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Age-related diseases as vicious cycles

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ABSTRACT

The mortality rates of age-related diseases (ARDs) increase exponentially with age. Processes described by the exponential growth function typically involve a branching chain reaction or, more generally, a positive feedback loop. Here I propose that each ARD is mediated by one or several positive feedback loops (vicious cycles). I then identify critical vicious cycles in five major ARDs: atherosclerosis, hypertension, diabetes, Alzheimer's and Parkinson's. I also propose that the progression of ARDs can be halted by selectively interrupting the vicious cycles and suggest the most promising targets.

1. Introduction

Nationwide mortality and disease incidence statistics are perhaps the most powerful and least biased datasets on human diseases that we currently have. These data are derived from humans living in the complex environment and developing diseases naturally, and not from distantly related animals contained in laboratory conditions under disease-inducing regimens. Whilst clinical studies share the same advantages, the number of human subjects is orders of magnitude lower, and a bias related to study design is always present.

By studying the incidence statistics of 20 most prevalent cancer types in relation to patients' age, I have previously shown that it closely follows the probability density function of the Erlang distribution (Belikov, 2017). The Erlang distribution describes the probability of several independent random events occurring by the given time, but not earlier or later. This fits well with the widely accepted multiple-hit hypothesis of carcinogenesis, which states that cancers arise after several successive events (Armitage and Doll, 2004). Whilst no consensus has been reached on the nature of these events, driver mutations are the most probable candidate. Such mutations confer the growth advantage, apoptosis resistance or other oncogenic properties to the cell, as opposed to inconsequential passenger mutations (Pon and Marra, 2015). Overall, these results suggest that cancer is essentially the result of several random events and not a true gradually developing ARD. Moreover, the decrease in cancer incidence after particular age (Harding et al., 2012) and the existence of cancers that appear only in childhood, such as neuroblastoma and retinoblastoma, also argue against classifying cancer as an ARD. Nevertheless, aging may create a proinflammatory tissue microenvironment that is supportive for malignant cell growth (Caruso et al., 2004; Davalos et al., 2010; Schwartsburd, 2004). By preventing cell senescence, e.g. with mTOR inhibitors, it may be possible to reduce local inflammation and thus cancer progression (Blagosklonny, 2008).

I have then decided to use disease statistics to elucidate the underlying nature of five major ARDs: atherosclerosis, hypertension, diabetes, Alzheimer's and Parkinson's. As large-scale incidence data for these diseases is not readily available, I have instead evaluated the age distribution of mortality (see Appendices for details). Unlike incidence rates, mortality rates represent the hazard function derived from the probability density function. They are usually approximated by the hazard function of the Gompertz distribution, which is essentially the exponential function. However, the exponential function does not have an upper limit, whereas the mortality rate does (100,000 deaths per 100,000 people), so it cannot be the mathematically correct choice. Instead, the logistic function, which initially behaves like the exponential but then asymptotically approaches the upper limit, appears more appropriate and indeed provides an excellent fit to the data (Fig. 1).

It can be seen that the exponential function provides a reasonable approximation for mortality from atherosclerosis, diabetes and Alzheimer's, but is inadequate for mortality from essential hypertension and Parkinson's. The slightly more complex but mathematically correct

Abbreviations: APP, amyloid precursor protein; ARD, age-related disease; AT_1, angiotensin II receptor type; Aβ, amyloid beta; Aβ40, 40 amino acids long Aβ; Aβ42, 42 amino acids long Aβ; BH_4, tetrahydrobiopterin; eNOS, endothelial nitric oxide synthase; H_2O_2, hydrogen peroxide; LDL, low-density lipoprotein; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; NO, nitric oxide; NOX, NADPH oxidase; $O_2^{\cdot -}$, superoxide; $ONOO^-$, peroxynitrite; oxLDL, oxidized LDL; ROS, reactive oxygen species; SOD, superoxide dismutase; αS, alpha synuclein

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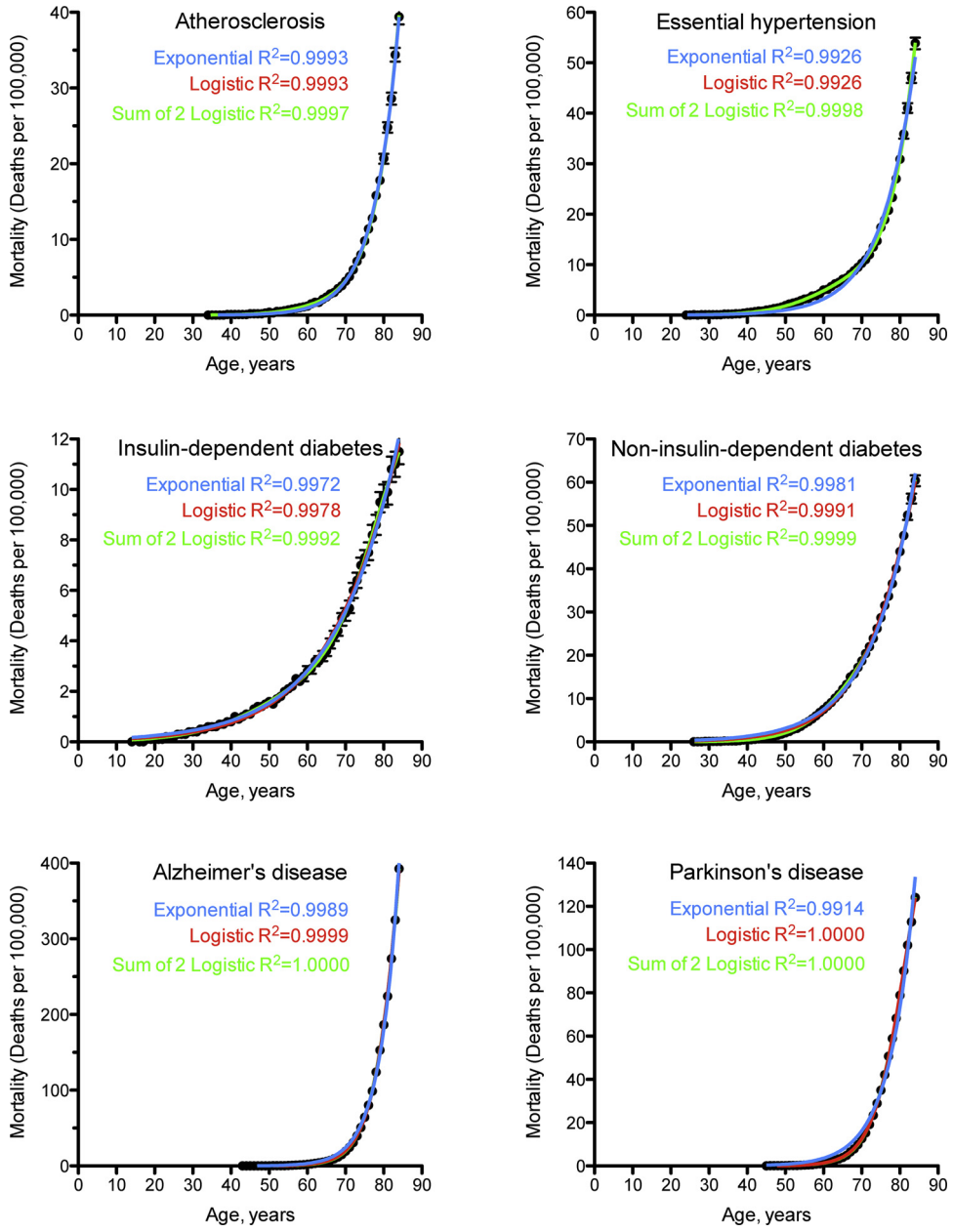

Fig. 1. The logistic function approximates the age distributions of mortality rates for age-related diseases. Dots indicate actual data for one-year age intervals. Curves indicate the exponential (blue), logistic (red) and the sum of two logistic (green) functions fit to the data. A simpler model is plotted on top of a more complex model (exponential > logistic > sum of 2 logistic).

logistic function provides the fits that are at least as good as for the exponential function, and in addition provides the perfect fit for Parkinson's disease mortality. Finally, the sum of two logistic functions is required for the adequate fit to mortality from essential hypertension. This may indicate that essential hypertension is a heterogeneous disease composed of two major subtypes with different mortality kinetics. Indeed, essential hypertension is defined as hypertension with an unknown cause. It has to be noted that hazard functions of common statistical distributions, including Weibull and gamma, as well as the sum of two exponential functions, failed to provide fits as good as logistic function.

