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Linking Stress, Catecholamine Autotoxicity, and Allostatic Load with Neurodegenerative Diseases:

A Focused Review In Memory of Richard Kvetnansky

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Abstract

In this Focused Review we provide an update about evolving concepts that may link chronic stress and catecholamine autotoxicity with neurodegenerative diseases such as Parkinson's disease. Richard Kvetnansky's contributions to the field of stress and catecholamine systems inspired some of the ideas presented here. We propose that coordination of catecholaminergic systems mediates adjustments maintaining health and that senescence-related disintegration of these systems leads to disorders of regulation and to neurodegenerative diseases such as Parkinson's disease. Chronically repeated episodes of stress-related catecholamine release and reuptake, with attendant increases in formation of the toxic dopamine metabolite 3,4-dihydroxyphenylacetaldehyde, might accelerate this process.

Keywords

Homeostasis; Biocybernetics; Allostasis; Stress; Autonomic

In this Focused Review we provide an update about evolving concepts linking chronic stress and catecholamine autotoxicity with neurodegenerative diseases such as Parkinson's disease (PD) (Goldstein 2012). The many contributions of Richard Kvetnansky to the field of stress and catecholamine systems inspired some of the ideas presented here.

Kvetnansky's role in the evolution of knowledge about stress and catecholamines

In the area of stress and catecholamines, Richard was a true scientific pioneer. About 45 years ago, it was he who brought stress research to the National Institute of Mental Health. There, applying the "frustrating mental stress of immobilization" (Selye, 1952), he demonstrated that in rats repeated exposure to this stressor increases the adrenal medullary activities of tyrosine hydroxylase, phenylethanolamine-N-methyltransferase (Kvetnansky et

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al. 1970; Kvetnansky and Mikulaj 1970), and dopamine-beta-hydroxylase (Kvetnansky et al. 1971a), key enzymes in catecholamine biosynthesis (Kvetnansky et al. 1971b).

His subsequent development of an elegant experimental model to obtain blood via an indwelling cannula in rats exposed to various stressors ushered in an era of increased understanding about sympathetic noradrenergic and adrenomedullary responses to stress (Kvetnansky et al. 1978), stress-associated noradrenergic activation in brain centers such as the paraventricular nucleus of the hypothalamus (Pacak et al. 1992), and interactions between the hypothalamic-pituitary-adrenocortical system and peripheral (Kvetnansky et al. 1993) and central (Pacak et al. 1993a) catecholaminergic systems (Kvetnansky et al. 1995). He provided important evidence for stressor-specific patterns of activation of central (Pacak et al. 1998a) and peripheral (Kvetnansky et al. 1998) catecholamine systems and for the phenomenon of dishabituation upon exposure of chronically stressed animals to a novel stressor (Dronjak et al. 2004; Kvetnansky 2004; Ma et al. 2008). With the expansion of molecular biologic techniques, along with Esther Sabban he described in a series of experiments adaptive changes in the expression of catecholamine-synthesizing enzymes in response to different stressors (Kvetnansky et al. 2009).

Over a span of more than 40 years Dr. Kvetnansky also initiated, expertly organized, and graciously hosted a series of symposia on catecholamines and other neurotransmitters in stress. These were held at the majestic Smolenice Castle belonging to the Slovak Academy of Sciences. The symposia brought together an international cadre of scientists to present their recent advances in the field and to establish multiple collaborative ventures that significantly advanced and expanded the scope of stress research. It was at one of the Smolenice meetings that the present conception linking stress and allostatic load with PD was first presented (Goldstein 2011).

For his scientific contributions and leadership Richard will long be remembered. He was a fitting successor to Hans Selye, who first popularized stress as a medical condition (Selye 1936, 1950, 1956, 1974).

Stress and Distress

Selye defined stress as the non-specific response of the body to any demand imposed upon it (Selye 1976). Selye described the non-specific response, which he called the “General Adaptation Syndrome” (Selye 1956), as occurring in three stages—alarm, mediated by release of hormones from the adrenal cortex and medulla; resistance, in which the body attempts to resist or adapt; and exhaustion, leading to slow recovery or death.

