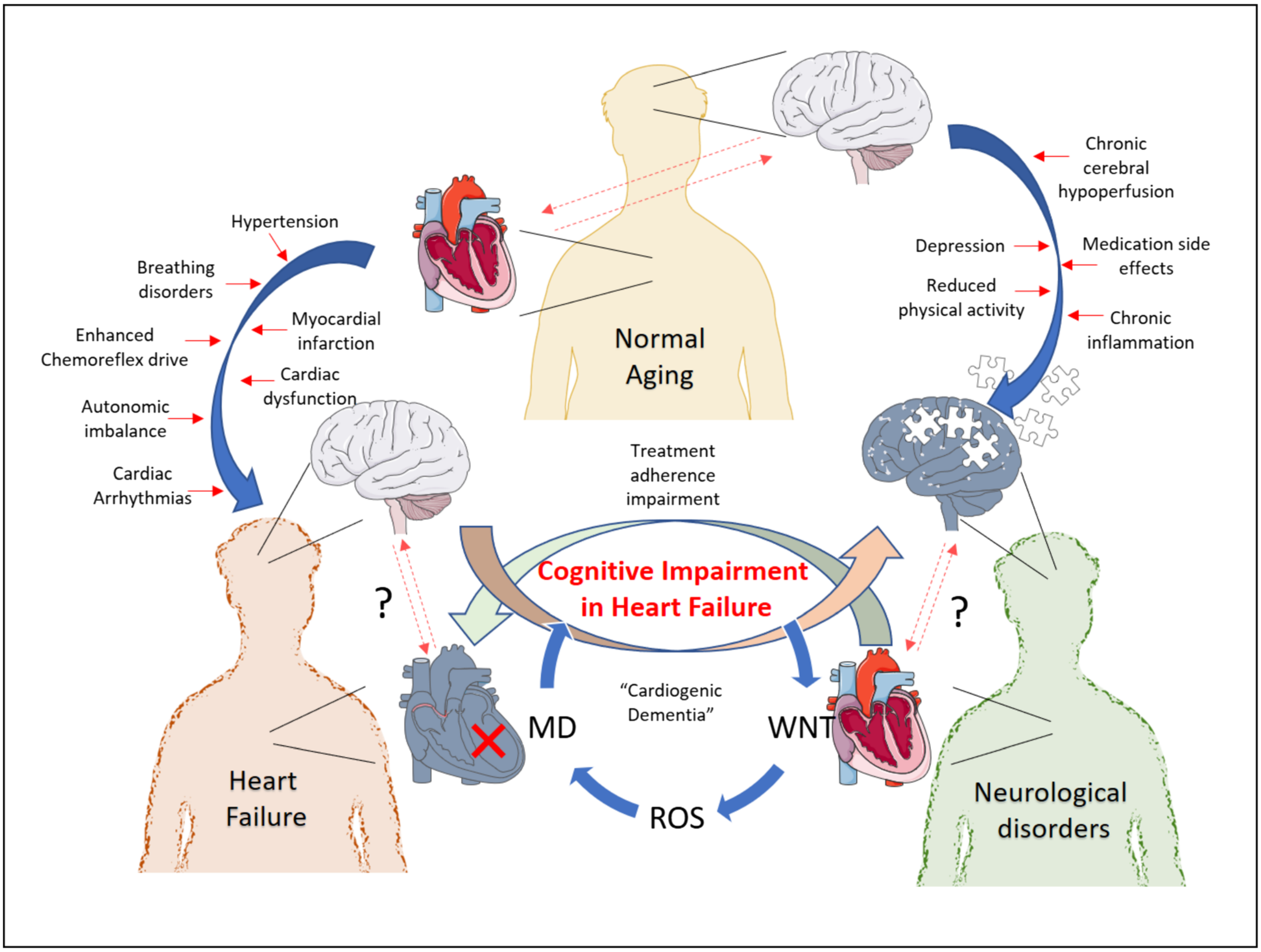

Fig. 1 Neurocognitive disorders in heart failure. Alterations in the heart and brain function normally occur with age. HF is the most common cardiovascular disease in elderly persons. Although there is epidemiological evidence showing cognitive impairment in HF patients, little is known about the molecular mechanism underpinning neurocognitive disorders in this condition. Oxidative stress, alterations in Wnt signaling, and mitochondrial dysfunction are all well-known molecular scaffolds that participate in cognitive function impairment in neurological diseases. Alterations in Wnt signaling within the brain in the setting of HF and its contribution to cognitive decline remains to be determined.

multiple cognitive domains (i.e., memory, attention, and executive functions). However, in patient with severe HF, cognitive dysfunction, especially anxiety and depression, can also affect their ability to comply with treatment regimens. It has been described that up to 80% of patients with advanced HF have severe memory deficits and other cognitive abilities [33]. Cline et al. [34] showed that about 60% of patients with severe HF could not remember the name or the dose of the medication that they were receiving for the HF treatment. Mostly, they do not follow prescribed medication, and in these cases, it may increase hospitalization frequency due to decompensation, that could even be fatal.

Cognitive Impairment in HF Patients: Epidemiology

Cognitive deficit is one of the most common concurrent chronic conditions among elderly people with HF [8, 10, 35, 36]. In HF patients, occurrence of cognitive impairments has often been viewed as coincidental, because the prevalence of both HF and cognitive impairments increase with age [37, 38]. However, results of population-based studies on elder patients have shown that HF patients show up to 2-fold increased risk of impaired cognitive function compared with age-matched controls [30, 39]. Significantly, assessment and documentation of cognitive impairment seemed to be important to improve patient care. In a study with HF patients, among those with cognitive deficits, only 22.7% were reported as such by physicians [40]. Indeed, HF patients without documented cognitive impairment had significantly greater 6-month mortality or hospital re-admissions than patients without cognitive impairment, while hospital re-admissions were not significantly higher in patients whose cognitive impairment was correctly reported [40].

In a study among 414 participants (249 patients with HF, 63 healthy participants, and 102 participants with major medical conditions distinct than HF), patients with HF showed more memory impairments (related to Hopkins verbal learning test), diminished psychomotor speed (trail making test A, TMT-A), and less executive function (controlled oral word association, COWA) compared with the other groups [41]. In other systematic studies made by Vogels et al. [14], HF patients showed diminished performance in memory, psychomotor speed/attention (assessed by TMT-A), and global cognition (tested by mini mental state examination, MMSE) compared to healthy subjects. In a cross-sectional descriptive study on HF patients, from 23 HFrEF patients with New York Heart Association (NYHA) class III or IV (~76 years), cognitive impairment, defined as a score on Montreal cognitive assessment (MOCA) test < 26, was detected in over 70% of the subjects [35].

In general, studies demonstrating long-term memory impairment or cognitive impairment in HF were performed in HFrEF patients, and predominantly in men. Most of the studies reviewed previously have focused on individuals with systolic dysfunction; with previous myocardial infarction, with symptoms of HF in NYHA III-IV, with no previous history of neurological or psychiatric disease and a left ventricular ejection fraction (LVEF) < 40% (mean age 70 years) [14, 33, 42]. Few studies have included both diastolic and systolic dysfunction [43]; therefore, it is plausible to ask if there is any difference in the incidence of cognitive impairments between HFrEF and HFpEF. Data to address this issue are limited. However, and despite that brain structures involved in neurocognitive impairment are not completely known, individuals with different types of cardiac dysfunction show differential patterns of performance on neuropsychological tests, with faster cognitive decline in HFrEF compared with HFpEF patients, but both with statistical significance correlation for decline of executive function, attention, abstraction, and memory compared with healthy people age-matched [43, 44]. It is important to note that previous data are cross-sectional, which limits the ability to assess the degree of change that may occur across the disease progression in people with HF who had reduced versus preserved ejection fraction. In fact, a recent longitudinal study confirmed that the rate of cognitive decline after HF incident did not differ significantly by whether ejection fraction was reduced or preserved [45]. Therefore, answering the previous question will require further investigation.

On the other hand, it is important to note that cognitive impairment in HF, like what happens in men, is a significant health problem for women, particularly elderly women [33, 46, 47]. In a study on 282 patients hospitalized for HF, average age 80 years, cognitive impairment was present in 46.8% of the subjects, of which more than a half of them were females [40]. Also, in 577 hospitalized patients with acute HF, mean age 71 years, females about 50% of the sample, 33% showed memory problems, 40% slower processing speed, and 56% impairment in executive tasks [46].

Impairment of Cognitive Domains in Heart Failure

Cognitive functioning covers different specific aspects known as cognitive domains that include both basic cognitive functions: attention, working memory, long-term memory, perception, and psychomotor speed; and higher-level cognitive functions: decision-making and executive control, speech and language, and visuospatial and constructional function [32, 48]. Several cerebral areas can be involved in patients with HF developing deficits in cognition [31]. Cognitive damage in HF involves different domains that include learning memory and delay recall, attention, executive function, and working memory. Brain imaging studies comparing HF patients with age-matched healthy participants showed the following: global cortical thinning in the frontal, parietal, temporal, and occipital lobes; hippocampal atrophy; and altered resting states in neural networks which are areas related to short- and medium-term memory and cognitive processes [49, 50]. In addition, Frey et al. [31] showed that in 148 HF patients (~65 years), subject to cardiological examination, laboratory assessment, neurology examination, neuropsychological test battery, and cerebral magnetic resonance imaging, displayed cognitive deficits in the domains of attention (41%) and memory (47%), and advanced medial temporal lobe atrophy. Nevertheless, this study does not separate the data by HF types. Accordingly, future studies need to determine whether any difference exist regarding the structure of the brain areas associated to cognitive dysfunction among HFrEF and HFpEF patients.

Cognitive Impairment in HF Patients: Clinical Impact

Cognitive impairment in HF patients is a source of disability and functional impairment that represents a devastating medical and financial problem for patients [46]. Impairment of memory, attention, executive function, and psychomotor speed can affect the ability of patients with HF to control their disease, recognize the symptoms of worsening, make appropriate decisions about their health, and adhere to specific therapeutic regimes, often complex [51]. The self-care heart failure index (SCHFI) was created to assess self-care maintenance, self-care management, and self-care self-confidence in people with HF [52]. In a sample of 93 hospitalized patients with moderate to severe HF (average age of 70 years), 40–60% of subjects had an inadequate self-care maintenance, poor self-care management, and low self-care confidence, compared with subjects with normal cognition [53]. The consequences of cognitive decline are not clear, but it is conceivable that HF patients with cognitive impairment show increased risk for poor outcomes, such as hospitalization and mortality compared with age-matched community controls [54, 55], even compared with HF patients without cognitive impairment [56, 57]. In a study among 1092 hospitalized elderly (mean age 80 years), the 6-month mortality was 129 of the total sample; of those, 5.7% corresponded to patients without HF or cognitive impairment, 19% for patients with HF but no cognitive impairment, 31% for patients without HF but with cognitive impairment, and 35.6% for patients with both HF and cognitive impairment [56]. In 1113 hospitalized HF patients (mean age 78 years), mortality occurred in 18% of subjects with cognitive impairment versus 3% of patients with normal cognition [57]. Importantly, 1-year mortality was 27% among patients with cognitive impairment and 15% in other participants.

Pathophysiology of Impaired Cognitive Function in Patients with Heart Failure

The link between cardiac diseases and cognitive deterioration has been accepted from late 1970s.The precise molecular mechanisms that underlie the development of cognitive impairment in HF has not been elucidated. Different pathophysiological processes such as inadequate cerebral perfusion due to altered cardiac output, chronic hypoxic brain damage, cerebrovascular reactivity, arterial hypotension, and the production of pro-inflammatory cytokines could be determining structural or neurodegenerative changes which cannot be reversed and/or functional neuronal dysfunction which may progress to neuronal cell damage [58, 59] (Fig. 1).

