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Dual-therapy strategy for modification of adiponectin receptor signaling in aging-associated chronic diseases

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Abstract

Given the paradigm of anti-insulin resistance in therapies for metabolic syndrome, there has been considerable interest in adiponectin (APN), an adipocyte-derived sensitizer of insulin receptor signaling. In contrast to hypoadiponectinemia in metabolic syndrome, evidence suggests that Alzheimer's disease (AD) and other diseases, including chronic heart failure (CHF) and chronic kidney disease (CKD), are characterized by hyperadiponectinemia as well as the APN/obesity paradoxes, indicating that a decrease in APN might also be beneficial for these diseases. Thus, distinct from metabolic syndrome, it is anticipated that APN receptor antagonists rather than agonists might be effective in therapy for some chronic diseases.

Introduction

The increasing prevalence of aging-related disorders, including neurodegeneration, cardiovascular disease (CVD), sarcopenia, osteoporosis, and immunological disorders, is associated with expansion of the older population worldwide [1]. Given that metabolic disorders, such as type 2 diabetes mellitus (T2DM), are linked to these diseases, anti-insulin resistance has become a paradigm of therapy [1]. This is particularly important for aging-associated neurodegenerative diseases, including AD and Parkinson's disease (PD), for which no therapies are available [2]. Insulin, glucagon like peptide-1 receptor agonists, and inhibitors of dipeptidyl peptidase 4 have been studied [3–5] with promising results in small-scale trials [3,4], but the results require validation in larger clinical studies.

APN is a multifunctional adipocytokine that is also referred to as GBP-28, apM1, AdipoQ, and Acrp30 [6]. It is produced predominantly in adipose tissues, in which it is synthesized

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as a 28-kDa monomer, followed by post-translational modifications, such as glycosylation and oligomerization, to different molecular weight multimers [6–8]. APN is involved in diverse biological processes, including sensitization of the insulin receptor signaling pathway, suppression of inflammation, and stimulation of mitochondria biogenesis [6]. At the cellular level, the effects of APN are mediated through activation of transmembrane receptors, AdipoR1 and -R2, and their downstream signaling pathways. In the nervous system, this signaling is mediated by molecules such as AMP-activated protein kinase and peroxisome proliferator-activated receptor γ, which have essential roles in insulin sensitivity and oxidative metabolism, whereas other kinases, such as p38 MAP kinase and GSK-3β, are involved in neurogenesis and suppression of neurodegeneration [6,8].

It is well characterized that APN is beneficial for metabolic syndrome and related diseases. Similarly, it is generally believed that APN might be protective in other types of disease, including cardiovascular and neurodegenerative diseases [9]. However, accumulating evidence suggests that APN is not simply a protective molecule. Indeed, APN might exacerbate various chronic diseases in advanced stages, including CHF and CKD [8,10]. Furthermore, a recent prospective cohort study showed that hyperadiponectinemia was correlated with cognitive deficits and amyloid deposits in older patients, suggesting that APN is a risk factor for AD [11]. In this context, here we discuss the role of altered serum APN levels in some chronic diseases and propose a novel therapy strategy using antagonists of APR receptors for such disorders, which is distinct from the current strategy using APN agonists for the therapy of metabolic syndrome.

Hypoadiponectinemia in metabolic syndrome

APN belongs structurally to the complement 1q family and is found at high concentrations (>0.01% of total protein) in the serum of healthy individuals [6]. Given the abundance of APN in plasma, it is assumed that alterations in plasma levels of APN might affect various aspects of health and disease. Indeed, hypoadiponectinemia is observed in metabolic disorders, such as T2DM, obesity, dyslipidemia, hypertension, and atherosclerosis, and is inversely correlated with the severity of the disease (Fig. 1) [6]. In addition, hypoadiponectinemia is associated with risks of obesity-linked diseases, including osteoporosis, depression, hyperuricemia, sleep apnea, and visceral diseases, such as nonalcoholic fatty liver disease, gastritis/gastroesophageal reflux disease, inflammatory bowel disease, and pancreatitis (Fig. 1) [10]. Hypoadiponectinemia has also been found in endometrial cancer, postmenopausal breast cancer, and leukemia, colon, gastric, and prostate cancers (Fig. 1), and APN might have antimetabolic, antiangiogenesis, and antitumor activities in cancers [6,11]. Moreover, in osteoporosis, which is common in postmenopausal women, hypoadiponectinemia might contribute to the activation of osteoclasts and suppression of osteoblasts and osteocytes [12,13]. Finally, psychiatric diseases, such as depression and post-traumatic stress disorder, are also associated with hypoadiponectinemia [14,15]. Obesity is linked to these diseases, but not to hypoadiponectinemia, which suggests that obesity is not be the cause of hypoadiponectinemia in patients with psychiatric diseases.