According to Selye’s “doctrine of non-specificity,” specific and non-specific responses meet all challenges to homeostasis. It is the shared element, the non-specific response, that reflects stress. It took more than a half century for Selye’s doctrine of non-specificity to be examined critically (Pacak et al. 1998b). The experimental data were inconsistent with the doctrine of non-specificity and argued against the existence of a unitary stress syndrome. An alternative proposal is that each stressor has a “signature,” involving relatively distinctive

patterns (“primitive specificity”) of physiological, biochemical, and behavioral responses (Kvetnansky et al. 1998; Kvetnansky 2004; Goldstein 2006).

Selye did not consider stress always to be harmful. He viewed “distress” as damaging or unpleasant stress (Selye 1974). Selye’s definition of distress may be misunderstood to indicate that it is solely associated with pathology, although he does include “unpleasant.” To be more precise, we regard distress as a form of stress that is conscious, aversive, generates instinctively communicated signs, and is associated with adrenocortical and adrenomedullary activation (Goldstein 2006).

Catecholamine Autotoxicity

Concepts about pathogenetic mechanisms of neurodegenerative diseases have imputed genetic predispositions, environmental exposures, and their interactions (Bronstein et al. 2009). In conditions that feature prominent catecholamine depletion, such as in PD, another mechanism, “autotoxicity,” may be a significant factor (Goldstein et al. 2014a).

The autotoxicity theory posits that toxic products of oxidation of cytoplasmic catecholamines challenge homeostasis in—and eventually kill—the neurons that contain them (Figure 1). PD, multiple system atrophy (MSA), and pure autonomic failure (PAF) all involve profound catecholamine depletion in the brain, periphery, or both (Kish et al. 1988; Goldstein et al. 2015a; Goldstein et al. 2003b; Goldstein et al. 2003a). According to the autotoxicity theory the unusual vulnerability of catecholamines to oxidation and the cytotoxicity of the oxidized catecholamine metabolites produce selective degeneration of this class of neurons.

Autotoxicity can occur by two routes (Figure 1). The first is via spontaneous oxidation of cytoplasmic catecholamines (e.g., dopamine, DA) to form reactive oxygen species and quinones (DA-quinone) (Herrera et al. 2017). The quinones can undergo rearrangement and cycles of reduction/oxidation to form chromes, indoles, and melanins. These in turn can react with proteins such as alpha-synuclein (Bisaglia et al. 2007). DA-quinone can also bind covalently to glutathione or cysteine to form 5-S-cysteinyl-DA (Cys-DA) (Fornstedt et al. 1986), which may be cytotoxic (Spencer et al. 2002).

The second—and probably predominant—route of autotoxicity is via enzymatic oxidation catalyzed by monoamine oxidase (MAO). The products of the reaction are hydrogen peroxide and aldehydes (e.g., 3,4-dihydroxyphenylacetaldehyde, DOPAL, from DA).

DOPAL and the Catecholaldehyde Hypothesis

The “catecholaldehyde hypothesis” states that increased levels of DOPAL cause or contribute to the death of nigrostriatal dopaminergic neurons in PD (Burke et al. 2003). There are several ways that DOPAL may act alone or in concert with other compounds to cause death of dopaminergic neurons. DOPAL can bind covalently to DA to form tetrahydropapaveroline (Walsh et al. 1970; Marchitti et al. 2007), it can react with hydrogen peroxide and divalent metal cations to produce extremely harmful hydroxyl radicals (Li et al. 2001), and it can oxidize spontaneously to form reactive oxygen species and DOPAL-

quinone. DOPAL-quinone, in turn, forms adducts with lysine residues in proteins (Follmer et al. 2015), thereby altering their functions or causing them to form toxic oligomers (Anderson et al. 2016; Follmer et al. 2015).