As mentioned above, the logistic function describes exponential growth that slows down when some limiting factors start to play a role. Processes that exhibit an exponential growth behavior are common in natural and artificial systems. They include, but are not limited to, nuclear chain reactions, exothermal heat-accelerated chemical reactions, crystallization of water into ice, avalanches, growth of bacteria, growth of prey population after removal of predators, viral epidemics, as well as the acoustic feedback in microphone-amplifier-loudspeaker systems. All these processes involve either a branching chain reaction or, more generally, a positive feedback loop. In lay terms, they can be described as "A produces more of B, and B produces more of A", with possible intermediates C, D, E, F, etc., or in the simplest case, "A produces more of A".

The well-known property of systems containing positive feedback loops is the progressive amplification of initially small disturbances that leads to system instability and, eventually, destruction, if no negative feedback loops are in place. The vivid examples include nuclear and chemical explosions. I propose that age-related diseases are initiated by relatively small disturbances that are amplified through positive feedback loops (vicious cycles) and lead to the destabilization of organism physiology and, eventually, to death. In the following sections, I will

describe specific vicious cycles likely underlying five major ARDs: atherosclerosis, hypertension, diabetes, Alzheimer's and Parkinson's. Potential ways to interrupt these cycles will also be suggested.

2. The vicious cycle of atherosclerosis

Atherosclerosis and hypertension are the major factors responsible for the myocardial infarction (heart attack) and the cerebrovascular insult (stroke). These events typically occur upon the rupture of a vulnerable atherosclerotic plaque in the artery wall, leading to thrombosis of a coronary artery or an artery in the brain. Vulnerable plaques are defined primarily by the large lipid-rich necrotic core and thin fibrous cap (Celeng et al., 2016). They progressively develop from initial benign fatty streaks, which are present already in infancy (McGill et al., 2000; Napoli et al., 1997; Stary, 1990). Notably, the number of advanced lesions and the lesion size grow exponentially with age (McGill et al., 2000; Stary, 1990), whereas the fibrous cap thins (Ota et al., 2009).

I propose the following mechanism involved in the development of a necrotic lipid core (for a similar idea, see (Hulsmans and Holvoet, 2010)):

(1) Low-density lipoprotein (LDL) concentrations in the bloodstream and in the subendothelial space (intima) of arteries are in dynamic equilibrium (Deng et al., 1995) and do not substantially change with age (Kaufman et al., 2013)
(2) Endothelial cells and vascular smooth muscle cells produce reactive oxygen species (ROS) via NADPH oxidases (NOX), which are required for normal intercellular signaling (Lassègue and Griendling, 2010)
(3) Occasionally, some LDL in the intima becomes oxidized by ROS from NOX, forming oxLDL (Steinberg and Witztum, 2010)
(4) oxLDL promotes the expression of adhesion molecules on endothelial cells that mediate recruitment of monocytes from the bloodstream (Gleissner et al., 2007; Khan et al., 1995; Napoli et al., 1997; Takei et al., 2001)
(5) Recruited monocytes differentiate into macrophages that engulf oxLDL (mainly via the scavenger receptor CD36) and try to digest it (Febbraio et al., 2000; Park, 2014)
(6) Phagocytosis of macrophages is accompanied by the release of large amounts of ROS via NOX-2 (the so called respiratory burst) (Dupre-Crochet et al., 2013; Judkins et al., 2010)
(7) These ROS oxidize more LDL (Hulsmans and Holvoet, 2010; Peluso et al., 2012)

Steps 4–7 are repeated many times: the key vicious cycle is formed (Fig. 2a). It is supplemented by additional cytokine-mediated positive feedback loops: oxLDL-activated macrophages release cytokines that enhance macrophage recruitment, oxLDL phagocytosis, ROS production and cytokine production, either directly or via the activation of T cells, endothelial cells and vascular smooth muscle cells (Ramji and Davies, 2015). Eventually, the amount of oxLDL generated by the congregation of ROS-producing macrophages exceeds their digestion capacity (Chistiakov et al., 2016). Macrophages turn into foam cells and die, leading to necrotic core growth (Tabas, 2010). Fibrous cap thinning is likely the byproduct of the vicious cycle of lipid core growth. Indeed, thinning occurs due to the destruction of extracellular matrix collagens and elastins by matrix metalloproteinases (MMPs) (Dollery and Libby, 2006), which are secreted by macrophages that are recruited to the lipid core (Newby, 2008) (Fig. 2a).

In the end, it is not very important what exactly initiates this feedback loop – an increase in the intimal concentration of LDL, e.g. due to excessive fatty meal intake, or the burst of ROS production by endothelial cells, e.g. due to angiotensin II stimulation, or both factors. After all, fatty streaks are present already in the human fetus (Napoli et al., 1997). Once the loop is formed, it becomes self-sustainable, so no repeated external influences are required to keep it functioning. The only possible way to prevent the progression of the disease is to interrupt the vicious cycle, at any of its steps.

For example, ROS can be scavenged with antioxidants, decreasing oxLDL formation; the expression of adhesion molecules on endothelial cells can be downregulated, interfering with monocyte recruitment; CD36 and NOX-2 expression or function in macrophages can be inhibited, abolishing oxLDL uptake and ROS production; the secretion of cytokines and MMPs by macrophages can also be reduced to prevent additional feedback loops and fibrous cap degradation. However, ROS, adhesion molecules, macrophages, CD36, NOX-2, cytokines and MMPs also serve many physiological functions in the arterial wall and elsewhere, so their complete elimination or inhibition will do more harm than good. This may explain the failure of traditional approaches based on antioxidants and inhibitors. Instead, the success can be achieved when these same targets will be hit selectively in the atherosclerotic plaque. This approach will likely be based on the targeted delivery of inhibitor cocktails within nanoparticles guided by plaque-specific markers (Antoniades et al., 2010).

3. The vicious cycles of hypertension

As mentioned in the previous section, hypertension (high blood pressure) is one of the two leading causes of acute cardiovascular events, along with atherosclerosis. For example, the rupture of a vulnerable plaque or of an aneurism is more likely to occur when blood pressure is high. Also, hypertension imposes greater load on the heart muscle, which may lead to the congestive heart failure.

Hypertension can be subdivided into two types: increased mean arterial pressure and increased pulse pressure. Mean arterial pressure increases until age 60, when it reaches a plateau, whereas pulse pressure increases exponentially until the oldest observed age (Franklin et al., 1997). Thus, these two types of hypertension likely correspond to the two subtypes of hypertension mortality discussed in the Introduction. Indeed, the contribution of the minor mortality component to overall mortality from hypertension starts to decrease at age 60 (Fig. 1).

An increase in mean arterial pressure occurs upon an increase in cardiac output and/or total peripheral (systemic) vascular resistance (Mayet and Hughes, 2003; Tanaka et al., 2016). The former is often responsible for prehypertension, whereas the latter mediates the established form of the disease (Julius, 1988; Messerli et al., 1983). Systemic vascular resistance is determined predominantly by the lumen diameter of small arteries and arterioles, also called resistance vessels (Mayet and Hughes, 2003). Increased vascular resistance can thus be due to increased vasoconstriction or impaired vasodilation.

The constriction of blood vessels can be caused by angiotensin II released by the renin-angiotensin-aldosterone system, mostly in response to decreased salt reabsorption in the kidneys and the related loss of blood volume (te Riet et al., 2015). However, the activity of the renin-angiotensin-aldosterone system does not increase with age, but rather decreases, both in hypertensives and in controls (Messerli et al., 1983; Nakamaru et al., 1981; Noth et al., 1977; Ogihara et al., 1979). The hyperactivity of the sympathetic nervous system can also result in marked vasoconstriction (Guyenet, 2006). Interestingly, the sympathetic activity correlates positively with mean arterial pressure (Kjeldsen et al., 1989; Philipp et al., 1978) and age (Yamada et al., 1989). However, the complexity of the central nervous system and our insufficient knowledge of it hinder the identification of potential vicious cycles. The relaxation of blood vessels is achieved chiefly by nitric oxide (NO), which is produced by endothelial nitric oxide synthase (eNOS) primarily in response to shear stress (Dudzinski et al., 2006). Reduced NO availability, endothelial dysfunction and impaired vasodilation are commonly implicated in essential hypertension (Forte et al., 1997; Hermann et al., 2006; Node et al., 1997).