Given that APN signaling is required for the activity of the insulin receptor signaling pathway [6], it naturally follows that loss of APN function might contribute to insulin

resistance, leading to metabolic disorders. Hypoadiponectinemia is likely to be the result of the decreased production and secretion of APN in adipose tissue, and expression of APN mRNA in adipocytes might be affected by polymorphisms in the gene encoding APN [6] and by cadherin 13 genotypes [16]. Alternatively, expression of APN in adipocytes might be suppressed by environmental factors and lifestyle patterns, such as a high-fat diet and lack of exercise [6]. Expression of APN in adipocytes might also be decreased under hypoxic conditions induced by obesity [17]. Hypoxia might also activate macrophages to produce inflammatory cytokines, such as TNFα and IL-6, which could inhibit the local production of APN in adipose tissue [18]. Moreover, there are marked gender differences in the distribution of APN [19], with women having higher circulating levels of high-molecular-weight isoforms, because of the effect of steroid hormones [19].

Hyperadiponectinemia in a healthy state

Given that APN can ameliorate metabolic syndrome and related disorders, increased levels of plasma APN might be beneficial for health and longevity. Consistent with this view, hyperadiponectinemia has been found in disease prevention during aging [20]. Specifically, centenarians, a model of healthy aging [21], have few cardiovascular risk factors and a low prevalence of diabetes mellitus, carotid atherosclerotic plaques, and dementia, which could be associated with high levels of circulating APN (Fig. 1) [9]. Notably, APN activated PGC-1α and mitochondria by Ca^{2+} and AMPK/SIRT1, indicating that APN might be involved in the regulation of mitochondria-related longevity [9]. Thus, it is likely that APN might be beneficial for aging-related diseases. Curiously, it has also been shown that paradoxical hyperadiponectinemia is associated with a metabolically healthy obese phenotype in African-Americans with high high-density lipoprotein cholesterol, and low insulin, triglyceride, and glucose (Fig. 1) [22]. Furthermore, a recent study found hyperadiponectinemia during therapy for pediatric Crohn's disease [23], indicating that hyperadiponectinemia might cure inflammation in Crohn's disease (Fig. 1). Taken together, these findings suggest, but do not prove, that hyperadiponectinemia could counteract obesity and contribute to health, leading to a prolonged life span.

Hyperadiponectinemia in disease conditions

Other evidence indicates that hyperadiponectinemia does not necessarily always imply a healthy outcome. Indeed, a recent study suggested that hyperadiponectinemia occurs in various diseases. Given that the risk for AD and vascular dementia is increased in metabolic dysfunction, plasma levels of APN might be reduced in AD. However, several studies have described increased levels of plasma APN in AD (Fig. 1) [8,24]. In particular, the Framingham Heart Study in a prospective cohort (N = 840, mean age 72 years) showed that elevated APN was a predictor for all-cause dementia and AD [24]. Furthermore, the Mayo Clinic Study of Aging in a large prospective cohort (N = 535, age ≥70 years without dementia) showed that levels of plasma APN were elevated, accompanied by amyloid deposits and cognitive deficits [25]. Studies of autopsied brains from patients with AD were consistent with these reports, because it was found that expression of APN was upregulated and associated with accumulation in neurofibrillary tangles in the AD brain (Fig. 2a) [26]. Collectively, these results suggest that APN is a risk factor for AD. Notably,

hyperadiponectinemia has similarly, but inconsistently, been described for patients with PD. In support of this possibility, it was found that APN accumulates in Lewy bodies of brains from patients with α-synucleinopathies, such as PD and dementia with Lewy bodies (DLB) (Fig. 2c) [27].