There is indirect evidence that elevated levels of DOPAL play a pathogenetic role in PD. Exogenous DOPAL is cytotoxic (Panneton et al. 2010), decreased DOPAL detoxification by aldehyde dehydrogenase (ALDH) is associated with aging-related parkinsonism in genetic animal models (Wey et al. 2012), and exogenous agents that elevate DOPAL levels produce acquired parkinsonism in animals (Lamensdorf et al. 2000a; Lamensdorf et al. 2000b; Sherer et al. 2003). Nevertheless, as yet there is no evidence that manipulations decreasing DOPAL formation or DOPAL oxidation to DOPAL-quinone slows the neurodegenerative process in PD.

A “Triple Whammy” May Kill Catecholaminergic Neurons

Vesicular Sequestration

A catecholaminergic neuron has several mechanisms to minimize autotoxicity. A major mechanism is vesicular sequestration of intra-neuronal catecholamines, mediated by the type-2 vesicular monoamine transporter (VMAT2). Vesicular uptake is a key neuroprotective process in catecholaminergic neurons (Guillot and Miller 2009). Interference with vesicular uptake augments the toxicity of methamphetamine (Fumagalli et al. 1999; Guillot et al. 2008; Vergo et al. 2007), MPTP (Staal and Sonsalla 2000; German et al. 2000; Mooslehner et al. 2001), and 6-hydroxydopamine (Sun et al. 2004). Blockade of VMAT increases endogenous DOPAL production (Goldstein et al. 2012), and produces nigrostriatal neurodegeneration (Caudle et al. 2007). Conditional knockout of VMAT2 in dopaminergic neurons is lethal in mice (Isingrini et al. 2016), while increased VMAT2 expression is protective against methamphetamine toxicity in PC12 cells (Vergo et al. 2007) and in mice (Lohr et al. 2015).

Since vesicular sequestration limits the accumulation of toxic products of enzymatic and spontaneous oxidation of catecholamines, a vesicular storage defect could play a pathogenic role in the death of catecholaminergic neurons in a variety of neurodegenerative diseases. Thus, hypofunctional mutation of the gene encoding VMAT2 produces a lethal pediatric syndrome that includes parkinsonism (Rilstone et al. 2013).

In the putamen, deficient vesicular storage is reflected *in vivo* by accelerated loss of ^{18}F -DOPA-derived derived radioactivity (Goldstein et al. 2015a) and post-mortem by decreased ratios of DA/DOPA and of DA to the sum of its cytoplasmic metabolites (Goldstein et al. 2017). In the heart, deficient vesicular storage is reflected *in vivo* by accelerated loss of ^{18}F -DA-derived derived radioactivity and increased arterial plasma ^{18}F -dihydroxyphenylacetic acid (^{18}F -DOPAC) levels for a given amount of myocardial ^{18}F -DA uptake (Goldstein et al. 2011a; Goldstein et al. 2015a) and post-mortem by increased myocardial tissue ratios of 3,4-dihydroxyphenylglycol/norepinephrine (DHPG/NE), NE/DA, DA/DOPAC, DHPG/DOPAC, and DOPAC/NE (Goldstein et al. 2014b).

We retrospectively analyzed data from 20 conditions with decreased or intact catecholaminergic innervation, involving different etiologies, pathogenetic mechanisms, and lesion locations (Goldstein et al. 2015a). All parkinsonian conditions had an accelerated loss of putamen ^{18}F -DOPA-derived radioactivity; in those with post-mortem data there were also decreased putamen DA/DOPA ratios. All conditions in which there was cardiac sympathetic denervation had accelerated loss of myocardial ^{18}F -dopamine-derived radioactivity; in those with post-mortem data there were increased myocardial DHPG/NE ratios. All conditions in which there was localized loss of catecholaminergic innervation there was also decreased vesicular storage specifically in the denervated regions. Thus, across neurodegenerative diseases, loss of catecholaminergic neurons seems to be associated with decreased vesicular storage in the residual neurons.