I propose the following chain of events underlying the reduced NO availability (a similar concept has been suggested before (Landmesser

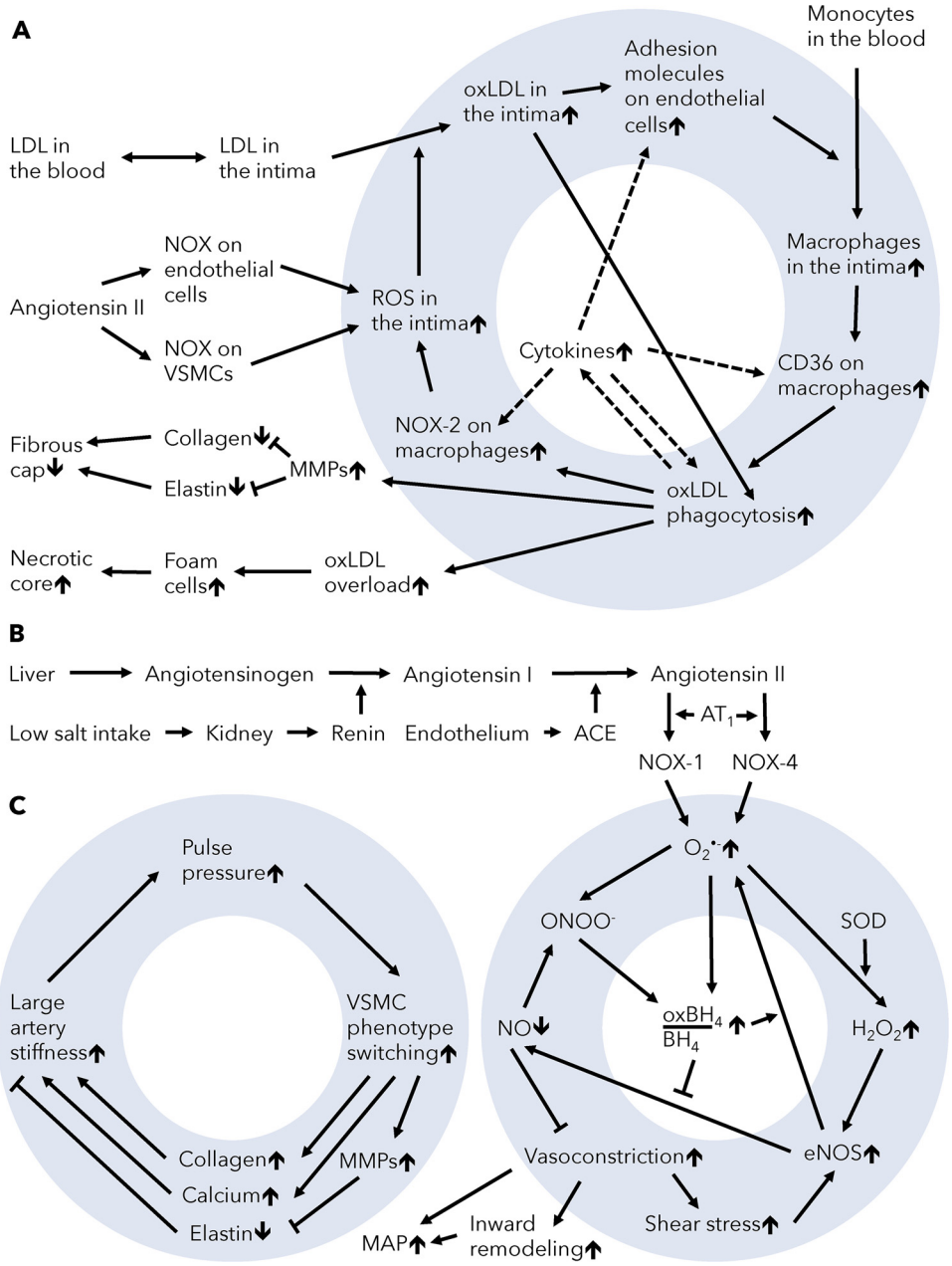

Fig. 2. The vicious cycles of atherosclerosis (a), increased mean arterial pressure (b) and increased pulse pressure (c). Short vertical arrows indicate increase (↑) or decrease (↓) in parameters that are likely to change exponentially or logistically with age. LDL – low density lipoprotein, oxLDL – oxidized LDL, MMPs - matrix metalloproteinases, NOX – NADPH oxidase, ROS – reactive oxygen species, VSMCs – vascular smooth muscle cells, ACE – angiotensin converting enzyme, AT_1 – angiotensin II receptor type 1, $O_2^{\cdot -}$- superoxide, SOD – superoxide dismutase, H_2O_2 – hydrogen peroxide, eNOS – endothelial nitric oxide synthase, NO – nitric oxide, $ONOO^-$ - peroxynitrite, BH_4 – tetrahydrobiopterin, $oxBH_4$ – oxidized BH_4, MAP – mean arterial pressure.

et al., 2003)):

(1) Low salt intake activates the renin-angiotensin-aldosterone system, which releases angiotensin II (Graudal et al., 2012)
(2) Angiotensin II activates its receptor (AT_1) on endothelial and vascular smooth muscle cells (Higuchi et al., 2007)
(3) AT_1 triggering leads to the increased expression and activation of NOX-1 and NOX-4 that start to produce superoxide ($O_2^{\cdot -}$) (Akasaki et al., 2006; Gavazzi et al., 2006; Matsuno et al., 2005)
(4) Some $O_2^{\cdot -}$dismutates to hydrogen peroxide (H_2O_2), either spontaneously or with the help of superoxide dismutase (SOD) (Liochev and Fridovich, 2007)
(5) H_2O_2 promotes the activation of eNOS, which increases the synthesis of NO (Cai et al., 2002)
(6) Some $O_2^{\cdot -}$reacts with NO, producing peroxynitrite ($ONOO^-$) (Szabo et al., 2007)
(7) Both $O_2^{\cdot -}$(Vasquez-Vivar et al., 2001) and $ONOO^-$ (Milstien and Katusic, 1999) oxidize and inactivate eNOS cofactor tetrahydrobiopterin (BH_4)
(8) When the ratio of intact BH_4 to oxidized BH_4 derivatives decreases, eNOS undergoes uncoupling and switches from the production of NO to the production of $O_2^{\cdot -}$ (Landmesser et al., 2003; Vasquez-Vivar et al., 1998, 2002)

Steps 4–8 comprise the vicious cycle (Fig. 2b). After some time, BH_4 becomes severely oxidized, most eNOS enzymes switch to producing $O_2^{\cdot -}$, NO synthesis dramatically reduces, and NO availability approaches zero. These events impair the relaxation of small arteries and arterioles, increase systemic vascular resistance, and ultimately raise mean arterial pressure to the observed plateau. Moreover, prolonged functional vasoconstriction causes inward eutrophic remodeling of small arteries, leading to the structural fixation of the abnormality (Feihl et al., 2008). Importantly, inward eutrophic remodeling can be induced by the chronic inhibition of NO production (Arribas et al., 1997). Fortunately, vasodilator agents have been shown to reverse this process by inducing outward remodeling (Mulvany, 2012).