Similarly, circulating APN levels are increased in proportion to the disease severity of CHF and might be centrally involved in CHF-associated metabolic failure and muscle wasting [28]. Likewise, end-stage CKD, such as polycystic kidney and renal cell carcinoma, is characterized by increased cardiovascular risk associated with hyperadiponectinemia. Therefore, common mechanisms might underlie hyperadiponectinemia in CHF and CKD because cardiovascular complications remain the main cause of mortality in the CKD population [29]. In addition, chronic obstructive pulmonary disease (COPD) is characterized by cachexia and increased mortality because of respiratory failure, which is associated with elevated levels of circulating APN [30].

Hyperadiponectinemia might also associate with chronic autoimmune diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [31]. In addition, hyperadiponectinemia has been implicated in a variety of diseases, including type I diabetes mellitus (T1DM), cystic fibrosis, anorexia nervosa, and hepatocellular carcinoma [31–33].

Potential mechanism of hyperadiponectinemia

One could predict that multiple mechanisms might contribute to hyperadiponectinemia. First, plasma APN might be upregulated because of decreased expression and/or decreased activity of APN receptor signaling; namely, APN resistance. Similar to insulin and leptin resistances, APN resistance might be caused by various mechanisms, including dysregulation of signal transduction, endoplasmic reticulum (ER) stress, and inflammation, and reduced expression of receptors AdipoR1 and -R2 [8]. Second, upregulation of plasma APN might reflect compensatory feedback in response to reduced activity of insulin/IGF-1 receptor signaling pathways, given that the network of these pathways is crucial in various biological systems, including the nervous and cardiovascular systems [8]. Third, based on the previous observation that APN accumulated in cytoplasmic inclusion bodies, including neurofibrillary tangles [26] and Lewy bodies [27], it is probable that hyperadiponectinemia is partially attributable to impairment of degradation systems, such as ubiquitin proteasomes and autophagy. Fourth, it is possible that some genetic factors, including single nucleotide polymorphisms, might contribute to the high expression of APN. Finally, APN might be ectopically produced. In support of this notion, production of APN was shown in extra-adipose tissue, such as osteoblast and vascular smooth muscle cells [34,35]. Thus, further studies are warranted to address this critical issue. In particular, APN receptor signaling has not been examined in terms of pathologies such as cardiovascular dysfunction and neurodegeneration.

The disease-stimulatory effects of hyperadiponectinemia in patients contradict a previous view based on studies of preclinical models showing that APN might be beneficial for AD [8]. Indeed, despite the action of APN as a risk factor in patients with AD, APN is protective against oxidative stress-induced cytotoxicity in Aβ neurotoxicity associated with

the Swedish mutation of amyloid precursor protein (APP) (Fig. 2b) [34]. Furthermore, osmotin, a plant homolog of APN, attenuates Aβ42-induced neurotoxicity and tau hyperphosphorylation in the mouse hippocampus [37], and APN-knockout mice develop an AD-like pathology during aging, suggesting that loss of APN function leads to AD [35]. Thus, the widening gap between findings in preclinical models of APN and those from clinical observations in patients with neurodegenerative diseases result in the so-called ‘APN paradox’ [39]. Similarly, APN was shown to ameliorate neuropathological features, such as protein aggregation and impaired motor activity, in a mouse model of α-synucleinopathies (Fig. 2d) [27]. The relationship between APN and AD is clearly not fully established, and further studies are needed to determine whether this might also be the case for PD.

The APN paradox has already been recognized in various chronic wasting disorders. Although APN is protective for cardiomyocyte and vascular cell function [40], and is antiatherogenic in animal models [41], hyperadiponectinemia is correlated with the severity of circulatory diseases, such as CHF and CKD [28,29]. Furthermore, the APN paradox might also be involved in COPD. Despite the protective effect of APN on bronchial epithelial cells [42], hyperadiponectinemia is associated with COPD [30]. Further studies are warranted to determine whether the APN paradox is involved in other diseases with hyperadiponectinemia.

The mechanism by which high levels of APN impair the normal functions of the cells is unclear. Although many studies support the beneficial effects of APN on metabolic syndrome, some have demonstrated proinflammatory and proapoptotic actions of APN [31,43]. Therefore, we speculate that similar mechanisms might be involved in the impairment of cell function by APN, underlying the APN paradox.