Direct post-mortem evidence has been obtained for decreased uptake by vesicles isolated from putamen tissue in PD (Pifl et al. 2014). Both decreased tetrabenazine binding and decreased ^3H -DA uptake per VMAT2 binding site were noted, suggesting that decreased vesicular storage may reflect both decreased VMAT2 availability and function. Decreased vesicular storage could be due to multiple factors, such as limited availability of ATP required for the energy-requiring vesicular uptake process, decreased expression or activity of VMAT2 (Taylor et al. 2014), decreased axonal transport of vesicles or vesicle-associated proteins (Chu et al. 2012; Gaugler et al. 2012; Lundblad et al. 2012), or vesicle permeabilization (Plotegher et al. 2017).

Decreased ALDH Activity

After vesicular sequestration, probably the main mechanism minimizing catecholamine autotoxicity is the sequential action of two enzymes—MAO, which converts DA to DOPAL, and ALDH, which converts DOPAL to DOPAC. Decreased ALDH activity, allowing accumulation of DOPAL, has been proposed as a mechanism of PD (Fitzmaurice et al. 2013). Consistent with this view, mice with double knockout of the ALDH1A1 and ALDH2 genes provide an animal model of PD (Wey et al. 2012), while ALDH1A1 and ALDH2 are protective in dopaminergic neurons (Chiu et al. 2015; Cai et al. 2014). ALDH1A1 gene expression and activity have been reported to be decreased in the substantia nigra of PD patients (Grunblatt and Riederer 2014, 2016; Werner et al. 2008), and post-mortem neurochemical evidence has indicated decreased putamen ALDH activity in PD (Goldstein et al. 2011b; Goldstein et al. 2013) and MSA (Goldstein et al. 2015c).

Alpha-Synucleinopathy

PD, MSA, and PAF are characterized not only by loss of catecholamine neurons but also by deposition of the protein, alpha-synuclein. Alpha-synuclein is abundant in Lewy bodies (Spillantini et al. 1997) and in glial cytoplasmic inclusions (Wakabayashi et al. 1998), which are respective pathologic hallmarks of PD and MSA. Mutation of the gene encoding alpha-synuclein was the first identified genetic cause of familial PD (Polymeropoulos et al. 1997), now called PARK1. Replication of the normal alpha-synuclein gene also produces a form of familial PD (Singleton et al. 2003), now called PARK4. Both PARK1 and PARK4 are associated with physiological evidence of baroreflex-sympathoneural failure and neuroimaging evidence of cardiac noradrenergic denervation (Goldstein et al. 2001;

Singleton et al. 2004), establishing a causal link between alpha-synucleinopathy and catecholaminergic neurodegeneration in the brain and periphery.

Alpha-synuclein overexpression increases cytoplasmic DA concentrations (Mosharov et al. 2006), inhibits VMAT2 activity (Guo et al. 2008), and down-regulates VMAT2 gene expression (Lotharius et al. 2002). Conditional over-expression of the protein in PC12 cells exerts a cytotoxic effect that is prevented by blocking DA synthesis (Ito et al. 2010). Furthermore, cytoplasmic catechols—specifically DOPAL—oligomerize alpha-synuclein (Burke et al. 2008; Mazzulli et al. 2006), and the oligomers are thought to be toxic (Winner et al. 2011). DOPAL-induced oligomers of alpha-synuclein impede vesicular sequestration of catecholamines by permeabilizing vesicles (Plotegher et al. 2017). Interactions of DOPAL with alpha-synuclein, via decreased vesicular uptake or augmented vesicular leakage, could therefore set the stage for multiple pathogenic positive feedback loops (Figure 2).

DOPAL spontaneously oxidizes to form DOPAL-quinone. DOPAL-quinone may be responsible for DOPAL-induced oligomerization of alpha-synuclein, since anti-oxidants interfere with or prevent the oligomerization (Follmer et al. 2015). The oxidation of DOPAL also generates reactive oxygen species, which can lead to lipid peroxidation via formation of hydroxyl radicals (Li et al. 2001). Lipid peroxidation products inhibit ALDH and therefore build up cytoplasmic DOPAL (Florang et al. 2007)—another positive feedback loop.