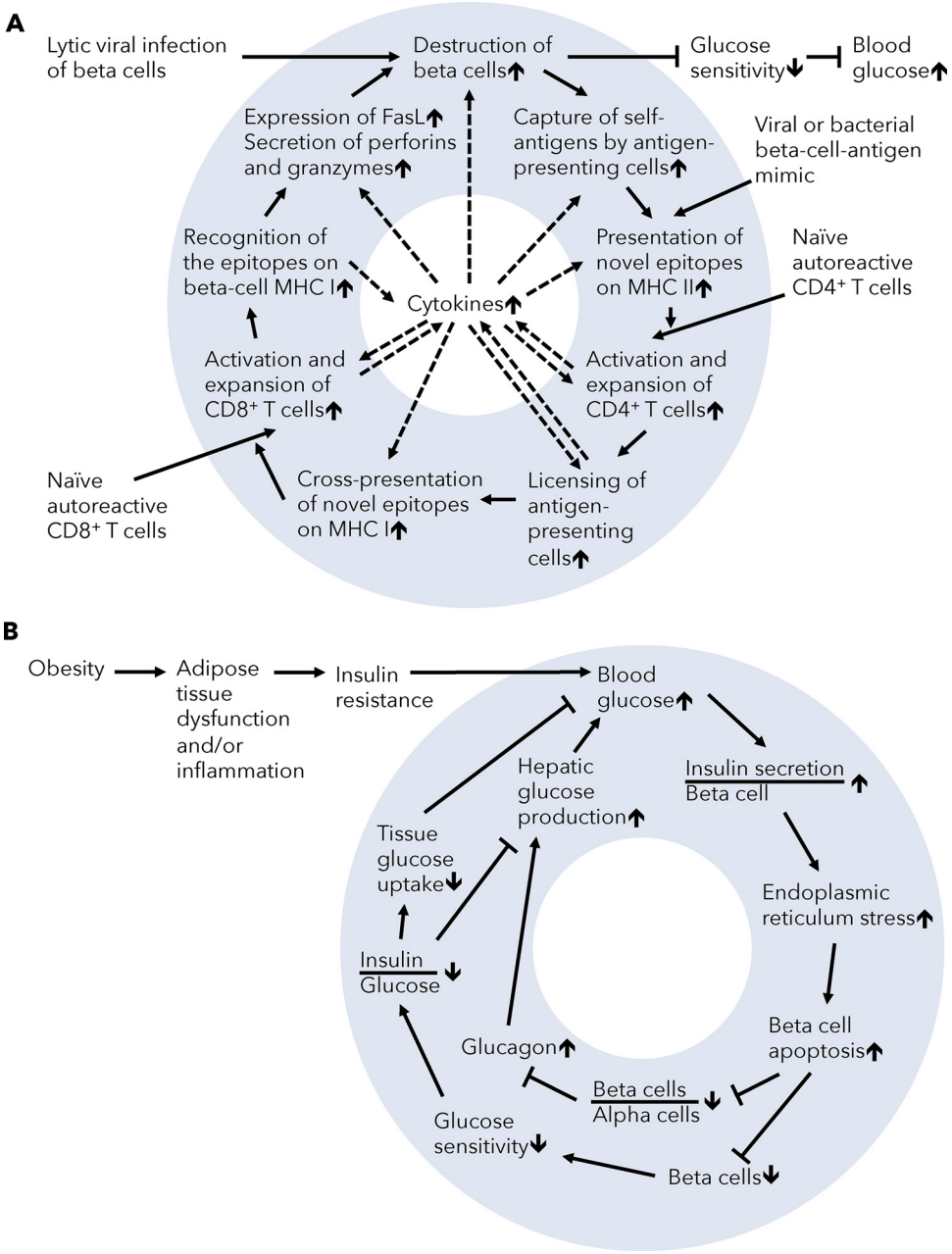

Fig. 3. The vicious cycles of type 1 diabetes (a) and type 2 diabetes (b). Short vertical arrows indicate increase (↑) or decrease (↓) in parameters that are likely to change exponentially or logistically with age. MHC – major histocompatibility complex, FasL – Fas ligand.

Interestingly, the same vicious cycle may be present in large arteries where it may be interwoven with the atherosclerosis cycle, as both cycles generate, and are propelled by, increasing ROS levels.

Most effective strategies to interrupt this vicious cycle would be using the scavengers of $O_2^{\cdot -}$ (d'Uscio et al., 2003) and $ONOO^-$ (McCarty et al., 2009) and increasing SOD expression and BH_4 synthesis (Crabtree and Channon, 2011) in endothelial and vascular smooth muscle cells, whereas exogenous supplementation of BH_4 is ineffective due to its rapid oxidation and slow reduction (Cunnington et al., 2012; Whitsett et al., 2013). Inhibiting vascular NADPH oxidases, AT_1 or angiotensin II synthesis also appears much less effective, as once the positive feedback loop (steps 4–8) is initiated, these molecules are no longer critical for the progression of the disease.

Pulse pressure is determined predominantly by the elasticity (or stiffness) of large arteries (Mayet and Hughes, 2003; Tanaka et al., 2016). Arterial stiffening causes increased pulse pressure by attenuating the compensatory arterial stretching during systole and shrinking during diastole (Quinn et al., 2012). Arterial stiffening progresses exponentially (AlGhatrif et al., 2013) and appears to predict hypertension (Dernellis and Panaretou, 2005; Liao et al., 1999; Takase et al., 2011) and acute cardiovascular events (Vlachopoulos et al., 2010). Interestingly, pulse pressure (McEniery et al., 2010) also predicts arterial stiffening, suggesting the possibility of a positive feedback loop between hypertension and arterial stiffening (Franklin, 2005; Franklin et al., 1997; Humphrey et al., 2016; Tomiyama and Yamashina, 2012). Arterial stiffening results from the fragmentation of elastin, deposition of collagen and calcium, as well as elastin and collagen crosslinking (Rattazzi et al., 2012; Tsamis et al., 2013). It is not known how exactly hypertension triggers these processes, but the transformation of vascular smooth muscle cells in the arterial wall to the synthetic and osteoblastic phenotypes in response to mechanical forces is the likely candidate (Lemarie et al., 2010; Liu, 2012) (Fig. 2c). Thus, further

research into the vascular smooth muscle cell phenotype switching will help to uncover the ways to interfere with or even reverse this pathological remodeling of large arteries.

4. The vicious cycles of diabetes

Diabetes mellitus is the group of metabolic diseases characterized by increased blood glucose levels (hyperglycemia). There are two major types of diabetes. Type 1 (insulin-dependent) diabetes is caused mainly by the autoimmune destruction of insulin-producing beta cells in the islets of Langerhans in the pancreas and accounts for 5–10% of all cases (Lehuen et al., 2010). Type 2 (non-insulin-dependent) diabetes also involves the dysfunction and death of beta cells, but is triggered primarily by insulin resistance and comprises 90% of cases (Prentki and Nolan, 2006). Diabetes may lead to serious health complications, such as neuropathy, retinopathy, nephropathy, seizures, nonketotic hyperosmolar coma, blindness, muscle wasting, chronic kidney disease, ketoacidosis, foot ulcers, cardiovascular diseases, and finally death.

The events underlying the development of type 1 diabetes are typical for a T cell-mediated autoimmune disease (Pietropaolo et al., 2008) and can be described as follows:

(1) The infection of beta cells by a virus leads to their destruction and the subsequent capture of their self-antigens by antigen-presenting cells, which include macrophages and dendritic cells (Morel, 2013; Van Gassen et al., 2015); alternatively, viral or bacterial antigens that mimic beta-cell antigens are captured by antigen-presenting cells elsewhere in the body (Filippi and von Herrath, 2008; Paun et al., 2016)
(2) Antigen-presenting cells migrate to lymph nodes and present captured antigens on Major histocompatibility complex class II (MHC II) in the form of short peptides (Unanue, 2014)
(3) Naïve $CD4^+$ T cells with T-cell receptor (TCR) complementary to the presented peptide-MHC II complex become activated, license antigen-presenting cells, proliferate, exit the lymph node and migrate to the pancreas (Unanue, 2014)
(4) Licensed antigen-presenting cells activate naïve autoreactive $CD8^+$ T cells by antigens cross-presented on MHC I, inducing their proliferation and migration to the pancreas (de Jersey et al., 2007)
(5) In the pancreas, $CD4^+$ T cells are restimulated by resident antigen-presenting cells via peptide-MHC II and start to secrete cytokines, which stimulate $CD4^+$ T cells, $CD8^+$ T cells and antigen-presenting cells (Calderon et al., 2014)
(6) Activated $CD8^+$ T cells recognize self-antigens in complex with MHC I on beta cells and destroy these cells with FasL, perforins and granzymes (Skowera et al., 2015; Thomas et al., 2010)
(7) Antigen-presenting cells capture beta-cell debris that contain novel antigens and epitopes (Di Lorenzo et al., 2007; McGinty et al., 2015)

Steps 2–7 form the vicious cycle, leading to epitope spreading (Vanderlugt and Miller, 2002; von Herrath et al., 2007) and the progressive destruction of beta cells (Fig. 3a). The avidity maturation of T-cell clones may also be involved in the escalating kinetics of the disease (Amrani et al., 2000). The loss of beta cells leads to acceleratingly decreasing glucose sensitivity, resulting in exponentially increasing blood glucose and the onset of diabetes (Ferrannini et al., 2010; Koskinen et al., 2016). Treatment for type 1 diabetes clearly should be directed against the escalation of autoimmune response in the pancreas. The selective elimination (Hess et al., 2007; Wang et al., 2016) or suppression (Casares et al., 2002) of cytotoxic and helper T cells bearing receptors against beta-cell antigens appears to be the most promising approach.