Indeed, the discrepancy between findings from preclinical models and those from clinical observations is central to various aspects of disease biology, including that of neurodegenerative disease [44]. To the best of our knowledge, the APN paradox has been observed in patients, but not in animal models. Hypothetically, the late stages of various chronic disorders might behave in different ways in patients and experimental animals, especially given the extended postreproductive aging period in humans compared with animals [45]. In addition, a mutually nonexclusive possibility is that late-stage chronic diseases become prolonged in humans by virtue of sustained medical care in the absence of radical treatments to cure such conditions. Thus, late-stage chronic disease might exhibit a distinct human-specific pathology.

The obesity paradox and some chronic disease

An ‘obesity paradox’ or ‘reverse epidemiology’ of cardiovascular risk has also been observed in cancer, AIDS, and RA, in addition to the disorders with an APN paradox (CHF, CKD, and COPD), in which morbidity and mortality in the end stage are mitigated in obese patients [46,47]. It predictably follows that AD might also be associated with the obesity paradox. In support, a retrospective cohort study from the United Kingdom Clinical Practice Research Datalink recently showed that obesity exerts a protective effect on dementia [48]. Interestingly, the obesity paradox has also been observed in metabolic disorders, such as

T2DM, hypertension, and CVD [49–51]. Given that serum levels of APN are decreased in obesity, it is predicted that the toxicity of APN might also be reduced. Thus, the APN paradox and the obesity paradox conceptually overlap to a significant degree. Thus, because the obesity paradox is observed in many disease types, the overlap between these two paradoxical phenomena could be a common feature of advanced stages of chronic disorders.

A novel therapeutic strategy based on the APN and obesity paradoxes

As shown above, the relationship of the serum APN concentration with health and disease states shows an inverted-U correlation, suggesting that moderate concentrations of serum APN are beneficial (Fig. 3). Given that both hypo- and hyperadiponectinemia might promote chronic disease states, both should be targeted therapeutically.

Given that loss of function of APN might associate with metabolic syndrome, stimulating the APN receptor using an agonist could be effective for disease prevention (Fig. 3). Indeed, a small-molecule APN receptor agonist, adipoRon, has been shown to be beneficial in animal models of T2DM and obesity [53]. By contrast, hyperadiponectinemia might be a risk factor of AD and other chronic diseases, in which APN gain of function could be mitigated by suppression of APN receptor signaling (Fig. 3). Based on a previous report showing that serum APN was increased in both AD and mild cognitive impairment, a prodromal stage of AD [54], it is assumed that APN receptor antagonists might be initiated from the early stage of the disease. Collectively, the differential use of APN receptor agonists and antagonists depending on the types of disease might be important.

Notably, there are few reports on APN receptor antagonists compared with the extensive studies on agonists. However, recent advances in computer modeling software (e.g., docking methods) should allow easier identification of APN receptor antagonists for clinical application [55,56]. In this context, molecular docking methods have recently been applied for G-protein-coupled receptors (GPCRs) [57]. Given that adipo-R1 and -R2 are GPCRs [58], antagonists of APN receptors should be identifiable without difficulty.

Given that serum APN levels are expected to shift from hypo- to hyperadiponectinemia during disease progression, serum APN might also be a promising disease biomarker. Many studies are underway to identify and use biomarkers for diagnosis and assessment of therapeutic effects in AD. These include a variety of neuroimaging candidate markers, such as hippocampus and entorhinal cortex volumes, basal forebrain nuclei, cortical thickness, deformation-based and voxel-based morphometry, and structural and effective connectivity [59]. Cerebrospinal fluid (CSF) might also be promising as a source of biomarkers, such as Aβ42, BACE1, and total-/phospho-tau [59]. However, there are still no good candidates identified in blood and, thus, APN might be an attractive target in this respect.

Conceivably, therapeutic compounds based on the APN paradox might not only be effective for aging-associated chronic disorders, but also for other conditions, especially for cancers. For instance, it is generally believed that metabolic syndrome is a risk factor for obesity-liked cancers [60]. By contrast, it is firmly established that hormonal alterations, such as hyperinsulinism and elevated insulin-like growth factor levels, are associated with breast

cancer [60]. Furthermore, increased APN might contribute to hepatocellular carcinoma at least in part through its activation of AKT signaling [33]. Given that APN sensitizes the insulin receptor signaling pathway associated with activation of AKT signaling, it is intriguing to consider that a similar dual strategy of APN receptor stimulation and inhibition can be applied to malignancies.