Heart Failure and Cerebral Perfusion

Cognitive decline in HF may result from a direct mechanism related to cardiac failure but may also be associated with several HF comorbidities. Indeed, vascular risk factors may contribute to cognitive impairment by affecting the blood flow to the brain [60, 61]. Reduction in cerebral blood flow triggered by a low cardiac output and impaired vascular tone autoregulation may promote cognitive deficits [62–65]. Particularly, reductions in cerebral blood flow have been tightly associated with an inadequate O_2 supply to subcortical regions which may progress into white matter ischemia, lacunar strokes, and brain microinfarcts [66, 67]. Likewise, other pathophysiological factors in HF that impact cardiac output regulation can also add more stress to the brain which ultimately may contribute to further loss of cognitive performance. Indeed, atrial fibrillation is the most prevalent form of cardiac arrhythmia in HF and can exacerbate cognitive deficits in HF by reducing systemic cardiac output which may further reduce perfusion to cerebral territories with already precarious blood supply and/or arterial territories already compromised by arterial stenosis [68, 69]. In addition, cerebral blood vessel dysfunction (i.e., hemorheological factors, increased resistance to flow, blood–brain barrier impairment, and dilatation of perivascular spaces) has also been linked to cognitive decline [70]. In heart diseases, microvascular dysfunction in the brain trigger loss of neurovascular coupling which results in inappropriate distribution of oxygen, glucose, and other nutrients to several areas including but not limited to cognitive-related areas such as the hippocampus [71, 72]. Then, neurons, endothelial cells, astrocytes, and pericytes may all contribute to brain perfusion alterations in the setting of a cardiovascular disease.

On the other hand, hemodynamic alterations such as hypotension may aggravate subcortical ischemia both in older patients and in patients with neurodegenerative diseases [60]. Indeed, it has been shown that low systolic blood pressure is associated with cognitive impairment in patients with heart failure [63, 65]. Resting blood pressure is lower in patients with heart failure independent of its etiology (reduced versus preserved ejection fraction heart failure) when compared with age-matched controls. Importantly, systolic blood pressure values below 130 mmHg in HF patients appear to predict the development of cognitive impairment [63]. It is well known that reductions in blood pressure alter the blood flow. Then, lower blood pressure in HF patients could contribute to decreases in blood flow to several territories. However, brain blood flow autoregulatory mechanisms may partially mask the real effect of blood pressure reductions on regional brain blood perfusion. Indeed, it is important to note that the cerebral autoregulation maintained constant cerebral blood flows across a wide range of cerebral perfusion pressures. Therefore, the precise contribution of blood pressure, if any, on blood flow regulation and endothelial function in HF and its overall impact on cognitive function deserves future investigations.

Importantly, most of the current studies showing cerebral hypoperfusion-related cognitive impairment in HF have been done in patients with systolic heart failure, with left ventricular ejection fractions less than 35% [64, 68, 73, 74]. Nevertheless, it is worth noting that the incidence of impaired cognitive function in HFrEF and HFpEF is not significantly different [45]. Particularly, HFpEF patients did not display brain blood flow reductions or decreases in oxygen supply to the brain. Furthermore, concomitant cardiovascular events associated with cognitive decline, such as strokes, are also not different between HF etiologies. Indeed, the prevalence of stroke did not differ between patients with HEpEF and those with HFrEF and ranged between 2.4 and 5.8% in HFrEF and 3.8 and 7.4% in HFpEF [75]. Therefore, other factors that come into play contribute to cognitive dysfunction in HF besides blood flow regulation. Then, it is plausible to speculate about the existence of a common pathophysiological mechanism present in both HFrEF and HFpEF, independent of hemodynamic changes that contribute to the development of cognitive impairment in HF. Further research should focus on identifying novel mechanisms that contribute to cognitive decline in HF.

Autonomic Nervous System, Heart Failure, and Cognitive Impairment

The sympathetic and parasympathetic nervous system regulates several physiological functions, including cardiovascular and respiratory modulation. HFrEF and HFpEF share common pathophysiological features such as the presence of autonomic nervous system imbalance and breathing irregularities which are directly related to the progression of the disease [76–78]. Autonomic imbalance, with a prevalence of the sympathetic tone over vagal activity, is one of the most important neuro-hormonal mechanisms underlying HF pathogenesis and progression and occurs as early as a compensatory adjustment to preserve cardiac output [79]. However, this early compensatory mechanism increases progressively over time and becomes maladaptive, increasing sympathetic outflow to the heart which further stresses the failing heart [80]. In HF patients, it has been described that plasma norepinephrine levels are increased, reflecting activation of sympathetic nervous system, which is associated with heightened mortality rate [81, 82]. HF patients exhibit enhanced sympathetic tone and sleep-related breathing disorders suggesting alterations on specific regions of the brain involved in chemoreception integrative mechanisms and/or autonomic control [77] as well regions involved in cognitive functions [83–85] (Fig. 1). In HF, hyperactivation of cardiorespiratory areas within the brainstem occurs early in the progression of the disease [78, 86, 87]. Indeed, HF rats show breathing disturbances 1 week after HF induction [86]. Interestingly, it has been shown that pre-sympathetic neurons located in the rostral ventrolateral medulla (RVLM), considered the most important nodal point of the cardiovascular sympathetic control network, since RVLM neuron destruction causes sympathetic activity to fall to zero [88], become hyperactivated in HF, independent of its etiology [78, 86]. Considering that both types of HF displayed different blood flow to the brain, but with similar RVLM activation, it is plausible that RVLM neurons may contribute, at least in part, in disturbing normal cognitive function in HF.

Related to cardiorespiratory pathophysiological hallmarks of HF and cognitive function, Woo et al. [84], analyzing changes in regional gray matter volumes, showed a significant gray matter loss in the hippocampal and frontal cortex, CO_2 homeostasis, and sympathetic and parasympathetic control areas in HF patients. Both cerebellar cortex and deep cerebellar nuclei involved in the autonomic and respiratory control were affected thus compromising response to CO_2 and increasing the risk of developing Cheyne–Stokes breathing pattern [84]. This work highlights the association of cognitive impairment, autonomic disturbances, and sleep-disordered breathing in HF; therefore, a more detailed understanding about these integrated pathophysiological mechanisms would thrust better design, precise, and clean treatments. For the moment, it is possible to hypothesize that cardiorespiratory alterations may precede the development of cognitive impairments in HF, but also altered cardiorespiratory neuron activity may trigger alterations in cognitive-related areas (i.e., hippocampus).

The processes governing cognition are complex. Indeed, only from a neurochemical point of view, it is possible to appreciate the diversity in transmitters and receptors for the correct synaptic processes. Several different neurotransmitters have been implicated in attention, executive functioning, and memory, including norepinephrine (NE), dopamine, serotonin, histamine, glutamate, and gamma-aminobutyric acid among others [89]. Accordingly, alterations of cognitive function in pathological conditions are also complex in terms of their molecular basis. In HF condition, there are several pathophysiological mechanisms that may contribute to the generation of cognitive decline. However, there is a lack of studies providing compelling evidence proposing a common pathophysiological pathway to both cardiac failure progression and cognitive decline in HF. Importantly, it has been shown that patients with neurodegenerative diseases and patients with HF exhibited marked abnormalities in cardiovascular autonomic regulation evidenced by poor baroreflex gain [90] and parasympathetic/sympathetic dysfunction [91]. Therefore, altered neural control of autonomic regulation rises as a plausible common pathological footprint in both conditions (HF and neurodegenerative diseases). Interestingly, Borson et al. showed a blunted stress-related sympathetic response in patients with AD. Furthermore, the sympathetic response to postural stimulation of the baroreflex remains intact in AD patients suggests the presence of central nervous system alterations above the brainstem vasomotor center that interacts synaptically with brainstem cardioregulatory centers [32].

Recently, adrenergic system alterations have been implied also in the pathogenesis of CI and dementia opening the window for new fascinating and promising therapeutic opportunities [85]. Interestingly, it has been shown that pre-sympathetic catecholaminergic neurons located in the RVLM, one of the most important autonomic control regions in the brainstem [88], become hyperactivated in HF [78, 86]. Then, it is plausible to hypothesize that RVLM-C1 neurons may contribute, at least in part, in disturbing normal cognitive function in HF.

Ongoing research on cognitive function during aging has primarily focused on how the alterations in a subset of cortical and forebrain limbic structures influence cognition. However, there is evidence showing that both the rostral and the caudal part of the ventral medulla and pons (i.e., locus coeruleus) projected towards hippocampal areas [92, 93]. Indeed, NE, an important neurotransmitter that can regulate cardiovascular function in the brainstem, plays an important role in the regulation of synaptic plasticity, learning, and memory by modulating hippocampal neuron excitability [94, 95].

The Locus Coeruleus and Adrenergic System Modulation of Cognition in Heart Failure

The locus coeruleus (LC) provide the primary source of NE to the forebrain [96, 97]. Importantly, the LC-norepinephrine (LC-NE) system participates in cognitive and behavioral functions, including enhanced arousal and attention [98]. In healthy individuals, activation of LC neurons results in norepinephrine (NE) release in LC projecting areas such as the hippocampus, amygdala, and prefrontal cortex which increases the activity of excitatory inputs and decreases inhibitory inputs being the outcome an improved long-term memory consolidation [99]. Decreases in the number of noradrenergic LC neurons negatively impact cognitive function, particularly by disrupting hippocampus-related memory and learning processes by inducing an impaired redox homeostasis and the loss of neuronal plasticity in hippocampal neurons [100]. Intriguingly, in AD, a marked loss of noradrenergic LC projections to the hippocampus along with memory and arousal alterations [95] has been shown. In addition, AD patients showed autonomic nervous system impairment associated but not limited to the loss of cortical perivascular cholinergic nerve terminals. In addition, data obtained in experimental AD showed that the loss of NE drive to the hippocampus triggers a neurotoxic pro-inflammatory response and reduces amyloid-beta clearance negatively impacting the overall condition [100].

While adequate central nervous system noradrenergic activity enhances cognition in healthy conditions, it has been proposed that excessive noradrenergic drive may have opposite effects. Raskind et al. [101] found chronic elevations in plasma NE concentrations in patients with advanced AD. Also, increases in plasma NE correlates with the degree of cognitive function impairment in AD [102]. In addition, animal studies have shown that acute or chronic increases in noradrenergic drive impair attention and working memory [96, 103]. More importantly, higher cerebrospinal fluid NE concentrations are associated with poorer performance on attention and executive function tasks in humans [104]. Remarkably, elevated sympathetic outflow and higher NE circulating levels are a hallmark in HF pathophysiology. In addition, pre-sympathetic neurons located in the rostral ventrolateral medulla (RVLM-C1), a pivotal region involved in the control of sympathetic outflow that projects to the LC, become hyperactivated in HF independent of the etiology [77, 78, 105, 106]. Therefore, disturbances in central nervous system cognitive areas may occur as an independent pathological process related to aging during the progression of HF or may be linked to alterations in cardiorespiratory control areas in HF. This hypothesis is highly innovative since there are no current studies addressing the potential role of sympathetic brainstem neurons in the modulation of memory and cognitive processes, neither in health nor in disease conditions. Consequently, further research investigating the relationship between the noradrenergic system and its interactions with cognition areas in the setting of HF is needed.