To explain the progressive development of type 2 diabetes, I propose the following sequence of events (see (Meier and Bonadonna, 2013) for a similar concept):

(1) Overeating (the consumption of more calories than spent) leads to obesity
(2) Obesity causes insulin resistance, likely through the dysfunction (Eissing et al., 2013; Lavau et al., 1979) and/or inflammation (Feuerer et al., 2009; Strissel et al., 2007; Winer et al., 2011) of the adipose tissue. However, insulin resistance does not directly participate in the main vicious cycle of diabetes, because it appears early, when blood glucose levels are still normal, and then changes little, when glucose concentrations in the blood rise exponentially, and beta-cell function dramatically deteriorates (Heianza et al., 2012; Levy et al., 1998; Mason et al., 2007; Saad et al., 1989; Tabak et al., 2009)
(3) Nevertheless, insulin resistance places increased demand on pancreatic beta cells, as they need to produce more insulin to keep blood glucose levels within the normal range (Dankner et al., 2009; Kahn et al., 1993)
(4) An increase in the secretion of insulin per beta cell leads to an increase in the endoplasmic reticulum stress (Song et al., 2008) and apoptosis (Butler et al., 2003; Deng et al., 2004; Inaishi et al., 2016; Rahier et al., 2008; Yoon et al., 2003) of beta cells
(5) A decrease in the number of functional beta cells leads to a decrease in the total pancreatic rate of insulin secretion relative to a given glucose level (decreased glucose sensitivity, $\Delta I/\Delta G$, HOMA-B) (Levy et al., 1998; Meier et al., 2009; Tabak et al., 2009), assuming that the glucose sensitivity of each individual beta cell does not change
(6) A decrease in the total relative insulin secretion rate leads to a decrease in the insulin-mediated glucose uptake by liver, muscle and adipose tissues and a decrease in the insulin-mediated suppression of hepatic glucose production (both also relative to glucose levels in blood) (DeFronzo et al., 1989; Ferrannini et al., 1988), thus increasing blood glucose levels
(7) Moreover, a decrease in the ratio of beta to alpha cells (Deng et al., 2004; Inaishi et al., 2016; Yoon et al., 2003) (due to beta-cell apoptosis) leads to a decrease in the suppression of glucagon secretion (Henkel et al., 2005; Meier et al., 2006; Reaven et al., 1987), promoting an increase in hepatic glucose production (Exton and Park, 1968) and a further increase in glucose levels
(8) An increase in blood glucose levels causes each beta cell to secrete more insulin (Toschi et al., 2002)

Steps 4–8 form the vicious cycle, leading to impaired glucose tolerance and type 2 diabetes (Fig. 3b). It should be noted that the same vicious cycle can be operating in type 1 diabetes in parallel with the autoimmune destruction cycle, as the number of beta cells and glucose sensitivity decrease, and endoplasmic reticulum stress increases, in both cases (Ferrannini et al., 2010; Ravelli et al., 2013; Tersey et al., 2012). In fact, both diseases might differ only by the factor (autoimmune response vs. insulin resistance) that triggers the vicious cycle.

To break this cycle, blood glucose needs to be lowered for the period of time sufficient for the pancreas to recover proper beta cell numbers (Meier, 2008). This can be achieved by the supplementation of exogenous insulin (Chen et al., 2008; Cusi et al., 1995; Pennartz et al., 2011; Pistrosch et al., 2013), by decreasing insulin resistance (Group, 2013; Hanley et al., 2010; Kahn et al., 2011; Wallace et al., 2004), by inhibiting glucagon secretion and hepatic glucose production (Bi et al., 2013; Lu et al., 2013), by diminishing glucose reabsorption in kidneys (Ferrannini et al., 2014; Polidori et al., 2014) or simply by very low calorie diet (Lim et al., 2011; Steven and Taylor, 2015). Treatment appears to be most effective when initiated early (Kramer et al., 2016; Raz and Mosenzon, 2013), perhaps because less cells need to be regenerated. Increasing insulin sensitivity will also help to prevent the reinitiation of the cycle.

5. The vicious cycle of Alzheimer's disease

Alzheimer's disease is the most common neurodegenerative disorder

in the elderly. The progressive deterioration of memory, reasoning and language skills leads to confusion, anxiety, frustration and abnormal behavior. Finally, death from aspiration pneumonia may occur. Alzheimer's disease is classically characterized by the build up of amyloid plaques in the brain, along with the appearance of neurofibrillary tangles, synaptic degeneration and neuronal death (Terry et al., 1991; Wilcock and Esiri, 1982). Amyloid plaques consist of amyloid fibrils, which in turn are composed of amyloid beta (Aβ) (Colvin et al., 2016; Walti et al., 2016). Aβ is a peptide of unknown function, cleaved from amyloid precursor protein (APP) by the sequential action of β- and γ-secretases (Thinakaran and Koo, 2008).

The elongated form of Aβ (Aβ42) can be released as the result of incomplete processing, which is dramatically increased by mutations in APP or presenilins, the key subunits of γ-secretase (Alzforum, 2017; Kumar-Singh et al., 2006; Scheuner et al., 1996). If these mutations are inherited, the familial autosomal dominant early-onset Alzheimer's disease appears, comprising around 5% of total Alzheimer's cases, with the rest 95% called late-onset (sporadic) Alzheimer's. Moreover, all known mutations in early-onset familial Alzheimer's map to APP or presenilins, and almost all of them lead to the increased production of Aβ42 (Alzforum, 2017; Kumar-Singh et al., 2006; Scheuner et al., 1996).

Aβ42 has a particular conformation that is prone to oligomerization and subsequent fibril formation (Bartolini et al., 2011; Chen and Glabe, 2006; Kuperstein et al., 2010; Meisl et al., 2014). The few mutations that do not lead to increased Aβ42 formation nevertheless appear to promote Aβ oligomerization by other means (Alzforum, 2017; Gessel et al., 2012). Recent studies suggest that Aβ oligomers/protofibrils, rather than mature fibrils, are the primary neurotoxic species (Benilova et al., 2012; Calabrese et al., 2007; Kuperstein et al., 2010; Shankar et al., 2007). The most remarkable feature of amyloid is that its molecules in an altered conformation can induce a similarly altered conformation in normal amyloid molecules, as in prion diseases (Frost and Diamond, 2010; Goedert et al., 2010; Jucker and Walker, 2011; Ridley et al., 2006). This amyloid property allows the chain reactions of amyloid oligomerization to occur.