Rotenone and the Triple Whammy

The pesticide, rotenone, produces an animal model of PD (Betarbet et al. 2000). Effects of rotenone include the three components of the triple whammy, because it inhibits vesicular sequestration (Watabe and Nakaki 2008; Holz 1978), decreases ALDH activity (Goldstein et al. 2015b), and promotes alpha-synuclein aggregation (Scherer et al. 2003).

As one would expect from the combination of decreased vesicular sequestration with decreased ALDH activity, rotenone increases DOPAL production (Lamensdorf et al. 2000a). Rotenone also increases monoamine oxidase (MAO) activity (Sai et al. 2008), which would be expected to enhance DOPAL formation for a given amount of cytoplasmic DA.

Consistent with a contribution of DOPAL to rotenone-related damage, MAO inhibition, which prevents rotenone-induced increases in DOPAL levels (Goldstein et al. 2016), attenuates the drug-induced generation of reactive oxygen species (Sai et al. 2008) and cytotoxicity (Lamensdorf et al. 2000b); and ALDH2 activation, which presumably limits DOPAL accumulation, is neuroprotective in rotenone-induced cellular and animal models of parkinsonism (Chiu et al. 2015). Whether DOPAL actually mediates the alpha-synuclein aggregation produced by rotenone remains unexplored.

Homeostasis, Allostasis, and Allostatic Load

Walter B. Cannon introduced the term, “homeostasis,” in 1926 to describe the stability of various constituents in body fluids and of core temperature.

Homeostasis of internal variables is often taught using the analogy of a thermostat regulating the interior temperature of a house (e.g., (Modell et al. 2015)). Although it may be tempting

to postulate that there are multiple internal homeostatic systems, each with its own “homeostat”—a “barostat” for regulating blood pressure (Folkow 1990), a thermostat for regulating core temperature, a “glucostat” for regulating blood glucose levels (Koeslag et al. 2003), an “osmostat” for regulating serum osmolality (Verbalis et al. 1986), and so forth—no comparator has been identified for any regulated internal variable. Instead, homeostats are metaphors or models for how the regulation happens—i.e., the body maintains homeostasis *as if* there were homeostatic comparators. The regulated variables are kept within bounds by the complementary actions of the effectors.

Cannon’s fifth postulate relating to homeostasis states, “The regulating system which determines a homeostatic state may comprise a number of cooperating factors brought into action at the same time or successively” (Cannon 1929). This was a prescient idea and predicted the existence of multiple effectors. There are numerous cases in which multiple effectors regulate levels of internal variables (Goldstein 2013). The complexity provided by the incorporation of multiple effectors extends the range of control and allows at least some regulation of the regulated variable if the primary effector fails, by compensatory activation of supplementary effectors (Goldstein 2013). Having multiple effectors also provides the requisite variety that enables evolution of specific, adaptive effector patterns (Goldstein 2006).

The concept of allostasis incorporates alterations in the tolerated steady state level—“stability through change” (Sterling and Eyer 1988). For example, a viral infection can be associated with a new steady state involving low grade fever, elevated heart rate, and malaise. Allostatic adjustments keep the regulated variables at altered but stable levels. Allostasis corresponds to movement to different sensory input-effector output curves.

Different homeostatic systems can share effectors (Goldstein 2013). In the setting of a shared effector, when one monitored variable is perturbed, its steady-state level may be maintained at the set value by negative feedback, but the level of another regulated variable may attain a new steady-state value—an allostatic state. A state of stress may be viewed as a type of allostasis, since the regulated internal variable remains out of bounds.

Although allostatic adjustments are both compensatory and adaptive, they can come at a cost—allostatic load—corresponding to a risk of an adverse effect or long-term “wear and tear.” Many examples of allostatic load in experimental animals as well as in humans involve the effects of repeated acute episodes or of chronic stress in which brain activation of several neuroendocrine functions plays a key role (McEwen, 2016).