In the central nervous system (CNS), the primary source of NE is the LC [107, 108]. Notably, the LC is essential for maintaining cognitive function in the aging brain [109] and RVLM-C1 neurons innervate LC neurons [105, 106]. The LC is the largest cluster of CNS noradrenergic neurons. The activity of this nucleus is state dependent and facilitates arousal and attention [98]. The LC innervates the hippocampus, providing the sole source of NE to hippocampal neurons [96, 97]. Acute elevations of NE levels increase neuronal excitability in the dentate gyrus and in the CA subfields, via activation of adrenergic receptors exerting specific effects on synaptic information encoding [94].

In the brain, adrenergic receptors are widely distributed in different regions, including the frontal cortex, midbrain, striatum, hippocampus, and thalamic nuclei [110]. NE exerts its effects in the CNS through three classes of adrenergic receptors: α1AR, α2AR, and β-AR, the latter divided into the β1, β2, and β3 subtypes. While the α1AR and β-AR are post-synaptic receptors, the α2AR is presynaptic and, when stimulated, it inhibits further NE release in the synaptic cleft [91]. β-ARs are G-protein-coupled receptors that exert an excitatory effect on the post-synaptic neuron mainly through the activation of Gs-type G proteins. It has been shown that NE acting through β-ARs contributes to long-lasting synaptic plasticity by recruiting molecular elements of synaptic signaling such as cAMP-dependent protein kinase (PKA) and CaMKII, regulating long-term potentiation (LTP), and modulating learning/memory processes [95]. Importantly, p42–44 MAP kinase (ERK1/2) cascade is also recruited in neurons for long-term synaptic plasticity [111]. One interesting feature of cAMP pathway is that it can recruit ERK activation in neurons to contribute to synaptic plasticity establishment. Furthermore, Winder et al. found that β1-AR-induced activation of ERK play a critical role for LTP development in Schaffer collateral–CA1 pyramidal cell synapse elicited by theta frequency (5 Hz) stimulation. Moreover, this effect requires PKA but not macromolecular synthesis suggesting a novel postsynaptic role for ERK as a physiologically relevant signaling molecule by which β-ARs and PKA regulate neuronal function [112]. Conversely, activation of β2-ARs impaired hippocampal neurons excitability via activation of Gi-type G proteins [113]. Although most of the actions of the β2-ARs are mediated through G proteins and the cyclic-AMP-dependent PKA system, beta-adrenergic receptors can also couple with Gi proteins [114]. The cAMP signaling cascade can facilitate the activation of ERK by PKA-mediated phosphorylation of an adaptor molecule, Rap1. Then, PKA-mediated phosphorylation of the β2-AR significantly decreased its ability to couple with G, while dramatically increasing its ability to couple with Gi [115]. Notably, studies indicate that NE is increased in the cerebrospinal fluid of AD patients [104] suggesting that enhanced NE spillover within the hippocampus may be involved in the progression of cognitive impairment [115] (Fig. 2). Importantly, increases in NE content in the synaptic space induces β-ARs internalization [116]. Indeed, chronic activation of the β-ARs leads to receptor phosphorylation by G-protein-coupled receptor kinases (GRKs) and subsequent binding of the protein β-arrestin which ultimately lead to receptor internalization [117]. Accordingly, it has been proposed that excessive β-AR activation in AD becomes maladaptive over time blunting adrenergic receptor signaling pathways [118]. Interestingly, it has been shown that RVLM-C1 neurons are chronically active in HF and that RVLM-C1 neurons display neuroanatomical projections to the LC, the major source of noradrenergic drive to the hippocampus. Then, it is plausible to hypothesize that in HF, the hyperactivation of RVLM-C1 neurons triggers tonic increases in hippocampal NE release through activation of hippocampus-projecting LC adrenergic neurons. Lately, increases in NE spillover at the hippocampus level may induce the loss of adrenergic signaling through desensitization of β-ARs; internalization and impaired Wnt signaling being the outcome of an impaired cognitive function in HF. In conclusion, while acute NE release may be relevant to induce neural plasticity in the hippocampus, chronic or tonic release of NE may exert the opposite effects due to desensitization/internalization of β-ARs and the subsequent loss of adrenergic signaling.

Also, evidence indicates that high concentrations of NE impair prefrontal cortex function through activation of α1 adrenergic receptors. Indeed, NE has higher affinity for α2A receptor compared with α1 receptors [119]; therefore, it is likely that at low NE levels (e.g., under basal or unstressed conditions), NE preferentially engage α2 receptors and improve prefrontal cortex function, while during conditions of high NE release, α1 receptors would become activated and override the effects of α2 receptor stimulation [120]. In particular, NE decreases glutamatergic excitatory postsynaptic potentials by the activation of α1-adrenergic receptors [121]. In addition, it has been shown that activation of the α2ARs decreases the excitability of hippocampal neurons by reductions in cAMP and inhibiting neurotransmitter release at pre-synaptic terminals [122]. Together, strong compelling evidence support the role of NE as a neuromodulator of neuronal activity in cognitive-related areas. Consequently, identifying the effects of NE and adrenergic signaling on cellular plasticity during HF may open new avenues for understanding the cognitive decline in this population.

It is interesting to note that first-line treatments for HF, regardless of its etiology, are based on: (a) the use of diuretics to decrease cardiac preload, (b) pharmacological blockers of the angiotensin-converting enzyme to decrease the vasoactive peptide angiotensin II, (c) pharmacological blockade of angiotensin II receptor 1, and (d) β-adrenergic receptor blockers [1, 26]. β-blockers are classified into: (a) first generation, which includes blockers that unselectively bind to both β1- and β2-

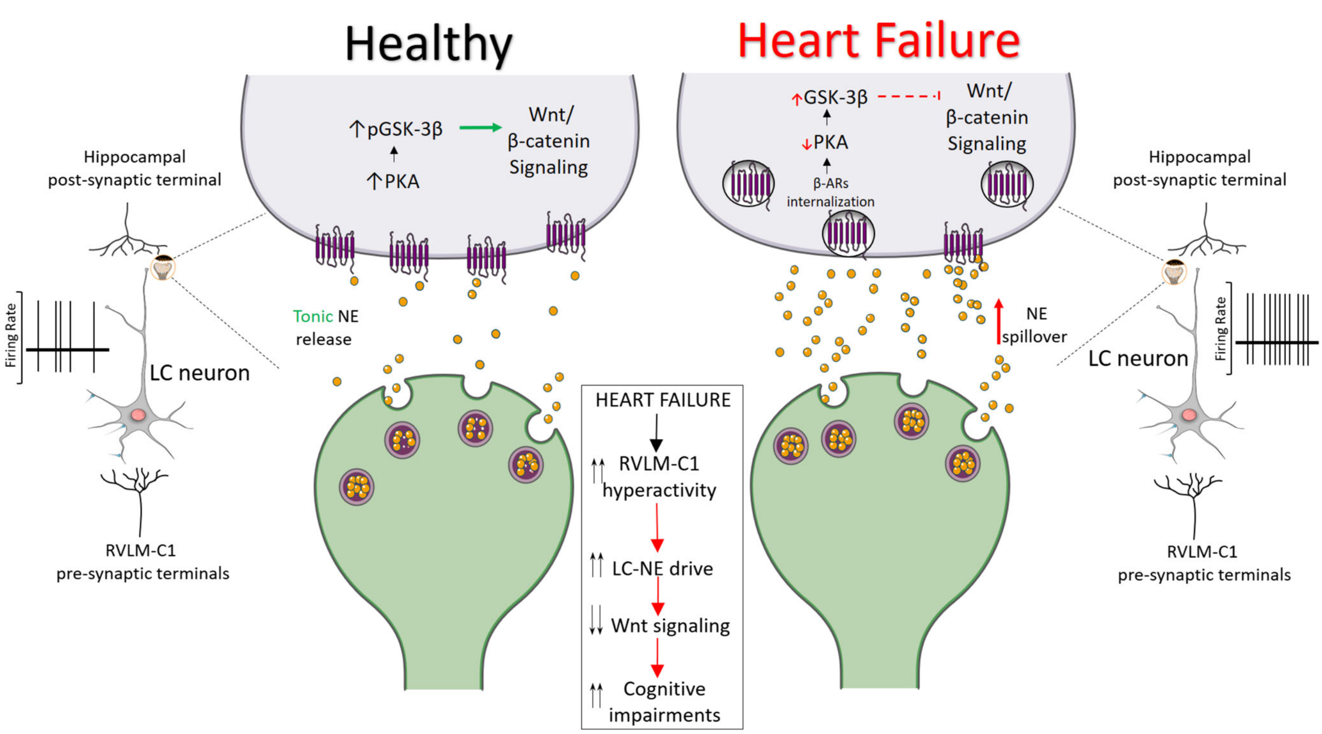

Fig. 2 Schematic representation showing the proposed physiological mechanisms underpinning cognitive impairments in HF. Hyperactivation of RVLM-C1 neurons in HF triggers tonic norepinephrine (NE) increase in the hippocampus through an excitatory synapsis from RVLM-C1 neurons to LC adrenergic neurons. Lately, increases in NE spillover in the hippocampus induce internalization of β-ARs and impaired Wnt/β-catenin signaling activation

AR subtypes (i.e., propanol and timolol); (b) second generation, including β-blockers with higher affinity for β1-AR than for β2-AR (i.e., metoprolol and bisoprolol); and (c) third generation, includes non-selective β-adrenergic receptor blockers, that acts on both β1 and β2 receptors, but also display additional α1 antagonistic activity (i.e., bucindolol). β-blocker agents are widely recommended for the treatment of mild-to-moderate HF. Current pharmacological treatments for HF (i.e., diuretics, β-blockers, and ACE inhibitors) are mostly targeted to relief cardiac workload and has omitted the overall complexity of HF pathophysiology which includes at least cognitive function impairment, excessive neural sympathetic drive, breathing disorders, systemic inflammation, and oxidative stress.

Importantly, β-AR stimulation has been known to play a critical role in long-term memory consolidation in the amygdala, dentate gyrus, and hippocampus [123]. For example, blockade of β-ARs with agents such as propranol attenuated the emotional enhancement of memory in both rodents and human, whereas infusion of a β-AR agonist improves memory consolidation [124]. Thus, β-blockers are less often prescribed to older adults, especially those with functional cognitive impairment or multiple comorbidities [125]. Indeed, different lines of evidence have shown a significant reduction in brain β-AR expression in neurodegenerative disease characterized by working memory and executive function impairment [126–128].

In HF, β-blocker treatment after acute myocardial infarction reduces mortality by 25 to 30%; however, β-blocker treatment has also been associated with the occurrence of CI in both normal and elderly HF patients [129]. Steinman et al. showed that β-blocker treatment following myocardial infarction was associated with a functional decline in older nursing home residents with substantial cognitive or functional impairment, but not in those with relatively preserved mental and functional abilities [130]. Unfortunately, less is known about the effect of β-blockers on functional cognitive status and evidences from pharmacological studies to activate or inhibit β-AR signaling remain controversial. Gelinas et al. found that isoproterenol, a β-AR agonist, improves memory consolidation and long-term potentiation in mice hippocampus [95]. Also, intra-amygdala injections of a selective β2-AR agonist, clenbuterol, enhance memory retention in mice [131]. Conversely, the non-selective β-AR antagonist, propranolol, also improves performance during cognitive flexibility tasks in rodent [132] while xamoterol, a partial β1-AR agonist, impairs hippocampal-dependent emotional memory retrieval in mice [133]. In addition, intracranial administration of β3-AR antagonists induces amnesia in chicks [134]. Then, current evidence suggests that β-AR may play a role in the regulation of cognitive functions. The exact and precise mechanism by which β-AR signaling may contribute to maintain/develop cognitive impairment in the setting of HF deserves future investigations.