However, for balance, our proposed therapeutic strategy might also have several disadvantages. Most notably, any form of APN antagonist therapy must 'trade off' any derived benefits against the protective effects of APN on other cell types. Thus, APN signaling blockade might instead promote metabolic dysfunction and cancer. Second, current preclinical disease paradigms might be incomplete because they have not reproduced the APN paradox. Lastly, the simplest of APN biological interactions in AD are still poorly understood, especially the differential roles of APN oligomers and of the heterogeneous APN receptors, Adipo-R1 and -R2, in addition to T-cadherin on the cell membrane [58,61].

Concluding remarks

Following the disappointing outcomes of Aβ immunotherapy trials for AD [62], the current prevailing concept is that disease-modifying therapy must be initiated from the presymptomatic stage of the disease because of the presumed incurability of chronic diseases once they become symptomatic [63]. Regardless, treatment should ideally be as aggressively as possible even in the advanced stage. In this context, we propose a novel concept of APN-related therapy, in which antagonist-driven inhibition of the APN receptor signaling pathway might further ameliorate disease pathology and symptoms (Fig. 3). Hopefully, therapeutic outcomes could be monitored and directed by measuring serum APN as a biomarker. This is important because no good biomarkers are presently available for assessment of therapeutic effects in AD. Furthermore, a similar dual strategy of stimulation and inhibition of the APN receptor might also be of benefit for the treatment of cancer and other chronic diseases that involve the obesity paradox. However, the benefit-risk 'trade-offs' with other diseases, the absence of good preclinical disease models of the APN paradox, and the lack of a fundamental understanding of APN activity under pathological conditions remain challenges in APN-based dual therapy. Further investigations are required to obtain a better understanding of the pathological roles of APN signaling in chronic disorders, such as AD, CHF and CKD, toward fulfilling the promise of APN-related drug discovery.

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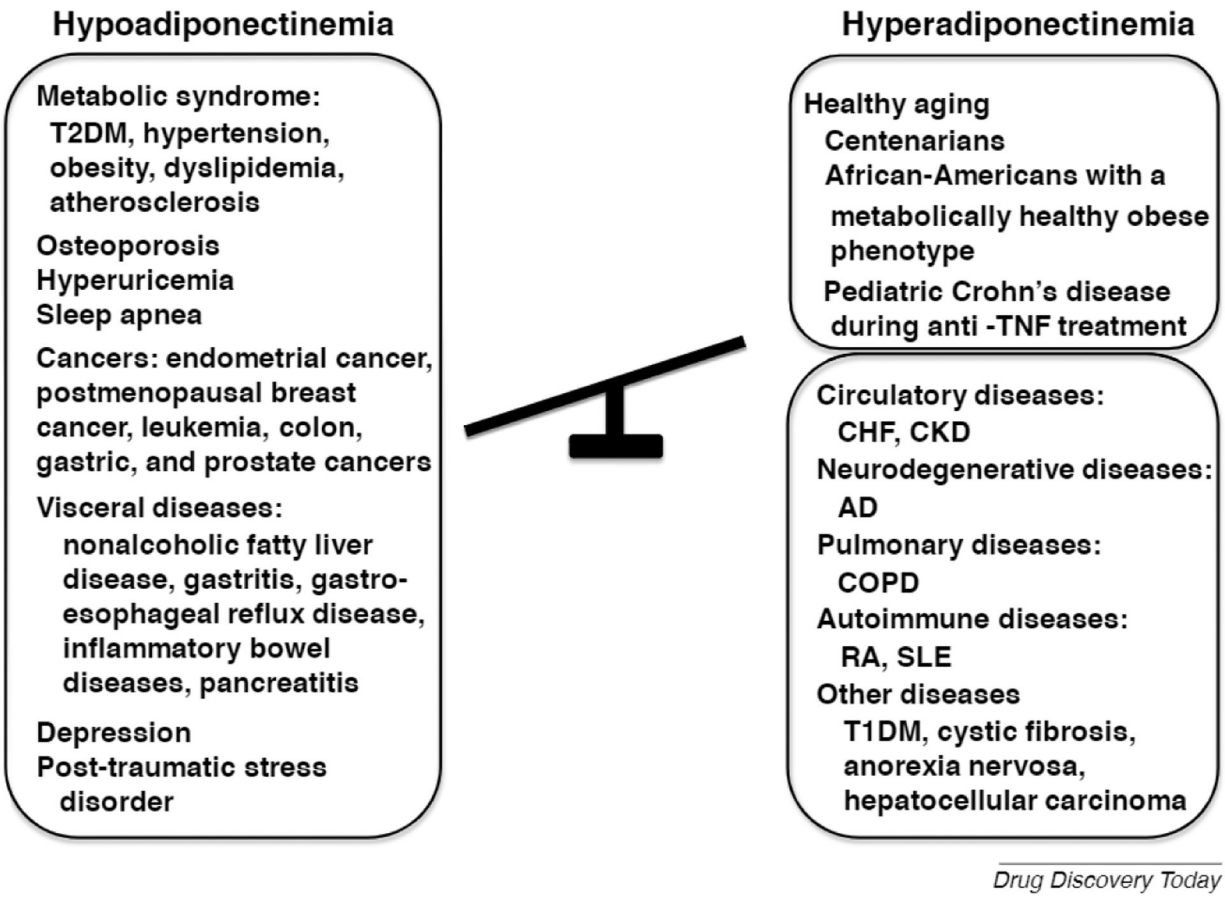