Pleiotropy and Senescence-Related Disorders

Pleiotropy is a situation where one gene produces more than one phenotypic trait. In the context of diseases of senescence, the pleiotropic theory states that genes that give a benefit in youth impose a cost with age. According to the evolutionary biologist George Williams, “...senescence results from genes that increase youthful vigor at the price of vigor later on...” (Williams 1957).

Individuals with relatively efficient central catecholamine systems might have survival advantages during their reproductive years, in terms of being able to increase rapidly and massively the delivery of catecholamines to their receptors as part of initiating behaviors, experiencing emotions, learning to respond to classically conditioned stimuli, or learning and retaining appetitive or avoidance behaviors. Such individuals might also have an augmented ability to compensate for loss of catecholaminergic nerve terminals by increasing pathway traffic to the residual terminals. The advantages associated with these allostatic adjustments, however, could come at the cost of accelerated senescence of catecholaminergic neurons.

With advancing age, the efficiency of effectors maintaining homeostasis declines, as pointed out by Cannon (Cannon 1939). For instance, elderly humans have decreased ability to maintain core temperature and to increase sympathetic noradrenergic system activity in response to intravenous infusion of cold saline (Frank et al. 2000). Putamen DA content declines with aging in humans, associated with increased ligand binding at post-synaptic D1 receptors (Morgan et al. 1987).

To maintain homeostasis, the effectors are increasingly activated, but this could accelerate wear and tear on the effectors—allostatic load (Figure 3). Alternative effectors may be activated (compensatory activation), but this allostatic adjustment could increase production of autotoxic metabolites in the residual terminals, setting the stage for induction of a variety of lethal positive feedback loops.

Does Stress Contribute to Catecholaminergic Neurodegeneration in PD?

It has been proposed that stress may trigger the development of PD in susceptible individuals (Djamshidian and Lees 2014). In this concluding section we summarize evidence that stress, catecholamine autotoxicity, synucleinopathy, and allostatic load are linked in the pathogenesis of PD and related disorders, as follows.

Vesicular-Cytoplasmic Shift of Intracellular Catecholamines

Most of released catecholamine is recycled by neuronal reuptake (Axelrod and Kopin 1969; Hertting and Axelrod 1961). Stressors that release catecholamines therefore shift intraneuronal catecholamines from vesicular to cytoplasmic pools. Repeated episodes of distress might then promote neuronal injury via autotoxicity.

Although direct evidence is lacking, the results of recent studies fit with this notion. In rats, chronic restraint—which Richard Kvetnansky showed evokes activation of catecholaminergic neurons inside and outside the brain (Pacak et al. 1992; Pacak et al. 1993b; Kvetnansky et al. 1992a; Kvetnansky et al. 1992b)—reduces the numbers of substantia nigra dopaminergic and locus ceruleus noradrenergic neurons (Sugama et al. 2016), as in PD (Zarow et al. 2003). In mice, chronic exposure to a mild stress paradigm augments MPTP-related neurodegeneration (Janakiraman et al. 2017).

Traumatic Brain Injury

It has long been suspected that traumatic brain injury (TBI) increases the risk of PD. Recent data have supported this view (Jafari et al. 2013; Gardner et al. 2015; Chase 2015). TBI with loss of consciousness is associated with increased risks of Lewy body accumulation, progression of parkinsonism, and PD (Crane et al. 2016). In rats, TBI decreases TH gene expression and augments alpha-synuclein accumulation in the substantia nigra (Acosta et al. 2015). In mice, TBI decreases nigral expression of TH and the cell membrane DA transporter (Impellizzeri et al. 2016). Although early, the evidence so far is consistent with TBI increasing PD risk in a manner related to synucleinopathy; however, no post-mortem clinical studies have evaluated the putamen contents of DA, DOPAL, or other catechols after TBI.

Allostatic Load

As catecholaminergic neurons are lost, there is a compensatory increase in NE release from the residual terminals (Snyder et al. 1990). This allostatic adjustment maintains neurotransmitter delivery to receptors but might come at the cost of allostatic load from autotoxic effects of chronically increased reuptake of released neurotransmitter into the cytoplasm. Similarly, both catecholamine neuronal loss (Bezard et al. 2000; Brimijoin and Molinoff 1971) and interference with vesicular uptake compensatorily increases tyrosine hydroxylase activity (Cubells et al. 1995) and thereby increase cytoplasmic dopamine synthesis, another potential source of allostatic load from autotoxicity.