Pathophysiological Mechanisms Associated with Cognitive Impairment in Heart Failure

In this section, we will discuss the contribution of the major signal transductions pathways and molecular pathological mechanism that has been implicated in the maintenance and progression of HF and in the processes underlying pathological brain aging.

Oxidative Stress and Inflammation

Inflammation triggered by oxidative stress has been implicated in both cardiovascular pathophysiology and neurodegeneration [135, 136]. Oxidative stress has also been proposed as a fundamental trigger for aging, where increased production of reactive oxygen species (ROS) and/or decreased antioxidant defenses lead to detrimental effects on cellular and organ function, and to the development of non-transmissible diseases, including cardiovascular diseases [137]. In addition, it has been proposed that oxidative stress contributes to age-related impairment in learning and memory. Indeed, there is a significant correlation between age, memory impairment, and the decrease in brain and plasma antioxidant defense [138]. Long-term potentiation (LTP), the major form of synaptic plasticity for learning and memory processes, has been used to examine age-related changes in hippocampal slices. Importantly, age-related LTP impairments in CA1 pyramidal neurons or from the dentate gyrus have been linked to increases in ROS levels [138]. Indeed, carbonylated protein levels (a marker of oxidative stress) are elevated in the hippocampus from aged brains [139, 140]. In addition, intracellular glutathione (GSH) concentration, a major antioxidant molecule, as well as the ratio of glutathione: glutathione disulfide (GSH:GSSG), were found to be decreased in aged rat brain (cortex, striatum, midbrain, cerebellum) of both genders [141]. Interestingly, this decrease in GSH level and/or GSH:GSSG ratio was also found in AD mouse models [142]. In a recent study performed by Hajjar et al. [143], decreased levels of GSH level were closely associated with a faster decline in cognitive function in an aged but healthy cohort. Furthermore, decreased circulating levels of glutathione predicted the age-related decline in executive memory [143]. Importantly, Palomera-Avalos et al., [144] showed that resveratrol treatment prevents cognitive impairment in aging by improving mitochondrial dynamics in the hippocampus by normalizing optic atrophy-1 protein (OPA1) and mitofusin 2 (MFN2) expressions and by targeting the Wnt-β-catenin pathways. Together, these evidences strongly supported a role for oxidative stress in the development and/or maintenance of cognitive impairment in pathological state.

Epidemiological and clinical studies indicate a causal relationship between heart disease and neurological diseases [145]. Indeed, cardiovascular diseases and AD share many pathological mechanisms, such as the presence of amyloid oligomers, alterations in mitochondrial DNA, oxidative stress, and inflammation [47, 135, 136, 144, 146–149]. Also, an increased systemic inflammatory profile is observed in patients with cardiovascular pathology particularly with HF [146, 150]. Importantly, in a murine experimental HF model, levels of mRNA and protein expression of AD-related protein markers (upregulation of amyloid precursor protein and BACE1) were altered in the hippocampus, triggering aberrant effect on amyloid-β (Aβ) metabolism [47]. Notably, authors found that inflammatory gene expressions such as TLR4, TNF-α, and IL-6 in the cortex and hippocampus were significantly upregulated in HF mice. Thus, a decreased heart function is able to alter the level of inflammatory markers within the brain.

As discussed previously, impairments in brain endothelial function in HF includes blood brain barrier permeability, blood flow local regulation and inflammatory activation appears all to be linked to the development of cognitive impairment in HF patients. Adamski et al. 2018 [151], using a HF mouse model, found that one of the key mechanisms of vascular-induced cognitive impairment in early HF pathology requires E-selectin upregulation in the brain cortex, a protein expressed almost exclusively on inflammatory-activated endothelium. Upregulation of E-selectin in HF mice results in blood–brain barrier leakage, cortical oxidative stress, and accumulation of β-amyloid in cortical areas. Additionally, peripheral inflammation may also contribute to cognitive decline since increases in circulating cytokines have been associated with lower cognitive performance. Indeed, it has been shown that pathogenic IL-1β plasma levels alter blood–brain barrier permeability by inducing a sustained disruption of the tight junction protein claudin-5. Furthermore, IL-1β can disrupt collagen-IV fibers located at the cerebrovascular basal lamina, then playing a critical role on the exacerbation of ischemic brain injury after transient middle cerebral artery occlusion [152]. Interestingly, it is well known that HF patients displayed increased circulating and tissue levels of pro-inflammatory cytokines [146, 150]. Indeed, pro-inflammatory mediators has been shown to be specifically upregulated in key sympathetic control areas within the brain, suggesting that a neuroinflammatory condition during HF may serve as a potent substrate for the development of autonomic imbalance in HF patients characterized by chronic sympathoexcitation [146]. In fact, inhibition of brain cytokine production improves cardiovascular outcome and reduces sympathetic activity in experimental HF [153, 154].

Mitochondrial Dysfunction, Cognitive Impairment, and Heart Failure

Mitochondria are the main organelles that supply energy to cells. This is extremely relevant to cells with energy expenditure, such as neurons, which are very sensitive to alterations in the production of mitochondrial ATP. Several studies have shown that dynamic changes in mitochondrial architecture have a major impact on the ability of the cell to survive stress and modify their energy production [155]. Deficits in energy production generally result in dysfunction of all energy-dependent cell functions. Importantly, a deregulated balance of mitochondrial dynamics in the function of the nervous system has been described in cognitive dysfunctions [156], mainly defined as imbalances between fusion and fission events, which are exacerbated during the aging process [157]. During aging, neurodegenerative diseases and extreme stress conditions caused by increased levels of ROS affects the replication and transcription of mitochondrial DNA resulting in mitochondria fragmentation and mitochondrial metabolism decline, leading to a progressive loss of function [158]. Thus, mitochondrial dysfunction increasingly appears to be a common factor connecting several hallmarks of aging, including cognitive decline and HF. Indeed, mitochondrial dysfunction plays a key role in different neurodegenerative disorders including Alzheimer's, Parkinson's, and Huntington's disease and amyotrophic lateral sclerosis, where cognitive functions are fundamentally impaired by mechanisms mediated by neuroinflammation and ROS [155, 159]. In addition, it has been demonstrated in mice that intact mitochondrial functions are required for proper regulation of synaptic transmission, brain function, and cognition in aging [160]. Mitochondria remove Ca^{2+} from the cytoplasm and accumulate it in their matrix and participate in many intracellular signaling processes involving Ca^{2+}-dependent mechanisms [161]. One of these processes is the NMDA receptor–mediated LTP, serving as the cellular model for memory functions and higher-order cognitive processes [162]. In summary, mitochondria-mediated oxidative stress and perturbed Ca^{2+} homeostasis may also contribute to the pathogenesis of neurocognitive diseases.

In HF, several components of cardiac muscle bioenergetics are altered, such as oxygen availability, substrate oxidation, and mitochondrial ATP production [147]. In general, it has been proposed that decreases in mitochondrial energy production may be a key player in the progression of HF. Indeed, alterations in mitochondrial biogenesis have been linked to cardiac muscle hypertrophy in HF due to altered signaling by PGC1α, the master regulator of mitochondrial biogenesis [163]. The mechanisms leading to changes in mitochondrial biogenesis in pathological cardiac hypertrophy and heart failure appear to be associated with high ROS production. In a study performed by Dai et al. [148], it was found that cardiac hypertrophy elicit by angiotensin II infusions in mice is dependent on higher mitochondrial ROS production and increases deletions on mitochondrial DNA. In conclusion, whereas these exact same alterations on mitochondrial function may serve as substrates for neuronal dysfunction in several brain areas, in HF remains to be determined.

Targeting Wnt Signaling in HF: Friend or Foe?

Wnt signaling pathway has been implicated largely in the regulation of synaptic assembly, as well as in neurotransmission and synaptic plasticity of adult nervous system [83]. Indeed, impairments in synaptic plasticity by decrease in LTP have been attributed in part to the deregulation of Wnt signaling in hippocampal neurons [164].

Wnt signaling has been proposed as a potential target for therapeutic intervention in cardiovascular diseases [149]. The Wnt signaling pathway is a group of signal transduction pathways formed by proteins that transfer signals from the outside of a cell through the receptor surface to the cytoplasm [165]. The roles of the Wnt signaling pathway in several developmental processes, including synaptic differentiation, are well characterized. The expression of Wnt ligands and Wnt signaling components in the central nervous system suggests that this pathway play a role in synaptic maintenance and cognitive function. Indeed, studies in humans indicate that Wnt signaling is directly related to neurogenesis and is altered or involved in the pathophysiology of AD and other CNS-related diseases [83]. In HF, Wnt signaling has been shown to be involved in mediating adverse cardiac remodeling, cardiac hypertrophy, and arrhythmogenesis [139, 166, 167]. Unfortunately, the results are often ambiguous when it comes to the question whether Wnt signaling in HF should be activated or inhibited.

The major mechanism proposed to recognize HF such as a risk factor for AD involves neurohumoral activation, promoting dysfunction of the neurovascular unit, causing an energy crisis in neurons. This leads to impaired clearance of Aβ and hyperphosphorylation of the tau protein, resulting in extracellular deposits of the Aβ into senile plaques, intracellular deposits of the microtubule-associated protein tau into neurofibrillary tangles, and neuronal cell death responsible for a decrease in the cognitive function and progressive loss of memory [168, 169]. Interestingly, Aβ-dependent neurotoxicity induces a loss of function of Wnt signaling [83, 165]. Li et al. [23] showed that the molecular mechanism by which presenilin mutations, a catalytic core of γ-secretase complex, lead to either early-onset familial Alzheimer's disease or cardiac dysfunction is triggered by the aberrant calcium channel receptor activities mediated by decreased expression of the component of Wnt signaling transduction pathway.

The underlying signal transduction mechanisms of HF-induced cognitive impairment are still unclear. However, it is well known that β1- or β2-AR activation increases cAMP and PKA [142]. Interestingly, it has been described that PKA regulates the activity of the canonical Wnt pathway [170, 171]. Phosphorylation of S675 of β-catenin by PKA may enhance transcriptional activity by promoting β-catenin stability [172]. Furthermore, glycogen synthase kinase 3 (GSK-3), another key enzyme involved in memory plasticity and cognitive function, is inhibited through phosphorylation of serine 9 in GSK-3 beta by PKA [173]. In addition, during aging-related cognitive impairments, there is a loss of function of Wnt activity, such as indicated by decreased β-catenin levels and increased phosphorylation of GSK-3β [165]. Therefore, a loss in adrenergic pathway (i.e., β-ARs internalization) could play an important role in the control/regulation of Wnt signaling function, affecting cognitive processes in HF (Fig. 2).

Conclusions

Considerable evidence exists that 15 to 70% of patients with chronic HF experience cognitive dysfunction, which is associated with difficulties in self-care and higher risks for hospitalization and mortality. Understanding age-related changes in cognition is important given the continuous growing of the elderly population and the importance of cognitive health for maintaining functional independence and effective communication with others. In general, systematic reviews and meta-analysis studies have confirmed a considerable proportion of HF patients suffering for cognitive decline but leave in evidence the urgent need of further and future research aimed to determine the underlying pathophysiology mechanisms. The mechanism of cognitive dysfunction in HF appears to be multifactorial, and several cardiac variables, laboratory parameters, and demographic and clinical elements should be taken into account during the evaluation process since all these elements can help in the identification of a potential risk profile for the development of cognitive impairment in HF.

