Vascular Targeting in ME/CFS

Cardiovascular Disturbances

in ME/CFS and Post-COVID-19 Syndrome

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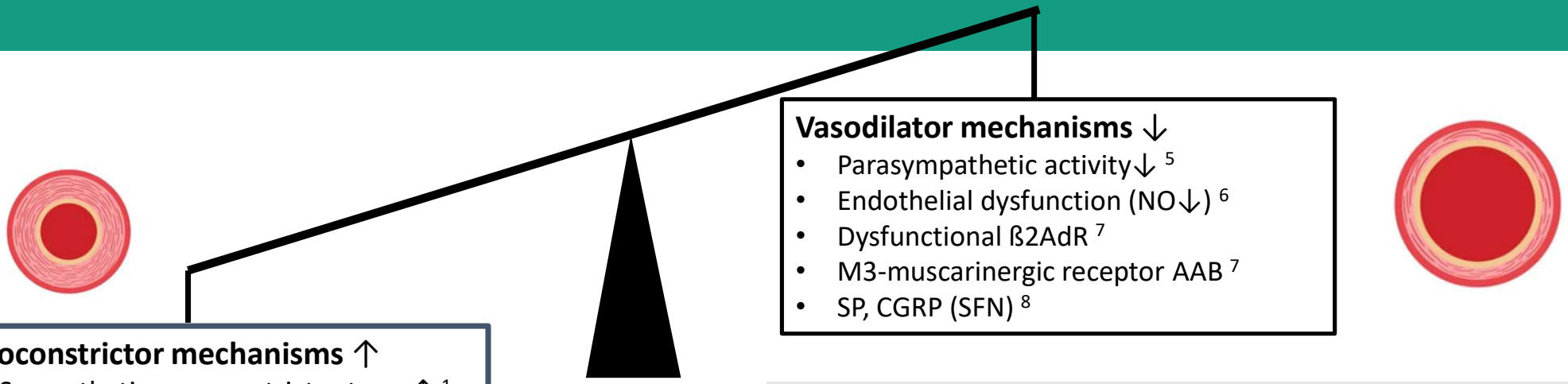
Disturbed Vasodilator/Vasoconstrictor Balance in ME/CFS



Vasodilator mechanisms ↓
- Parasympathetic activity↓ [5]
- Endothelial dysfunction (NO↓) [6]
- Dysfunctional ß2AdR [7]
- M3-muscarinergic receptor AAB [7]
- SP, CGRP (SFN) [8]

Vasoconstrictor mechanisms ↑
- Sympathetic vasoconstrictor tone ↑ [1]
- Endothelin ↑ [2]
- ROS ↑ [3]
- Direct vascular damage in PC and microcirculatory disturbances [4]

[1] Escorihuela et al. J Transl Med. 2020; 6;18:4, [2] Haffke et al., 2022 J. Transl. Med., 20,138
[3] Jammes et al. J Transl Med; 2020, 19;18(1), [4] Turner et al., Trends Endocrinol Metab,2023;S1043-2760(23)00055-3.s[5] Polli et al., Clin Ther. 2019;41(4):641-655,
[6] Sherbakov et al., ESC Heart Fail. 2020:1064-1071
[7] Loebel et al., Brain Behav Immun 201;52:32-39, [8] Joseph et al., Chest. 2021, 160:642-651

- Exercise starts with sympathetic activation – central command
- Sympathetic activation even at the start of exercise or mental effort may cause vasoconstriction (via alpha1-AR) instead of vasodilation (mainly via ß2AdR) **in skeletal muscles and brain** in ME/CFS

→ Hypoperfusion causing high muscular and mental fatigability?

Exertional Intolerance is the Hallmark of ME/CFS: Are Main Mechanisms of Exercise Disturbed?

Skeletal muscles, brain and heart are a functional unit:

- Muscles perform work, brain steers muscles and coordinates gait, and heart delivers blood flow
- **Rises in blood flow (vasodilation)** in muscles, brain and heart; **capacitance vessels constrict** to provide cardiac preload for a higher cardiac output

Perfusion disturbed in ME/CFS?

- **Mitochondrial energy production rises:**

Mitochondrial function disturbed in ME/CFS?