I propose the following sequence of events that leads to the formation of toxic Aβ oligomers in sporadic Alzheimer's disease:

(1) In the area of adult neurogenesis, such as the hippocampus (Henneman et al., 2009; Jin et al., 2004; Mu and Gage, 2011; Scheff et al., 2006), a mutation in APP or presenilin spontaneously arises in one cell, leading to the increased production of Aβ42 (Kumar-Singh et al., 2006; Scheuner et al., 1996) (mutations are unlikely to occur in postmitotic cells, such as differentiated neurons, as they normally emerge during DNA replication)
(2) Aβ42 molecules have an altered conformation that induces their oligomerization (primary nucleation/seed formation) when their local concentration is high enough, such as that created by the somatic mutation of APP or presenilin (Bartolini et al., 2011; Chen and Glabe, 2006; Cohen et al., 2013; Kuperstein et al., 2010; Meisl et al., 2014; Morris et al., 2008)
(3) Aβ42 monomers, which are released at low rates by cells without mutations in APP and presenilin, as well as Aβ40 monomers released at high rates, attach to the ends of growing Aβ protofibril chains (Bartolini et al., 2011; Gu and Guo, 2013; Kuperstein et al., 2010)
(4) Crucially, Aβ protofibrils also serve as secondary nucleation sites, catalyzing the formation of new oligomers, both from Aβ42 and Aβ40 (Cohen et al., 2013; Meisl et al., 2014; Morris et al., 2008)

Steps 3 and 4 are continuously repeated, constituting the chain reaction and resulting in the progressive spread of Aβ pathology (Cohen et al., 2013) (Fig. 4a). Recent studies also show that Aβ oligomers can be taken up by cells and can spread from synapse to synapse along the defined neurological pathways, such as from the hippocampus to cortical areas (Frost and Diamond, 2010; Goedert et al., 2010). Aβ oligomers are toxic to neurons (Benilova et al., 2012; Calabrese et al., 2007; Kuperstein et al., 2010; Shankar et al., 2007). Aβ aggregates can also induce the activation of microglia via the scavenger receptor CD36 (El Khoury et al., 2003; Paresce et al., 1996). Importantly, the deposition of Aβ with age has been shown to follow sigmoidal curve (Villemagne et al., 2013), in line with the *in vitro* kinetic models of Aβ aggregation (Cohen et al., 2013; Kuperstein et al., 2010; Meisl et al., 2014; Morris et al., 2008) and the logistic growth of Alzheimer's disease mortality (Fig. 1).

Considering the hypothetical mechanism proposed here, the only effective way to prevent Alzheimer's disease progression would be to interfere with the chain reaction of Aβ oligomerization. Chemical substances that bind to the oligomer/protofibril ends and block the addition of intact Aβ molecules (Belluti et al., 2013; Doig and Derreumaux, 2015; Nie et al., 2011), as well as substances that interfere with secondary nucleation (Cohen et al., 2015), appear to be the best candidates.

It is true that numerous clinical trials based on the amyloid hypothesis have not yet brought about a cure for Alzheimer's disease, but so have not any trials based on other hypotheses. There are two likely reasons for that. The first reason is that most trials have been aiming at clearing or preventing formation of mature Aβ fibrils and plaques, whereas only recently it became clear that the toxic species are Aβ oligomers. The second reason is the extreme difficulty of developing an efficient inhibitor of oligomerization that acts at the right place of the amyloid cascade and also has favorable pharmacokinetics, including the ability to cross the blood-brain barrier. Meanwhile, some promising results have been obtained recently with the amyloid beta oligomerization inhibitor ALZ-801 (Hey et al., 2018) and it was granted a fast track designation by FDA. The most convincing argument for the validity of the amyloid hypothesis is the absence of mutations in any other proteins, unrelated to the amyloid cascade, that could lead to Alzheimers's disease (Selkoe and Hardy, 2016). Nevertheless, an opinion exists that sporadic Alzheimers's disease has a different underlying mechanism compared to the early-onset form (Demetrius and Driver, 2013; Drachman, 2014).

Yet another important possibility is that the Aβ cycle triggers another vicious cycle – the cycle of abnormal tau. Tau protein is the major component of neurofibrillary tangles – another hallmark of Alzheimer's disease (Kosik et al., 1986). Although no tau mutations are known to cause Alzheimer's disease, they can cause frontotemporal dementia, without the presence of Aβ (Hutton et al., 1998). This suggests that in Alzheimer's, Aβ may serve as a trigger, whereas tau as an executor. Indeed, Aβ enhances formation of pathological tau aggregates (Bennett et al., 2017; Gotz et al., 2001; He et al., 2018; Lewis et al., 2001; Vasconcelos et al., 2016), whereas tau is required for Aβ toxicity (Rapoport et al., 2002; Roberson et al., 2007). Most importantly, aggregates of abnormal tau can convert wild-type tau to pathological conformation, initiating the chain reaction similar to the one described for Aβ (Clavaguera et al., 2009; Goedert and Spillantini, 2017; Guo et al., 2016). Moreover, abnormal tau can spread from cell to cell (Clavaguera et al., 2009; Goedert and Spillantini, 2017). If the tau vicious cycle indeed exists, then to successfully treat Alzheimer's disease an inhibitor of tau aggregation needs to be developed, in addition to the inhibitor of Aβ oligomerization, especially if treatment will be initiated relatively late in the course of the disease.

6. The vicious cycles of Parkinson's disease

Parkinson's disease is the second most common neurodegenerative disorder of old age. Its major symptom is the progressive loss of motor control, manifesting in resting tremor, muscle rigidity, and bradykinesia (slowness), as well as balance, posture and walking problems. Cognitive deficiencies may develop at the late stages of the disease, resulting in 'Parkinson's disease dementia'. If they develop earlier than

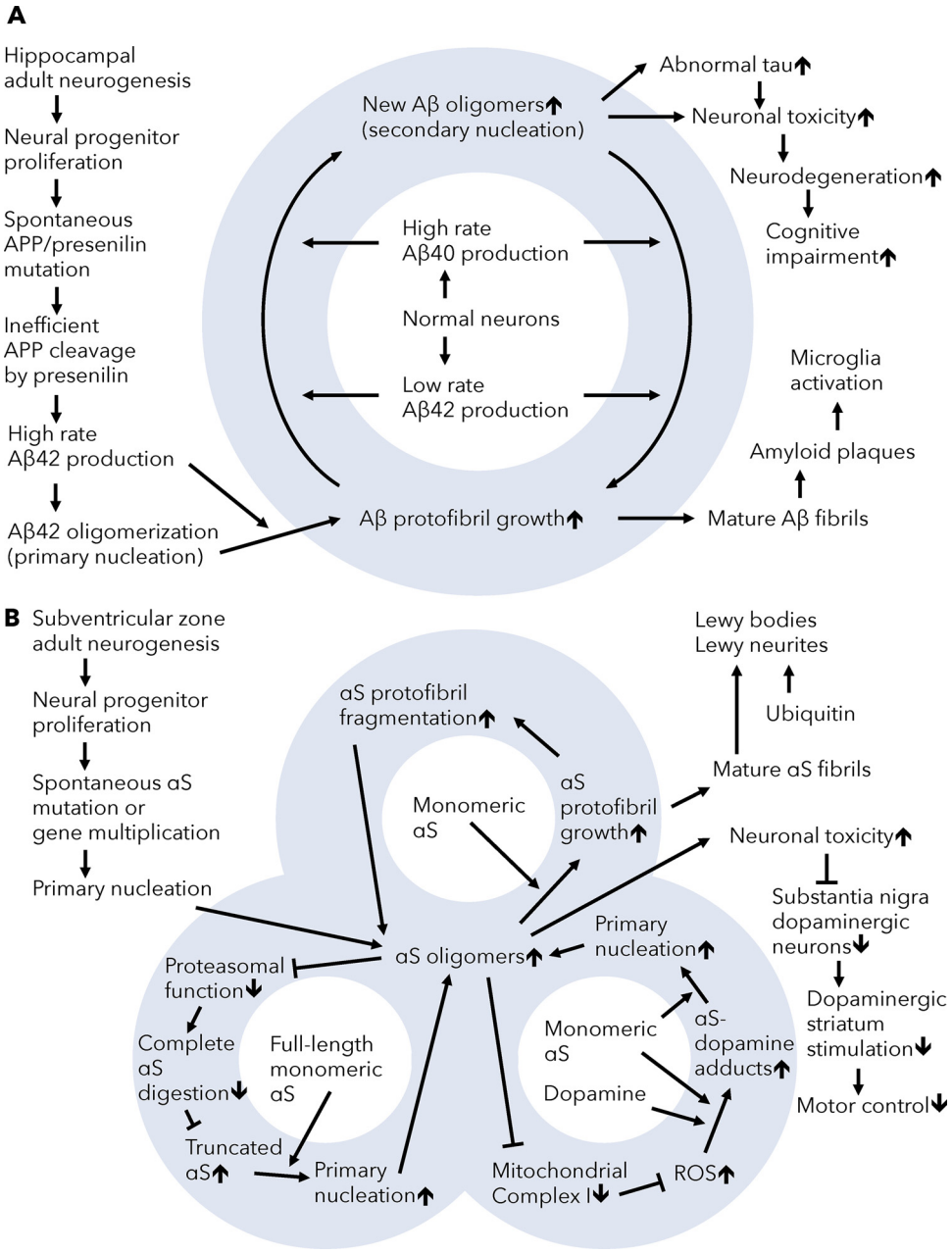

Fig. 4. The vicious cycles of Alzheimer's disease (a) and Parkinson's disease (b). Short vertical arrows indicate increase (↑) or decrease (↓) in parameters that are likely to change exponentially or logistically with age. APP – amyloid precursor protein, Aβ – amyloid beta, Aβ42 – 42 amino acids long Aβ, Aβ40 – 40 amino acids long Aβ, αS – alpha synuclein, ROS – reactive oxygen species.

motor deficits, the disorder is called 'dementia with Lewy bodies'.