Acknowledgments Figures were designed with elements provided by Servier Medical Art (https://smart.servier.com).

Funding Information This work was supported by the Fondo de Desarrollo Científico y Tecnológico (Fondecyt) (grant number 1180172), the Basal Center of Excellence in Aging and Regeneration (AFB 170005), and the special grant "Lithium in Health and Disease" from the Sociedad Química y Minera de Chile (SQM).

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

References

1. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, Nodari S, Lam CSP et al (2014) The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol 63(12):1123–1133. https://doi.org/10.1016/j.jacc.2013.11.053
2. Ponikowski P, Anker SD, AlHabib KF, Cowie MR, Force TL, Hu S, Jaarsma T, Krum H et al (2014) Heart failure: preventing disease and death worldwide. ESC Heart Fail 1(1):4–25. https://doi.org/10.1002/ehf2.12005
3. Mosterd A, Hoes AW (2007) Clinical epidemiology of heart failure. Heart 93(9):1137–1146. https://doi.org/10.1136/hrt.2003.025270

4. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S et al (2016) Heart disease and stroke statistics-2016 update: a report from the American Heart Association. Circulation 133(4):e38–e360. https://doi.org/10.1161/CIR.0000000000000350
5. Savarese G, Lund LH (2017) Global public health burden of heart failure. Cardiac Fail Rev 3(1):7–11. https://doi.org/10.15420/cfr.2016:25:2
6. Go YY, Allen JC, Chia SY, Sim LL, Jaufeerally FR, Yap J, Ching CK, Sim D et al (2014) Predictors of mortality in acute heart failure: interaction between diabetes and impaired left ventricular ejection fraction. Eur J Heart Fail 16(11):1183–1189. https://doi.org/10.1002/ejhf.119
7. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, Ikonomidis JS, Khavjou O et al (2013) Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail 6(3):606–619. https://doi.org/10.1161/HHF.0b013e318291329a
8. Leto L, Feola M (2014) Cognitive impairment in heart failure patients. J Geriatr Cardiol 11(4):316–328. https://doi.org/10.11909/j.issn.1671-5411.2014.04.007
9. Alagiakrishnan K, Mah D, Dyck JR, Senthilselvan A, Ezekowitz J (2017) Comparison of two commonly used clinical cognitive screening tests to diagnose mild cognitive impairment in heart failure with the golden standard European Consortium Criteria. Int J Cardiol 228:558–562. https://doi.org/10.1016/j.ijcard.2016.11.193
10. Cameron J, Gallagher R, Pressler SJ (2017) Detecting and managing cognitive impairment to improve engagement in heart failure self-care. Curr Heart Fail Rep 14(1):13–22. https://doi.org/10.1007/s11897-017-0317-0
11. Leto L, Feola M (2015) Cognitive impairment in heart failure patients: role of atrial fibrillation. J Geriatr Cardiol 12(6):690. https://doi.org/10.11909/j.issn.1671-5411.2015.06.011
12. Qiu C, Winblad B, Marengoni A, Klarin I, Fastbom J, Fratiglioni L (2006) Heart failure and risk of dementia and Alzheimer disease: a population-based cohort study. Arch Intern Med 166(9):1003–1008. https://doi.org/10.1001/archinte.166.9.1003
13. Tilvis RS, Kahonen-Vare MH, Jolkkonen J, Valvanne J, Pitkala KH, Strandberg TE (2004) Predictors of cognitive decline and mortality of aged people over a 10-year period. J Gerontol A Biol Sci Med Sci 59(3):268–274
14. Vogels RL, Scheltens P, Schroeder-Tanka JM, Weinstein HC (2007) Cognitive impairment in heart failure: a systematic review of the literature. Eur J Heart Fail 9(5):440–449. https://doi.org/10.1016/j.ejheart.2006.11.001
15. Mayou R, Blackwood R, Bryant B, Garnham J (1991) Cardiac failure: symptoms and functional status. J Psychosom Res 35(4-5):399–407
16. Dickson VV, Tkacs N, Riegel B (2007) Cognitive influences on self-care decision making in persons with heart failure. Am Heart J 154(3):424–431. https://doi.org/10.1016/j.ahj.2007.04.058
17. Wu JR, Moser DK, Lennie TA, Peden AR, Chen YC, Heo S (2008) Factors influencing medication adherence in patients with heart failure. Heart Lung 37(1):8–16, 16.e11. https://doi.org/10.1016/j.hrtlng.2007.02.003
18. Murad K, Goff DC Jr, Morgan TM, Burke GL, Bartz TM, Kizer JR, Chaudhry SI, Gottdiener JS et al (2015) Burden of comorbidities and functional and cognitive impairments in elderly patients at the initial diagnosis of heart failure and their impact on total mortality. Cardiovasc Health Study JACC Heart Fail 3(7):542–550. https://doi.org/10.1016/j.jchf.2015.03.004
19. Heckman GA, Patterson CJ, Demers C, St Onge J, Turpie ID, McKelvie RS (2007) Heart failure and cognitive impairment: challenges and opportunities. Clin Interv Aging 2(2):209–218
20. Oliveira BF, Nogueira-Machado JA, Chaves MM (2010) The role of oxidative stress in the aging process. TheScientificWorldJOURNAL 10:1121–1128. https://doi.org/10.1100/tsw.2010.94
21. Wei YH, Lee HC (2002) Oxidative stress, mitochondrial DNA mutation, and impairment of antioxidant enzymes in aging. Exp Biol Med (Maywood, NJ) 227(9):671–682
22. Duan MJ, Yan ML, Wang Q, Mao M, Su D, Sun LL, Li KX, Qu Y et al (2018) Overexpression of miR-1 in the heart attenuates hippocampal synaptic vesicle exocytosis by the posttranscriptional regulation of SNAP-25 through the transportation of exosomes. Cell Commun Signal 16(1):91. https://doi.org/10.1186/s12964-018-0303-5
23. Li A, Zhou C, Moore J, Zhang P, Tsai TH, Lee HC, Romano DM, McKee ML et al (2011) Changes in the expression of the Alzheimer's disease-associated presenilin gene in drosophila heart leads to cardiac dysfunction. Curr Alzheimer Res 8(3):313–322
24. Yancy Clyde W, Jessup M, Bozkurt B, Butler J, Casey Donald E, Colvin Monica M, Drazner Mark H, Filippatos Gerasimos S et al (2017) 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines and the Heart Failure Society of America. Circulation 136(6):e137–e161. https://doi.org/10.1161/CIR.0000000000000509
25. Cohn JN, Ferrari R, Sharpe N (2000) Cardiac remodeling–concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol 35(3):569–582
26. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Stromberg A, van Veldhuisen DJ et al (2008) ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the task force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur J Heart Fail 10(10):933–989. https://doi.org/10.1016/j.ejheart.2008.08.005
27. Oktay AA, Rich JD, Shah SJ (2013) The emerging epidemic of heart failure with preserved ejection fraction. Curre Heart Fail Rep 10(4):401–410. https://doi.org/10.1007/s11897-013-0155-7
28. Aguero-Torres H, Thomas VS, Winblad B, Fratiglioni L (2002) The impact of somatic and cognitive disorders on the functional status of the elderly. J Clin Epidemiol 55(10):1007–1012
29. Murman DL (2015) The impact of age on cognition. Semin Hear 36(03):111–121. https://doi.org/10.1055/s-0035-1555115
30. Cacciatore F, Abete P, Ferrara N, Calabrese C, Napoli C, Maggi S, Varricchio M, Rengo F (1998) Congestive heart failure and cognitive impairment in an older population. Osservatorio Geriatrico Campano Study Group. J Am Geriatr Soc 46(11):1343–1348
31. Frey A, Sell R, Homola GA, Malsch C, Kraft P, Gunreben I, Morbach C, Alkonyi B et al (2018) Cognitive deficits and related brain lesions in patients with chronic heart failure. JACC Heart Fail 6(7):583–592. https://doi.org/10.1016/j.jchf.2018.03.010
32. Borson S (2010) Cognition, aging, and disabilities: conceptual issues. Phys Med Rehabil Clin N Am 21(2):375–382. https://doi.org/10.1016/j.pmr.2010.01.001
33. Levin SN, Hajduk AM, McManus DD, Darling CE, Gurwitz JH, Spencer FA, Goldberg RJ, Saczynski JS (2014) Cognitive status in patients hospitalized with acute decompensated heart failure. Am Heart J 168(6):917–923. https://doi.org/10.1016/j.ahj.2014.08.008
34. Cline CM, Bjorck-Linne AK, Israelsson BY, Willenheimer RB, Erhardt LR (1999) Non-compliance and knowledge of prescribed