FIGURE 1.

Alteration of plasma adiponectin (APN) in healthy and diseased conditions. Hypoadiponectinemia is associated with metabolic disorders, such as type 2 diabetes mellitus (T2DM), hypertension, obesity, dyslipidemia and atherosclerosis; obesity-related disorders, including cancer, osteoporosis, hyperuricemia, sleep apnea; and visceral diseases, such as nonalcoholic fatty liver disease, gastritis and gastroesophageal reflux disease, inflammatory bowel diseases, and pancreatitis. Hypoadiponectinemia is also observed in psychiatric diseases, such as depression and post-traumatic stress disorder. By contrast, hyperadiponectinemia occurs in healthy people, including centenarians and African-Americans with a metabolically healthy obese phenotype, and during therapy for Crohn's disease. However, hyperadiponectinemia is also identified in disease conditions, such as circulatory diseases, including chronic heart failure (CHF) and chronic kidney disease (CKD); neurodegenerative diseases, such as Alzheimer's disease (AD); and pulmonary diseases, such as chronic obstructive pulmonary disease (COPD), autoimmune diseases; rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), and other diseases, including type 1 diabetes mellitus (T1DM), cystic fibrosis, anorexia nervosa, and hepatocellular carcinoma.

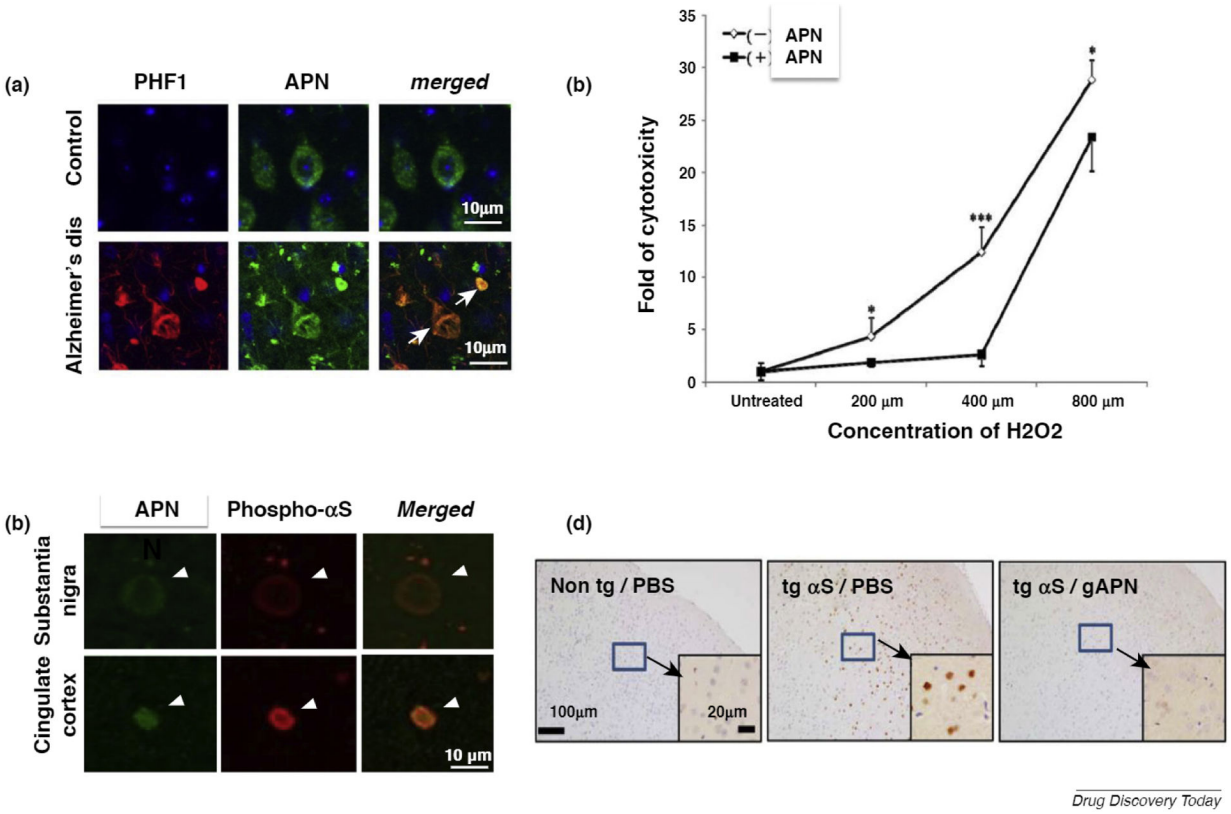

FIGURE 2.