The pathology of Parkinson's disease is characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, which project to the striatum (Damier et al., 1999). It is widely agreed that the loss of dopaminergic stimulation of the striatum is the direct cause of motor control deficits (Lewis and Barker, 2009). The remaining neurons in the substantia nigra show characteristic inclusions called Lewy bodies and Lewy neurites, which are composed primarily of alpha-synuclein (αS) and ubiquitin (Hughes et al., 1992; Kanazawa et al., 2008; Spillantini et al., 1997). When cognitive deficiencies are present alongside impairments in motor control, Lewy bodies and neurites are found in many other brain areas besides the substantia nigra (Gomperts, 2016).

Mutations in αS are the only known mutations necessary and sufficient for the development of familial autosomal dominant early-onset Parkinson's disease (Kruger et al., 1998; Polymeropoulos et al., 1997; Zarranz et al., 2004), implying the gain of toxic function by αS. Interestingly, the duplications and triplications of αS gene cause the same disease as missense mutations in αS, with the rate of progression proportional to the gene dosage (Chartier-Harlin et al., 2004; Ibanez et al., 2004; Singleton et al., 2003), indicating the toxicity of wild-type αS in elevated concentrations. Additionally, mutations in three other proteins – parkin (Kitada et al., 1998), PINK-1 (Valente et al., 2004) and DJ-1 (Bonifati et al., 2003) – are known to cause autosomal recessive early-onset Parkinson's, suggesting the loss of protective function by these proteins. Altogether, early-onset forms constitute only 5–10% of all Parkinson's cases but likely highlight the key players in the sporadic disease. Indeed, polymorphisms in the αS gene and promoter are the most significant SNPs associated with sporadic Parkinson's disease (Farrer et al., 2001; Pals et al., 2004; Simon-Sanchez et al., 2009).

The mechanism of Parkinson's disease initiation and progression might be analogous to that of Alzheimer's disease:

(1) A heterozygous mutation in αS (Kruger et al., 1998; Polymeropoulos et al., 1997; Zarranz et al., 2004) or the multiplication of the αS gene (Chartier-Harlin et al., 2004; Ibanez et al., 2004; Singleton et al., 2003) arises in a neural progenitor in the subventricular zone (van den Berge et al., 2011), which then travels to the striatum (Ernst et al., 2014) (as explained above, mutations are very unlikely to occur in postmitotic cells, such as differentiated neurons, as they normally emerge during DNA replication; the subventricular zone and the striatum are directly connected to the substantia nigra via dopaminergic afferents (Freundlieb et al., 2006); finally, the spontaneous somatic mutation explains the asymmetric disease manifestation and the random "selection" between the right and the left hemisphere (Djaldetti et al., 2006; Kempster et al., 1989), underscored by the symmetric manifestation when the mutation is inherited and hence present in all cells (Bonifati et al., 2005; Lucking et al., 2000))
(2) A mutation in αS (Choi et al., 2004; Conway et al., 1998; Giasson et al., 2002), or the locally increased concentration of αS (Kirik et al., 2003) due to the multiplication of the αS gene (Farrer et al., 2004; Miller et al., 2004), promotes αS oligomerization (primary nucleation/seed formation)
(3) Oligomers grow into protofibrils by the attachment of monomeric wild type αS (Yonetani et al., 2009)
(4) Growing protofibrils may fragment to oligomers (secondary nucleation/seed formation) (Yonetani et al., 2009)

Steps 3 and 4 are continuously repeated, constituting the chain reaction and resulting in the progressive spread of αS pathology (Frost and Diamond, 2010; Goedert et al., 2010) (Fig. 4b). Similarly to Alzheimer's disease, substances that bind to αS oligomers/protofibrils and block the addition of monomers appear to be the perfect drug candidates for the treatment of Parkinson's disease (Yedlapudi et al., 2016).

An additional positive feedback loop may exist (Liu et al., 2005) (Fig. 4b):

(1) As oligomers spread, they interfere with proteasomal functions (Chen et al., 2006; Chu et al., 2009), leading to the formation of incompletely digested (truncated) αS (Li et al., 2005; Liu et al., 2005)
(2) Truncated αS is aggregation-prone (Crowther et al., 1998; Tofaris et al., 2006) and promotes the aggregation of full-length monomeric αS into oligomers and fibrils (Li et al., 2005; Liu et al., 2005; Murray et al., 2003; Ulusoy et al., 2010)

Elucidating the exact mechanism of proteasome malfunction and αS truncation may help to design drugs that halt this vicious cycle. However, more promising approaches appear to be the inhibition of the attachment of full-length αS to the truncated one or the inhibition of protofibril elongation (Kim et al., 2010).

Accumulating oligomers are toxic to neurons (Winner et al., 2011). On the contrary, mature fibrils in Lewy bodies and neurites may be neuroprotective by sequestering toxic oligomers (McNaught et al., 2002). However, the elegant justification of Lewy body-associated toxicity has been proposed based on the stable percentage of Lewy body-bearing neurons (Greffard et al., 2010). Indeed, Lewy bodies can represent the failure of the ubiquitin-proteasome system (Bedford et al., 2008; Chu et al., 2009; McNaught et al., 2002), e.g. due to αS "poisoning" (Chen et al., 2006; Chu et al., 2009).

The third vicious cycle involving mitochondria may be present (Fig. 4b):

(1) Spreading αS oligomers inhibit mitochondrial Complex I (Devi et al., 2008; Liu et al., 2009)
(2) The inhibition of Complex I leads to an increase in ROS (Michelini et al., 2014)
(3) ROS modify αS and dopamine, promoting αS-dopamine covalent binding (Conway et al., 2001; Rekas et al., 2010; Xu et al., 2002)
(4) Dopamine adducts promote the conversion of αS into toxic oligomers/protofibrils but prevent the formation of mature fibrils (Conway et al., 2001; Rekas et al., 2010; Xu et al., 2002)

This mitochondrial cycle is supported by the involvement of parkin (Palacino et al., 2004), PINK-1 (Gautier et al., 2008) and DJ-1 (Andres-Mateos et al., 2007) in mitochondrial maintenance and antioxidant activity, by deficient Complex I activity in Parkinson's disease patients (Devi et al., 2008; Schapira et al., 1990), as well as by the induction of parkinsonism by mitochondrial Complex I inhibitors and ROS inducers (Betarbet et al., 2000; Langston et al., 1983; Tanner et al., 2011). Crucially, toxin-induced parkinsonism is progressive (Hantraye et al., 1993; Vingerhoets et al., 1994) and mediated by αS (Dauer et al., 2002). In fact, intriguing evidence indicates that an exposure to mitochondrial toxins via the gastrointestinal tract can lead to the accumulation of αS in the enteric nervous system and spreading of the pathology along the nerve fibers to the substantia nigra (Braak et al., 2006; Pan-Montojo et al., 2010). Mitochondria-targeted antioxidants (Jin et al., 2014) and substances that prevent the binding of oligomers to Complex I may help to slow down this vicious cycle. Surprisingly, the clinical trial of MitoQ showed no benefit for Parkinson's disease progression (Snow et al., 2010), which may indicate that the mitochondrial cycle is not the major one in the sporadic patients.