medication in elderly patients with heart failure. Eur J Heart Fail 1(2):145–149
35. Harkness K, Demers C, Heckman GA, McKelvie RS (2011) Screening for cognitive deficits using the Montreal cognitive assessment tool in outpatients >/=65 years of age with heart failure. Am J Cardiol 107(8):1203–1207. https://doi.org/10.1016/j.amjcard.2010.12.021
36. Bennett SJ, Sauve MJ, Shaw RM (2005) A conceptual model of cognitive deficits in chronic heart failure. J Nurs Scholarsh 37(3): 222–228
37. Premen AJ, Panel fNCAA (1996) Research recommendations for cardiovascular aging research. J Am Geriatr Soc 44(9):1114–1117. https://doi.org/10.1111/j.1532-5415.1996.tb02950.x
38. Zuccala G, Cattel C, Manes-Gravina E, Di Niro MG, Cocchi A, Bernabei R (1997) Left ventricular dysfunction: a clue to cognitive impairment in older patients with heart failure. J Neurol Neurosurg Psychiatry 63(4):509–512
39. Dodson JA, Truong TT, Towle VR, Kerins G, Chaudhry SI (2013) Cognitive impairment in older adults with heart failure: prevalence, documentation, and impact on outcomes. Am J Med 126(2):120–126. https://doi.org/10.1016/j.amjmed.2012.05.029
40. Cannon JA, Moffitt P, Perez-Moreno AC, Walters MR, Broomfield NM, McMurray JJV, Quinn TJ (2017) Cognitive impairment and heart failure: systematic review and meta-analysis. J Card Fail 23(6):464–475. https://doi.org/10.1016/j.cardfail.2017.04.007
41. Pressler SJ, Kim J, Riley P, Ronis DL, Gradus-Pizlo I (2010) Memory dysfunction, psychomotor slowing, and decreased executive function predict mortality in patients with heart failure and low ejection fraction. J Card Fail 16(9):750–760. https://doi.org/10.1016/j.cardfail.2010.04.007
42. Miller LA, Spitznagel MB, Alosco ML, Cohen RA, Raz N, Sweet LH, Colbert L, Josephson R et al (2012) Cognitive profiles in heart failure: a cluster analytic approach. J Clin Exp Neuropsychol 34(5):509–520. https://doi.org/10.1080/13803395.2012.663344
43. Bratzke-Bauer LC, Pozehl BJ, Paul SM, Johnson JK (2013) Neuropsychological patterns differ by type of left ventricle dysfunction in heart failure. Arch Clin Neuropsychol 28(2):114–124. https://doi.org/10.1093/arclin/acs101
44. Athilingam P, D'Aoust RF, Miller L, Chen L (2013) Cognitive profile in persons with systolic and diastolic heart failure. Congest Heart Fail (Greenwich, Conn) 19(1):44–50. https://doi.org/10.1111/chf.12001
45. Hammond CA, Blades NJ, Chaudhry SI, Dodson JA, Longstreth WT Jr, Heckbert SR, Psaty BM, Arnold AM et al (2018) Long-term cognitive decline after newly diagnosed heart failure: longitudinal analysis in the chs (Cardiovascular Health Study). Circ Heart Fail 11(3):e004476. https://doi.org/10.1161/circheartfailure.117.004476
46. Hajduk AM, Kiefe CI, Person SD, Gore JG, Saczynski JS (2013) Cognitive change in heart failure: a systematic review. Circ Cardiovasc Qual Outcomes 6(4):451–460. https://doi.org/10.1161/circoutcomes.113.000121
47. Hong X, Bu L, Wang Y, Xu J, Wu J, Huang Y, Liu J, Suo H et al (2013) Increases in the risk of cognitive impairment and alterations of cerebral beta-amyloid metabolism in mouse model of heart failure. PLoS One 8(5):e63829. https://doi.org/10.1371/journal.pone.0063829
48. Glisky EL (2007) Frontiers in Neuroscience Changes in Cognitive Function in Human Aging. In: Riddle DR (ed) Brain Aging: Models, Methods, and Mechanisms. CRC Press/Taylor & Francis Taylor & Francis Group, LLC., Boca Raton (FL)
49. Almeida OP, Garrido GJ, Beer C, Lautenschlager NT, Arnolda L, Flicker L (2012) Cognitive and brain changes associated with ischaemic heart disease and heart failure. Eur Heart J 33(14): 1769–1776. https://doi.org/10.1093/eurheartj/ehr467
50. Almeida OP, Garrido GJ, Etherton-Beer C, Lautenschlager NT, Arnolda L, Alfonso H, Flicker L (2013) Brain and mood changes over 2 years in healthy controls and adults with heart failure and ischaemic heart disease. Eur J Heart Fail 15(8):850–858. https://doi.org/10.1093/eurjhf/hft029
51. Gaviria M, Pliskin N, Kney A (2011) Cognitive impairment in patients with advanced heart failure and its implications on decision-making capacity. Congest Heart Fail (Greenwich, Conn) 17(4):175–179. https://doi.org/10.1111/j.1751-7133.2011.00242.x
52. Riegel B, Lee CS, Dickson VV, Carlson B (2009) An update on the self-care of heart failure index. J Cardiovasc Nurs 24(6):485–497. https://doi.org/10.1097/JCN.0b013e3181b4baa0
53. Cameron J, Ski CF, McLennan SN, Rendell PG, Whitbourn RJ, Thompson DR (2014) Development of the Heart Failure Screening Tool (Heart-FaST) to measure barriers that impede engagement in self-care. Eur J Cardiovasc Nurs 13(5):408–417. https://doi.org/10.1177/1474515113502461
54. Chaudhry SI, Wang Y, Gill TM, Krumholz HM (2010) Geriatric conditions and subsequent mortality in older patients with heart failure. J Am Coll Cardiol 55(4):309–316. https://doi.org/10.1016/j.jacc.2009.07.066
55. Sauve MJ, Lewis WR, Blankenbiller M, Rickabaugh B, Pressler SJ (2009) Cognitive impairments in chronic heart failure: a case controlled study. J Card Fail 15(1):1–10. https://doi.org/10.1016/j.cardfail.2008.08.007
56. Rozzini R, Sabatini T, Trabucchi M (2004) Cognitive impairment and mortality in elderly patients with heart failure. Am J Med 116(2):137–138. https://doi.org/10.1016/j.amjmed.2003.08.028
57. Zuccala G, Pedone C, Cesari M, Onder G, Pahor M, Marzetti E, Lo Monaco MR, Cocchi A et al (2003) The effects of cognitive impairment on mortality among hospitalized patients with heart failure. Am J Med 115(2):97–103
58. Bauer LC, Johnson JK, Pozehl BJ (2011) Cognition in heart failure: an overview of the concepts and their measures. J Am Acad Nurse Pract 23(11):577–585. https://doi.org/10.1111/j.1745-7599.2011.00668.x
59. Lepic T, Loncar G, Bozic B, Veljancic D, Labovic B, Krsmanovic Z, Lepic M, Raicevic R (2012) Cerebral blood flow in the chronic heart failure patients. Perspect Med 1(1):304–308. https://doi.org/10.1016/j.permed.2012.02.057
60. Roman GC (2004) Brain hypoperfusion: a critical factor in vascular dementia. Neurol Res 26(5):454–458. https://doi.org/10.1179/016164104225017686
61. Gruhn N, Larsen FS, Boesgaard S, Knudsen GM, Mortensen SA, Thomsen G, Aldershvile J (2001) Cerebral blood flow in patients with chronic heart failure before and after heart transplantation. Stroke 32(11):2530–2533
62. Iadecola C (2013) The pathobiology of vascular dementia. Neuron 80(4):844–866. https://doi.org/10.1016/j.neuron.2013.10.008
63. Zuccala G, Onder G, Pedone C, Carosella L, Pahor M, Bernabei R, Cocchi A (2001) Hypotension and cognitive impairment: selective association in patients with heart failure. Neurology 57(11): 1986–1992
64. Pullicino PM, Hart J (2001) Cognitive impairment in congestive heart failure?: embolism vs hypoperfusion. Neurology 57(11): 1945–1946
65. Gottesman RF, Grega MA, Bailey MM, Zeger SL, Baumgartner WA, McKhann GM, Selnes OA (2010) Association between hypotension, low ejection fraction and cognitive performance in cardiac patients. Behav Neurol 22(1-2):63–71. https://doi.org/10.3233/ben-2009-0261
66. Celutkiene J, Vaitkevicius A, Jakstiene S, Jatuzis D (2016) Expert opinion-cognitive decline in heart failure: more attention is needed. Cardiac Fail Rev 2(2):106–109. https://doi.org/10.15420/cfr.2016:19:2

67. Bangen KJ, Nation DA, Clark LR, Harmell AL, Wierenga CE, Dev SI, Delano-Wood L, Zlatar ZZ et al (2014) Interactive effects of vascular risk burden and advanced age on cerebral blood flow. Front Aging Neurosci 6:159. https://doi.org/10.3389/fnagi.2014.00159
68. Alosco ML, Spitznagel MB, Raz N, Cohen R, Sweet LH, Garcia S, Josephson R, van Dulmen M et al (2013) The interactive effects of cerebral perfusion and depression on cognitive function in older adults with heart failure. Psychosom Med 75(7):632–639. https://doi.org/10.1097/PSY.0b013e31829f91da
69. Madhavan M, Graff-Radford J, Piccini JP, Gersh BJ (2018) Cognitive dysfunction in atrial fibrillation. Nat Rev Cardiol 15(12):744–756. https://doi.org/10.1038/s41569-018-0075-z
70. de la Torre JC (2012) Cardiovascular risk factors promote brain hypoperfusion leading to cognitive decline and dementia. Cardiovasc Psychiatry Neurol 2012:367516. https://doi.org/10.1155/2012/367516
71. De Silva TM, Faraci FM (2016) Microvascular dysfunction and cognitive impairment. Cell Mol Neurobiol 36(2):241–258. https://doi.org/10.1007/s10571-015-0308-1
72. Ueno M, Sakamoto H, Tomimoto H, Akiguchi I, Onodera M, Huang CL, Kanenishi K (2004) Blood-brain barrier is impaired in the hippocampus of young adult spontaneously hypertensive rats. Acta Neuropathol 107(6):532–538. https://doi.org/10.1007/s00401-004-0845-z
73. Alves TC, Rays J, Fraguas R Jr, Wajngarten M, Meneghetti JC, Prando S, Busatto GF (2005) Localized cerebral blood flow reductions in patients with heart failure: a study using 99mTc-HMPAO SPECT. J Neuroimaging 15(2):150–156. https://doi.org/10.1177/1051228404272880
74. Choi BR, Kim JS, Yang YJ, Park KM, Lee CW, Kim YH, Hong MK, Song JK et al (2006) Factors associated with decreased cerebral blood flow in congestive heart failure secondary to idiopathic dilated cardiomyopathy. Am J Cardiol 97(9):1365–1369. https://doi.org/10.1016/j.amjcard.2005.11.059
75. Witt BJ, Gami AS, Ballman KV, Brown RD Jr, Meverden RA, Jacobsen SJ, Roger VL (2007) The incidence of ischemic stroke in chronic heart failure: a meta-analysis. J Cardiac Fail 13(6):489–496. https://doi.org/10.1016/j.cardfail.2007.01.009
76. Marcus NJ, Rio R, Schultz EP, Xia X-H, Schultz HD (2014) Carotid body denervation improves autonomic and cardiac function and attenuates disordered breathing in congestive heart failure. J Physiol 592(Pt 2):391–408. https://doi.org/10.1113/jphysiol.2013.266221
77. Del Rio R, Marcus NJ, Schultz HD (2013) Carotid chemoreceptor ablation improves survival in heart failure: rescuing autonomic control of cardiorespiratory function. J Am Coll Cardiol 62(25):2422–2430. https://doi.org/10.1016/j.jacc.2013.07.079
78. Toledo C, Andrade DC, Lucero C, Arce-Alvarez A, Díaz HS, Aliaga V, Schultz HD, Marcus NJ et al (2017) Cardiac diastolic and autonomic dysfunction are aggravated by central chemoreflex activation in HFpEF rats. J Physiol. https://doi.org/10.1113/JP273558
79. Florea VG, Cohn JN (2014) The autonomic nervous system and heart failure. Circ Res 114(11):1815–1826. https://doi.org/10.1161/circresaha.114.302589
80. Zucker IH (2006) Novel mechanisms of sympathetic regulation in chronic heart failure. Hypertension (Dallas, Tex : 1979) 48(6):1005–1011. https://doi.org/10.1161/01.hyp.0000246614.47231.25
81. Francis GS, Goldsmith SR, Levine TB, Olivari MT, Cohn JN (1984) The neurohumoral axis in congestive heart failure. Ann Intern Med 101(3):370–377
82. Kitzman DW, Little WC, Brubaker PH, Anderson RT, Hundley WG, Marburger CT, Brosnihan B, Morgan TM et al (2002) Pathophysiological characterization of isolated diastolic heart failure in comparison to systolic heart failure. JAMA 288(17):2144–2150
83. Inestrosa NC, Arenas E (2010) Emerging roles of Wnts in the adult nervous system. Nat Rev Neurosci 11(2):77–86. https://doi.org/10.1038/nrn2755
84. Woo MA, Macey PM, Fonarow GC, Hamilton MA, Harper RM (2003) Regional brain gray matter loss in heart failure. J Appl Physiol (Bethesda, Md : 1985) 95(2):677–684. https://doi.org/10.1152/japplphysiol.00101.2003
85. Femminella DG, Candido C, Conte M, Provenzano S, Rengo C, Coscioni E, Ferrara N (2016) Cognitive function and heart failure: the role of the adrenergic system. Recent Pat Endocr, Metab Immune Drug Discovery 10(1):40–49
86. Esler M, Lambert G, Brunner-La Rocca HP, Vaddadi G, Kaye D (2003) Sympathetic nerve activity and neurotransmitter release in humans: translation from pathophysiology into clinical practice. Acta Physiol Scand 177(3):275–284. https://doi.org/10.1046/j.1365-201X.2003.01089.x
87. Guyenet PG, Haselton JR, Sun MK (1989) Sympathoexcitatory neurons of the rostroventrolateral medulla and the origin of the sympathetic vasomotor tone. Prog Brain Res 81:105–116
88. Guyenet PG, Stornetta RL, Bochorishvili G, DePuy SD, Burke PGR, Abbott SBG (2013) C1 neurons: the body's EMTs. Am J Physiol Regul Integr Comp Physiol 305(3):R187–R204. https://doi.org/10.1152/ajpregu.00054.2013
89. Stormer VS, Passow S, Biesenack J, Li SC (2012) Dopaminergic and cholinergic modulations of visual-spatial attention and working memory: insights from molecular genetic research and implications for adult cognitive development. Dev Psychol 48(3):875–889. https://doi.org/10.1037/a0026198
90. Meel-van den Abeelen AS, Lagro J, Gommer ED, Reulen JP, Claassen JA (2013) Baroreflex function is reduced in Alzheimer's disease: a candidate biomarker? Neurobiol Aging 34(4):1170–1176. https://doi.org/10.1016/j.neurobiolaging.2012.10.010
91. Femminella GD, Rengo G, Komici K, Iacotucci P, Petraglia L, Pagano G, de Lucia C, Canonico V et al (2014) Autonomic dysfunction in Alzheimer's disease: tools for assessment and review of the literature. J Alzheimer's Dis 42(2):369–377. https://doi.org/10.3233/jad-140513
92. Zagon A, Totterdell S, Jones RS (1994) Direct projections from the ventrolateral medulla oblongata to the limbic forebrain: anterograde and retrograde tract-tracing studies in the rat. J Comp Neurol 340(4):445–468. https://doi.org/10.1002/cne.903400402
93. Westerhaus MJ, Loewy AD (2001) Central representation of the sympathetic nervous system in the cerebral cortex. Brain Res 903(1-2):117–127
94. Hagena H, Hansen N, Manahan-Vaughan D (2016) β-adrenergic control of hippocampal function: subserving the choreography of synaptic information storage and memory. Cereb Cortex (New York, NY : 1991) 26(4):1349–1364. https://doi.org/10.1093/cercor/bhv330
95. Gelinas JN, Tenorio G, Lemon N, Abel T, Nguyen PV (2008) Beta-adrenergic receptor activation during distinct patterns of stimulation critically modulates the PKA-dependence of LTP in the mouse hippocampus. Learn Mem (Cold Spring Harbor, NY) 15(5):281–289. https://doi.org/10.1101/lm.829208
96. Sara SJ (2009) The locus coeruleus and noradrenergic modulation of cognition. Nat Rev Neurosci 10(3):211–223. https://doi.org/10.1038/nrn2573
97. Mather M, Harley CW (2016) The locus coeruleus: essential for maintaining cognitive function and the aging brain. Trends Cogn Sci 20(3):214–226. https://doi.org/10.1016/j.tics.2016.01.001
98. Aston-Jones G, Cohen JD (2005) An integrative theory of locus coeruleus-norepinephrine function: adaptive gain and optimal