Aging-related declines in the efficiency of homeostatic mechanisms could result in multiple effectors being activated chronically; this could accelerate “wear and tear” and worsen efficiency of the effectors. McEwen and colleagues have emphasized the role of glucocorticoids in linking chronic psychosocial and metabolic stress with disease through mitochondrial allostatic load (Picard et al. 2014). Here we are emphasizing the role of catecholamines in linking stress with PD through a variety of autotoxic mechanisms, one of which may be mitochondrial allostatic load in striatal dopaminergic terminals.

In summary, a transition from homeostatic negative feedback regulation to pathogenic positive feedback may be relevant to senescence-related, neurodegenerative disorders such as PD that involve depletion of central and peripheral catecholamines. Chronically repeated episodes of stress-related catecholamine release and reuptake, with attendant increases in DA biosynthesis and DOPAL formation, might accelerate this process. We propose that efficient coordination of catecholaminergic systems mediates adjustments that serve to maintain health and that senescence-related disintegration of these systems leads to disorders of regulation resulting in neurodegenerative diseases such as PD.

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Figure 1. Overview of the catecholamine autotoxicity theory

The autotoxicity theory explains PD in terms of toxic effects of products of enzymatic and spontaneous oxidation of cytoplasmic dopamine. In particular, enzymatic oxidation of DA to DOPAL and spontaneous oxidation of DOPAL to DOPAL-quinone (DOPAL-Q) exerts toxic effects by generating reactive oxygen species and by modifying functions of a variety of intracellular proteins. Stress-related augmented release of catecholamines and consequently increased neuronal reuptake in effect shift intra-neuronal catecholamines from the vesicles, where they are inert, to the cytoplasm, where they can be rendered cytotoxic. Compensatorily increased traffic to residual terminals sets the stage for induction of lethal positive feedback loops.

Figure 2. Positive feedback loops related to catecholamine autotoxicity in dopaminergic neurons

Dopamine (DA) is formed in the cytosol from the action of L-aromatic-aminoacid decarboxylase (LAAAD) on DOPA, which is the immediate product of the rate-limiting enzymatic step in DA synthesis, hydroxylation of tyrosine mediated by tyrosine hydroxylase (TH). Cytosolic DA can auto-oxidize spontaneously or undergo enzymatic oxidation catalyzed by monoamine oxidase-A (MAO-A) in the outer mitochondrial membrane; however, the main fate of cytosolic DA is vesicular uptake via the type 2 vesicular monoamine transporter (VMAT2). Vesicular DA (DA_v) can leak from the vesicles into the cytosol or undergo exocytotic release. Most of released DA is taken back up into the cytosol via the cell membrane DA transporter (DAT). The action of MAO-A on cytosolic DA yields hydrogen peroxide (H₂O₂) and 3,4-dihydroxyphenylacetaldehyde (DOPAL). H₂O₂ reacts with metal ions to produce reactive oxygen species (in this case hydroxyl ions), resulting in oxidative injury including peroxidation of lipid membranes. DOPAL cross-links with amino acids in proteins; this can inactivate enzymes (e.g., TH) and transporters. DOPAL is detoxified mainly by aldehyde dehydrogenase (ALDH) to form 3,4-dihydroxyphenylacetic acid (DOPAC). A minor pathway of metabolism (not shown) is enzyme-catalyzed reduction to form 3,4-dihydroxyphenylethanol. Stimulatory relationships are indicated by (+) and inhibitory relationships by (−). De-stabilizing positive feedback loops are indicated when all signs in a loop are +.

Figure 3. Conceptual model relating stress-induced catecholamine release to autotoxicity, allostatic load, and progression of neurodegeneration in Parkinson's disease
The green (+) signs indicate positive relationships and red (-) signs negative relationships.