7. Conclusions

Although much effort has been spent to identify the most likely vicious cycles underlying each ARD, it was necessarily based on the limited and often controversial studies available to date. It is thus quite possible and even expected that when our knowledge expands and deepens, the cycles proposed here would be modified, or even replaced by the newly discovered cycles. To aid those future efforts, I would like to suggest a simple rule. Factors triggering the cycle in question should be distinguished from factors directly participating in that cycle. The former will likely show an association with the disease in epidemiological studies but do not have to change with age. The latter will also show an epidemiological association but in addition must change with age, preferably exponentially or logistically. The same principle can be used to verify each step of the cycles postulated here. The examples of triggering factors proposed here are LDL and angiotensin II concentrations in the blood, type 1 diabetes-associated viruses and obesity. The examples of cycle-participating factors are the amount of oxLDL in the plaques and Aβ oligomers in the brain, the level of $O_2^{\cdot -}$ in the endothelium and glucose in the blood, pulse pressure, and the number of activated T cells in the pancreas. Finally, interrupting the cycle at any step should halt the exponential progression of the disease, but is not expected to reverse or cure it. Thus, early diagnosis and intervention are extremely desired to preserve the maximum of healthy function.

This study showed that potential vicious cycles underlying ARDs are quite diverse and unique, triggered by diverse and unique factors that do not usually progress with age, thus casting doubts on the possibility of discovering the single molecular cause of aging and developing the single anti-aging pill. Rather, each disease appears to require an individual approach. However, it still cannot be excluded that some or all of these cycles are triggered by fundamental processes of aging, such as chronic inflammation (Franceschi and Campisi, 2014), accumulation of senescent cells (Childs et al., 2015; Yanai and Fraifeld, 2018), misregulated apoptosis (Tower, 2015), exhaustion of stem cell pool (Oh et al., 2014), shortening of telomeres (Blackburn et al., 2015), DNA damage (Moskalev et al., 2013; Vermeij et al., 2014), epigenetic changes (Brunet and Berger, 2014), activation of retrotransposons (Cardelli et al., 2016), intracellular garbage accumulation (Vilchez

et al., 2014), mitochondrial ROS overproduction (Dai et al., 2014), dysregulation of intracellular signaling (Blagosklonny, 2014) or neuroendocrine dysfunction (Dilman and Dean, 1992; Gupta and Morley, 2014). For example, inflammation and apoptosis have been implicated in most of the vicious cycles described above. Nevertheless, experimental data showing clear cause and effect relationships between fundamental aging processes and ARDs are still missing (Kennedy et al., 2014).

It could also be that the above-mentioned fundamental aging processes themselves are mediated by positive feedback loops. For example, chronic inflammation can amplify itself similarly to autoimmune diseases via cytokines and epitope spreading, as described for type 1 diabetes (section 4). Cellular senescence can propagate from cell to cell in a chain-reaction fashion via cytokines and ROS (Acosta et al., 2013; Nelson et al., 2012; Tasdemir and Lowe, 2013). Excessive apoptosis and exhaustion of stem cell pool can accelerate similarly to the death of pancreatic beta cells in type 2 diabetes – the fewer healthy functioning cells remain in a tissue, the more work (cell divisions, in case of stem cells) they need to do to produce the same required output and the faster they will exhaust themselves, leaving even fewer cells as a result. DNA damage may amplify by affecting the genes of more and more DNA repair enzymes. Similarly, epigenetic modification of genes responsible for epigenetic modification also has the potential to induce a vicious cycle. Retrotransposon replication is a chain reaction, because from each transcribed copy several new ones are produced. Accumulating intracellular garbage may impair the lysososmal function, leading to ever-accelerating garbage accumulation. Mitochondrial ROS can amplify itself by damaging mitochondrial DNA coding for electron transport chain subunits. Intracellular and neuroendocrine signaling are naturally prone to the appearance of vicious cycles, as various positive and negative feedback loops are integral to such systems. However, to test these propositions, longitudinal data on the kinetics of corresponding processes should be obtained.

It is known that in older individuals several diseases tend to be present simultaneously (Marengoni et al., 2011). Investigation of such multimorbidity patterns revealed a cluster of cardiometabolic diseases, reminiscent of the well-known metabolic syndrome (Prados-Torres et al., 2012). This association could be due to common risk factors, such as an unhealthy diet, insufficient physical exercise and obesity, or a common triggering factor, such as chronic inflammation (Fabbri et al., 2015), but could also mean that diseases tend to promote each other. For example, the vicious cycles of both atherosclerosis and hypertension involve endothelial oxidative stress, whereas diabetic hyperglycemia is known to induce ROS overproduction in the endothelium (Nishikawa et al., 2000). Thus, vicious cycles are likely to be interconnected, further accelerating the development of age-related pathologies.

It could be speculated that, beyond ARDs, other manifestations of aging, such as wrinkling of the skin, graying of hair, loss of muscle mass, etc., are also underlain by vicious cycles, although it is difficult to confirm, as there is no reliable statistics on progression of these changes with age. Thus, aging can be viewed as the host of interconnected exponentially progressing pathological processes mediated by positive feedback loops. Nevertheless, ARDs are the most relevant of them, as nobody apparently dies of “healthy aging” (Berzlanovich et al., 2005).

Declarations of interest

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Appendix A

A Data acquisition

‘Underlying Cause of Death, 1999-2015’ data were downloaded via Centers for Disease Control and Prevention Wide-ranging OnLine Data for Epidemiologic Research (CDC WONDER) online database: http://wonder.cdc.gov/controller/datarequest/D76.

The Underlying Cause of Death data are produced by the Mortality Statistics Branch, Division of Vital Statistics, National Center for Health Statistics (NCHS) at the Centers for Disease Control and Prevention (CDC), United States Department of Health and Human Services (US DHHS). Data are based on death certificates for U.S. residents. Each death certificate identifies a single underlying cause of death and demographic data. Mortality information is collected by state registries and provided to the National Vital Statistics System. The population estimates are U.S. Census Bureau estimates of the July 1 resident populations, based on the year 2000 and the year 2010 April 1 census counts. Crude Rates are expressed as the number of deaths reported each calendar year per 100,000 population. Rates and Populations are reported as "Not Applicable" for any subset of ages 85 and over, because population estimates are not available for those ages. The full dataset description is available here: http://wonder.cdc.gov/wonder/help/ucd.html#.

Results were grouped by Age Groups, Single-Year Ages were selected in demographics tab, and 2000–2015 years were selected in the next tab. 1999 was not included due to population estimates based on a separate 1990 census. All other settings were kept at default values. Then the data were downloaded separately for each disease, upon its selection in the ICD-10 Codes tab: Insulin-dependent diabetes mellitus (E10), Non-insulin-dependent diabetes mellitus (E11), Parkinson’s disease (G20), Alzheimer’s disease (G30), Essential (primary) hypertension (I10) and Atherosclerosis (I70).

B Data analysis

For analysis, the crude mortality rates were imported into GraphPad Prism 5. Data were analyzed with Nonlinear regression. User-defined equations were created for the exponential and logistic functions:

$$Y = A*\exp(b*x)$$

$$Y = A/(1+\exp(-b*(x-t)))$$

The sum of 2 logistic functions was modeled as follows:

$$Y1 = A1/(1+\exp(-b1*(x-t1)))$$

$$Y2 = A2/(1+\exp(-b2*(x-t2)))$$

$Y = Y1 + Y2$

The parameter *A* was constrained to "Must be between zero and 100000.0" and the parameters *b* and *t* to "Must be greater than 0.0". "Initial values, to be fit" for the parameters *A* and *t* were set to 1.0 and for the parameter *b* to 0.5. All other settings were kept at default values, e.g. Least squares fit and No weighting.

The hazard functions of the gamma, logistic, normal and Weibull distributions were also tested, but provided inferior fits compared to the logistic function or did not converge at all. The hazard functions of the Gumbel and Gompertz distributions are equivalent to the exponential function. The hazard function of the Weibull distribution is equivalent to the power function. Both functions have no upper limit. The sum of two exponential functions did not provide a dramatic improvement in fit over the single exponential function.

Appendix B. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.arr.2018.11.002.

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