Adiponectin (APN) paradox in Alzheimer's disease (AD), (a) Immunofluorescence of APN and tau. In autopsied AD brains, but not in controls, immunoreactivity of APN converged intracellularly with that of tau (PHF). (b) By contrast, a cellular study showed that APN was protective against oxidative stress-induced cytotoxicity in Aβ neurotoxicity in SH-SY5Y neuroblastoma cells expressing the Swedish mutant of amyloid precursor protein (APP). (c) Immunofluorescence of APN and phosphor-αS. In autopsied brains from patients with dementia with Lewy bodies (DLB), immunoreactivity of APN converged with that of phosphor αS in Lewy bodies, (d) Representative immunohistochemical images of the cortex stained with anti-pαS. αS transgenic mice and their nontransgenic littermates were treated with globular APN or PBS for 3 months, followed by various assessments. Insets are shown at a higher magnification for the cortex. Reproduced from Refs [26] (a), [36] (b), and [27] (c,d).

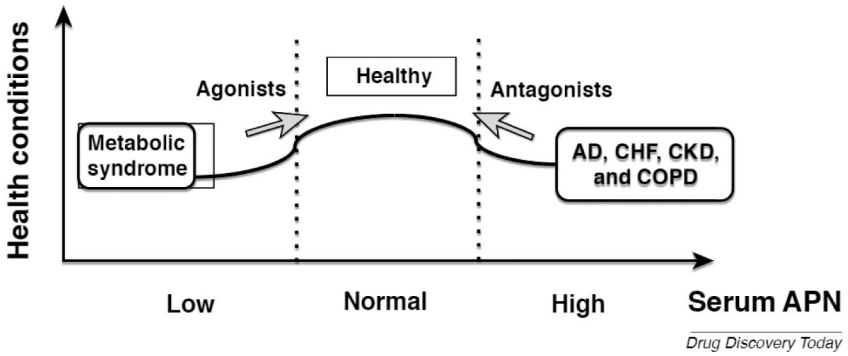

FIGURE 3.

A therapeutic strategy based on disease-specific adiponectin (APN) actions. Metabolic syndrome, such as obesity and type 2 diabetes mellitus (T2DM), are featured with hypoadiponectinemia. In this context, agonists of APN receptors have been considered for the therapy of the metabolic disorders. However, various chronic diseases, including Alzheimer's disease (AD), chronic heart failure (CHF), chronic kidney disease (CKD), and chronic obstructive pulmonary disease (COPD), are associated with hyperadiponectinemia and the APN and obesity paradoxes. Therefore, antagonism of the APN receptor signaling pathway could be effective for therapeutic purposes. Arrows indicate the therapeutic strategy using either agonists or antagonists.