performance. Annu Rev Neurosci 28:403–450. https://doi.org/10.1146/annurev.neuro.28.061604.135709

99. Berridge CW, Waterhouse BD (2003) The locus coeruleus-noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. Brain Res Brain Res Rev 42(1):33–84
100. Kelly SC, He B, Perez SE, Ginsberg SD, Mufson EJ, Counts SE (2017) Locus coeruleus cellular and molecular pathology during the progression of Alzheimer's disease. Acta Neuropathol Commun 5(1):8. https://doi.org/10.1186/s40478-017-0411-2
101. Borson S, Barnes RF, Veith RC, Halter JB, Raskind MA (1989) Impaired sympathetic nervous system response to cognitive effort in early Alzheimer's disease. J Gerontol 44(1):M8–M12
102. Lawlor BA, Bierer LM, Ryan TM, Schmeidler J, Knott PJ, Williams LL, Mohs RC, Davis KL (1995) Plasma 3-methoxy-4-hydroxyphenylglycol (MHPG) and clinical symptoms in Alzheimer's disease. Biol Psychiatry 38(3):185–188. https://doi.org/10.1016/0006-3223(94)00259-6
103. Jett JD, Morilak DA (2013) Too much of a good thing: blocking noradrenergic facilitation in medial prefrontal cortex prevents the detrimental effects of chronic stress on cognition. Neuropsychopharmacology 38(4):585–595. https://doi.org/10.1038/npp.2012.216
104. Wang LY, Murphy RR, Hanscom B, Li G, Millard SP, Petrie EC, Galasko DR, Sikkema C et al (2013) Cerebrospinal fluid norepinephrine and cognition in subjects across the adult age span. Neurobiol Aging 34(10):2287–2292. https://doi.org/10.1016/j.neurobiolaging.2013.04.007
105. Abbott SB, Kanbar R, Bochorishvili G, Coates MB, Stornetta RL, Guyenet PG (2012) C1 neurons excite locus coeruleus and A5 noradrenergic neurons along with sympathetic outflow in rats. J Physiol 590(12):2897–2915. https://doi.org/10.1113/jphysiol.2012.232157
106. Holloway BB, Viar KE, Stornetta RL, Guyenet PG (2015) The retrotrapezoid nucleus stimulates breathing by releasing glutamate in adult conscious mice. Eur J Neurosci 42(6):2271–2282. https://doi.org/10.1111/ejn.12996
107. Sara SJ, Vankov A, Hervé A (1994) Locus coeruleus-evoked responses in behaving rats: A clue to the role of noradrenaline in memory. Brain Res Bull 35(5):457–465. https://doi.org/10.1016/0361-9230(94)90159-7
108. Schwarz LA, Luo L (2015) Organization of the locus coeruleus-norepinephrine system. Curr Biol 25(21):R1051–r1056. https://doi.org/10.1016/j.cub.2015.09.039
109. Hammerer D, Callaghan MF, Hopkins A, Kosciessa J, Betts M, Cardenas-Blanco A, Kanowski M, Weiskopf N et al (2018) Locus coeruleus integrity in old age is selectively related to memories linked with salient negative events. Proc Natl Acad Sci U S A 115(9):2228–2233. https://doi.org/10.1073/pnas.1712268115
110. Weinreich P, Seeman P (1981) Binding of adrenergic ligands ([3H]clonidine and [3H]WB-4101) to multiple sites in human brain. Biochem Pharmacol 30(22):3115–3120. https://doi.org/10.1016/0006-2952(81)90502-5
111. Impey S, Obrietan K, Storm DR (1999) Making new connections: role of ERK/MAP kinase signaling in neuronal plasticity. Neuron 23(1):11–14
112. Winder DG, Martin KC, Muzzio IA, Rohrer D, Chruscinski A, Kobilka B, Kandel ER (1999) ERK plays a regulatory role in induction of LTP by theta frequency stimulation and its modulation by beta-adrenergic receptors. Neuron 24(3):715–726
113. Hein L (2006) Adrenoceptors and signal transduction in neurons. Cell Tissue Res 326(2):541–551. https://doi.org/10.1007/s00441-006-0285-2
114. Daaka Y, Luttrell LM, Lefkowitz RJ (1997) Switching of the coupling of the beta2-adrenergic receptor to different G proteins by protein kinase A. Nature 390(6655):88–91. https://doi.org/10.1038/36362
115. Zamah AM, Delahunty M, Luttrell LM, Lefkowitz RJ (2002) Protein kinase A-mediated phosphorylation of the beta 2-adrenergic receptor regulates its coupling to Gs and Gi. Demonstration in a reconstituted system. J Biol Chem 277(34):31249–31256. https://doi.org/10.1074/jbc.M202753200
116. Gurevich VV, Gurevich EV (2006) The structural basis of arrestin-mediated regulation of G-protein-coupled receptors. Pharmacol Ther 110(3):465–502. https://doi.org/10.1016/j.pharmthera.2005.09.008
117. Lan T-H, Kuravi S, Lambert NA (2011) Internalization dissociates β2-adrenergic receptors. PLoS One 6(2):e17361–e17361. https://doi.org/10.1371/journal.pone.0017361
118. Rao NP, Danivas V, Venkatasubramanian G, Behere RV, Gangadhar BN (2010) Comorbid bipolar disorder and Usher syndrome. Prim Care Companion J Clin Psychiatry 12(2):PCC.09l00792. https://doi.org/10.4088/PCC.09l00792yel
119. O'Rourke MF, Iversen LJ, Lomasney JW, Bylund DB (1994) Species orthologs of the alpha-2A adrenergic receptor: the pharmacological properties of the bovine and rat receptors differ from the human and porcine receptors. J Pharmacol Exp Ther 271(2):735–740
120. Birnbaum S, Gobeske KT, Auerbach J, Taylor JR, Arnsten AF (1999) A role for norepinephrine in stress-induced cognitive deficits: alpha-1-adrenoceptor mediation in the prefrontal cortex. Biol Psychiatry 46(9):1266–1274
121. Dinh L, Nguyen T, Salgado H, Atzori M (2009) Norepinephrine homogeneously inhibits alpha-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate- (AMPAR-) mediated currents in all layers of the temporal cortex of the rat. Neurochem Res 34(11):1896–1906. https://doi.org/10.1007/s11064-009-9966-z
122. Gelinas JN, Nguyen PV (2005) Beta-adrenergic receptor activation facilitates induction of a protein synthesis-dependent late phase of long-term potentiation. J Neurosci 25(13):3294–3303. https://doi.org/10.1523/jneurosci.4175-04.2005
123. Yu JT, Wang ND, Ma T, Jiang H, Guan J, Tan L (2011) Roles of beta-adrenergic receptors in Alzheimer's disease: implications for novel therapeutics. Brain Res Bull 84(2):111–117. https://doi.org/10.1016/j.brainresbull.2010.11.004
124. Cahill L, McGaugh JL (1996) Modulation of memory storage. Curr Opin Neurobiol 6(2):237–242
125. Soumerai SB, McLaughlin TJ, Spiegelman D, Hertzmark E, Thibault G, Goldman L (1997) Adverse outcomes of underuse of beta-blockers in elderly survivors of acute myocardial infarction. JAMA 277(2):115–121
126. Luong K, Nguyen LT (2013) The role of Beta-adrenergic receptor blockers in Alzheimer's disease: potential genetic and cellular signaling mechanisms. Am J Alzheimers Dis Other Dement 28(5):427–439. https://doi.org/10.1177/1533317513488924
127. Shimohama S, Taniguchi T, Fujiwara M, Kameyama M (1987) Changes in beta-adrenergic receptor subtypes in Alzheimer-type dementia. J Neurochem 48(4):1215–1221
128. Oppenheim G, Mintzer J, Halperin Y, Eliakim R, Stessman J, Ebstein RP (1984) Acute desensitization of lymphocyte beta-adrenergic-stimulated adenylate cyclase in old age and Alzheimer's disease. Life Sci 35(17):1795–1802
129. Gliebus G, Lippa CF (2007) The influence of beta-blockers on delayed memory function in people with cognitive impairment. Am J Alzheimers Dis Other Dement 22(1):57–61. https://doi.org/10.1177/1533317506295889
130. Steinman MA, Zullo AR, Lee Y, Daiello LA, Boscardin WJ, Dore DD, Gan S, Fung K et al (2017) Association of beta-blockers with functional outcomes, death, and rehospitalization in older nursing home residents after acute myocardial infarction. JAMA Intern

Med 177(2):254–262. https://doi.org/10.1001/jamainternmed.2016.7701
131. Introini-Collison IB, Miyazaki B, McGaugh JL (1991) Involvement of the amygdala in the memory-enhancing effects of clenbuterol. Psychopharmacology 104(4):541–544
132. Hecht PM, Will MJ, Schachtman TR, Welby LM, Beversdorf DQ (2014) Beta-adrenergic antagonist effects on a novel cognitive flexibility task in rodents. Behav Brain Res 260:148–154. https://doi.org/10.1016/j.bbr.2013.11.041
133. Schutsky K, Ouyang M, Thomas SA (2011) Xamoterol impairs hippocampus-dependent emotional memory retrieval via Gi/o-coupled beta2-adrenergic signaling. Learn Mem (Cold Spring Harbor, NY) 18(9):598–604. https://doi.org/10.1101/lm.2302811
134. Mirbolooki MR, Constantinescu CC, Pan ML, Mukherjee J (2011) Quantitative assessment of brown adipose tissue metabolic activity and volume using 18F-FDG PET/CT and β3-adrenergic receptor activation. EJNMMI Res 1(1):30. https://doi.org/10.1186/2191-219x-1-30
135. Csányi G, Miller Jr FJ (2014) Oxidative stress in cardiovascular disease. Int J Mol Sci 15(4):6002-6008. https://doi.org/10.3390/ijms15046002
136. Hatanaka H, Hanyu H, Hirose D, Fukusawa R, Namioka N, Iwamoto T (2015) Peripheral oxidative stress markers in individuals with Alzheimer's disease with or without cerebrovascular disease. J Am Geriatr Soc 63(7):1472–1474. https://doi.org/10.1111/jgs.13549
137. Finkel T, Holbrook NJ (2000) Oxidants, oxidative stress and the biology of ageing. Nature 408(6809):239–247. https://doi.org/10.1038/35041687
138. Serrano F, Klann E (2004) Reactive oxygen species and synaptic plasticity in the aging hippocampus. Ageing Res Rev 3(4):431–443. https://doi.org/10.1016/j.arr.2004.05.002
139. Abd El Mohsen MM, Iravani MM, Spencer JP, Rose S, Fahim AT, Motawi TM, Ismail NA, Jenner P (2005) Age-associated changes in protein oxidation and proteasome activities in rat brain: modulation by antioxidants. Biochem Biophys Res Commun 336(2):386–391. https://doi.org/10.1016/j.bbrc.2005.07.201
140. Rodrigues Siqueira I, Fochesatto C, da Silva Torres IL, Dalmaz C, Alexandre Netto C (2005) Aging affects oxidative state in hippocampus, hypothalamus and adrenal glands of Wistar rats. Life Sci 78(3):271–278. https://doi.org/10.1016/j.lfs.2005.04.044
141. Zhu Y, Carvey PM, Ling Z (2006) Age-related changes in glutathione and glutathione-related enzymes in rat brain. Brain Res 1090(1):35–44. https://doi.org/10.1016/j.brainres.2006.03.063
142. Zhang C, Rodriguez C, Spaulding J, Aw TY, Feng J (2012) Age-dependent and tissue-related glutathione redox status in a mouse model of Alzheimer's disease. J Alzheimer's Dis 28(3):655–666. https://doi.org/10.3233/jad-2011-111244
143. Hajjar I, Hayek SS, Goldstein FC, Martin G, Jones DP, Quyyumi A (2018) Oxidative stress predicts cognitive decline with aging in healthy adults: an observational study. J Neuroinflammation 15(1):17. https://doi.org/10.1186/s12974-017-1026-z
144. Palomera-Avalos V, Grinan-Ferre C, Puigoriol-Ilamola D, Camins A, Sanfeliu C, Canudas AM, Pallas M (2017) Resveratrol protects SAMP8 brain under metabolic stress: focus on mitochondrial function and Wnt pathway. Mol Neurobiol 54(3):1661–1676. https://doi.org/10.1007/s12035-016-9770-0
145. Firoz CK, Jabir NR, Khan MS, Mahmoud M, Shakil S, Damanhouri GA, Zaidi SK, Tabrez S et al (2015) An overview on the correlation of neurological disorders with cardiovascular disease. Saudi J Biol Sci 22(1):19–23. https://doi.org/10.1016/j.sjbs.2014.09.003
146. Xu B, Li H (2015) Brain mechanisms of sympathetic activation in heart failure: Roles of the renin-angiotensin system, nitric oxide and pro-inflammatory cytokines (Review). Mol Med Rep 12(6):7823–7829. https://doi.org/10.3892/mmr.2015.4434
147. Lane RK, Hilsabeck T, Rea SL (2015) The role of mitochondrial dysfunction in age-related diseases. Biochim Biophys Acta 1847(11):1387–1400. https://doi.org/10.1016/j.bbabio.2015.05.021
148. Dai DF, Johnson SC, Villarin JJ, Chin MT, Nieves-Cintron M, Chen T, Marcinek DJ, Dorn GW 2nd et al (2011) Mitochondrial oxidative stress mediates angiotensin II-induced cardiac hypertrophy and Galphaq overexpression-induced heart failure. Circ Res 108(7):837–846. https://doi.org/10.1161/circresaha.110.232306
149. Foulquier S, Daskalopoulos EP, Lluri G, Hermans KCM, Deb A, Blankesteijn WM (2018) WNT signaling in cardiac and vascular disease. Pharmacol Rev 70(1):68–141. https://doi.org/10.1124/pr.117.013896
150. Anker SD, von Haehling S (2004) Inflammatory mediators in chronic heart failure: an overview. Heart (British Cardiac Society) 90(4):464–470. https://doi.org/10.1136/hrt.2002.007005
151. Adamski MG, Sternak M, Mohaissen T, Kaczor D, Wieronska JM, Malinowska M, Czaban I, Byk K et al (2018) Vascular cognitive impairment linked to brain endothelium inflammation in early stages of heart failure in mice. J Am Heart Assoc 7(7). https://doi.org/10.1161/jaha.117.007694
152. McColl BW, Rothwell NJ, Allan SM (2008) Systemic inflammation alters the kinetics of cerebrovascular tight junction disruption after experimental stroke in mice. J Neurosci 28(38):9451–9462. https://doi.org/10.1523/jneurosci.2674-08.2008
153. Kang Y-M, Gao F, Li H-H, Cardinale JP, Elks C, Zang W-J, Yu X-J, Xu Y-Y et al (2011) NF-κB in the paraventricular nucleus modulates neurotransmitters and contributes to sympathoexcitation in heart failure. Basic Res Cardiol 106(6):1087–1097. https://doi.org/10.1007/s00395-011-0215-7
154. Kang YM, Zhang ZH, Xue B, Weiss RM, Felder RB (2008) Inhibition of brain proinflammatory cytokine synthesis reduces hypothalamic excitation in rats with ischemia-induced heart failure. Am J Physiol Heart Circ Physiol 295(1):H227–H236. https://doi.org/10.1152/ajpheart.01157.2007
155. Khacho M, Clark A, Svoboda DS, MacLaurin JG, Lagace DC, Park DS, Slack RS (2017) Mitochondrial dysfunction underlies cognitive defects as a result of neural stem cell depletion and impaired neurogenesis. Hum Mol Genet 26(17):3327–3341. https://doi.org/10.1093/hmg/ddx217
156. Finsterer J (2012) Cognitive dysfunction in mitochondrial disorders. Acta Neurol Scand 126(1):1–11. https://doi.org/10.1111/j.1600-0404.2012.01649.x
157. Itoh K, Nakamura K, Iijima M, Sesaki H (2013) Mitochondrial dynamics in neurodegeneration. Trends Cell Biol 23(2):64–71. https://doi.org/10.1016/j.tcb.2012.10.006
158. Chauhan A, Vera J, Wolkenhauer O (2014) The systems biology of mitochondrial fission and fusion and implications for disease and aging. Biogerontology 15(1):1–12. https://doi.org/10.1007/s10522-013-9474-z
159. Golpich M, Amini E, Mohamed Z, Azman Ali R, Mohamed Ibrahim N, Ahmadiani A (2017) Mitochondrial dysfunction and biogenesis in neurodegenerative diseases: pathogenesis and treatment. CNS Neurosci Ther 23(1):5–22. https://doi.org/10.1111/cns.12655
160. Picard M, McEwen BS (2014) Mitochondria impact brain function and cognition. Proc Natl Acad Sci 111(1):7–8. https://doi.org/10.1073/pnas.1321881111
161. Giacomello M, Drago I, Pizzo P, Pozzan T (2007) Mitochondrial Ca2+ as a key regulator of cell life and death. Cell Death Differ 14(7):1267–1274. https://doi.org/10.1038/sj.cdd.4402147
162. Herring BE, Nicoll RA (2016) Long-term potentiation: from camkii to ampa receptor trafficking. Annu Rev Physiol 78:351–365. https://doi.org/10.1146/annurev-physiol-021014-071753
163. Wang H, Zhang H, Wong YH, Voolstra C, Ravasi T, V BB, Qian PY (2010) Rapid transcriptome and proteome profiling of a non-model marine invertebrate, Bugula neritina. Proteomics 10(16):2972–2981. https://doi.org/10.1002/pmic.201000056

164. Cerpa W, Gambrill A, Inestrosa NC, Barria A (2011) Regulation of NMDA-receptor synaptic transmission by Wnt signaling. J Neurosci 31(26):9466–9471. https://doi.org/10.1523/JNEUROSCI.6311-10.2011
165. Oliva CA, Montecinos-Oliva C, Inestrosa NC (2018) Wnt signaling in the central nervous system: new insights in health and disease. Prog Mol Biol Transl Sci 153:81–130. https://doi.org/10.1016/bs.pmbts.2017.11.018
166. Gillers BS, Chiplunkar A, Aly H, Valenta T, Basler K, Christoffels VM, Efimov IR, Boukens BJ et al (2015) Canonical wnt signaling regulates atrioventricular junction programming and electrophysiological properties. Circ Res 116(3):398–406. https://doi.org/10.1161/circresaha.116.304731
167. Malekar P, Hagenmueller M, Anyanwu A, Buss S, Streit MR, Weiss CS, Wolf D, Riffel J et al (2010) Wnt signaling is critical for maladaptive cardiac hypertrophy and accelerates myocardial remodeling. Hypertension (Dallas, Tex : 1979) 55(4):939–945. https://doi.org/10.1161/hypertensionaha.109.141127
168. Cermakova P, Eriksdotter M, Lund LH, Winblad B, Religa P, Religa D (2015) Heart failure and Alzheimer's disease. J Intern Med 277(4):406–425. https://doi.org/10.1111/joim.12287
169. Price DL, Sisodia SS, Borchelt DR (1998) Alzheimer disease — when and why? Nat Genet 19:314. https://doi.org/10.1038/1196
170. Taurin S, Sandbo N, Qin Y, Browning D, Dulin NO (2006) Phosphorylation of beta-catenin by cyclic AMP-dependent protein kinase. J Biol Chem 281(15):9971–9976. https://doi.org/10.1074/jbc.M508778200
171. Verheyen EM, Gottardi CJ (2010) Regulation of Wnt/beta-catenin signaling by protein kinases. Dev Dyn 239(1):34–44. https://doi.org/10.1002/dvdy.22019
172. Hino S, Tanji C, Nakayama KI, Kikuchi A (2005) Phosphorylation of beta-catenin by cyclic AMP-dependent protein kinase stabilizes beta-catenin through inhibition of its ubiquitination. Mol Cell Biol 25(20):9063–9072. https://doi.org/10.1128/mcb.25.20.9063-9072.2005
173. Fang X, Yu SX, Lu Y, Bast RC Jr, Woodgett JR, Mills GB (2000) Phosphorylation and inactivation of glycogen synthase kinase 3 by protein kinase A. Proc Natl Acad Sci U S A 97(22):11960–11965. https://doi.org/10.1073/pnas.220413597