The Unique Role of ß2-Adrenergic Receptors (ß2AdR) for Exercise: the “Exercise Receptor”

- **Vascular actions:** vasodilator effects in skeletal muscles, heart and brain (unique)

  Heart: positive inotropic and chronotropic effects together with ß1AdR

- **Lung:** Bronchodilation
- **Activation of skeletal muscle Na^+/K^+-ATPase (sodium pump) by ß2AdR and CGRP [1]**: requires about 10-fold stimulation in exercise. ß2AdR and CGRP prevent rise in intramuscular Na^+ and subsequent Ca^{2+}-overload (mitochondrial damage)

[1] Clausen et al. , Front Physiol. 2017;8:371 [2] Petter et al., J Transl Med. 2022;20(1):580

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  - **Sodium rise in skeletal muscle of ME/CFS patients [2]** (MRI study with 23-Na^+)

→ **Dysfunction of ß2AdR impairs the ability to exercise**

Deficit of CGRP in small fiber neuropathy?

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[1] Clausen et al. , Front Physiol. 2017;8:371 [2] Petter et al., J Transl Med. 2022;20(1):580

Findings of Reduced Blood Flow and Circulatory Disturbances and Possible Consequences in ME/CFS or PCS

Reduced cerebral blood flow (CBF) [1,2], neurovascular coupling impaired [3], mild intracranial hypertension [4]

- Cognition impaired, mental fatigue, brain fog

Acrocyanosis (clinical observation)

Endothelial dysfunction, endothelin↑ [5], ROS ↑[6] (from mitochondrial dysfunction?)

Shunting of blood flow, reduced oxygen extraction in exercise, rise in lactate [7]

Vascular damage and disturbed microcirculation in COVID-19 [8]:

- Endothelial dysfunction
- Adhesivity of leukocytes ↑ Blood cell deformability ↓ Microclots
- Vascular inflamation and damage

[1] Van Campen et al., 2020,2021, 2023; [2] Ajčević et al. Sci Rep. 202313(1):5808.; [3] Shan et al, 2020. *Journal of Translational Medicine*, *18*(1), 335; [4] Bragée et al., 2020. *Frontiers in Neurology*, *11*(828).
[5] Haffke et al., J Transl Med. 2022;20(1):138; [6] Jammes et al. J Transl Med; 2020, 19;18(1)
[7] Joseph et al., Chest . 2021:160(2):642-651; [8] Turner et al., Trends Endocrinol Metab,2023;S1043-2760(23)00055-3.s

Potential Causes of Vascular Dysfunction in ME/CFS and PCS

Autonomic Dysfunction (cause?)

Autoantibodies

AAB against ß2AdR

AAB against M3AChR

AAB against vascular regulators (including alpha1AdR)

Sympathetic hyperactivity

- **Vasoconstriction ↑** -

Vasodilation ↓

Desensitization of ß2AdR

ß2AdR mutants particularly sensitive to desensitization and associated with ME/CFS [1]

Blood vessels affected

Endothelial dysfunction in ME/CFS

Vascular damage: Covid-19, Dengue…

Microcirculation disturbed: COVID-19, ANCA-vasculitis [2]

- Hypercoagulation, microclots, cell adhesion, reduced blood cell deformability, endothelial dysfunction

Ehlers-Danlos- and Marfan-Syndrome:

- Capacitance vessels distended? (OI)

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[1] Sommerfeldt et al. , Acta Paediatr 2011;100:293-8.[2] van Eeden, Lancet Reg Health Am. 2023;20:100460

The Cardiovascular Situation in ME/CFS

- **Disturbed vasodilator/vasconstrictor balance raises vascular resistance**
- **Low cardiac preload and output and low renin (paradox): hypertension prevented**
- **Causes of low cardiac preload**:
  - Hypovolemia
  - Dysfunction of capacitance vessels
    - Neuronal: autonomic dysfunction (neuroinflammation?, autoimmunity?)
    - Structural (connective tissue disorders (EDS) or direct damage (viral infections?))
    - Functional (autoantibodies against vascular regulators (alpha1AdR), circulating vasoactive mediators (histamine [1,2])

[1] Dachman et a., J Allergy Clin Immunol,1994, 93(3):606-14. [2] Müller-Schweinitzer, Folia Haematol Int Mag Klin Morphol Blutforsch . 1979;106(5-6):690-704

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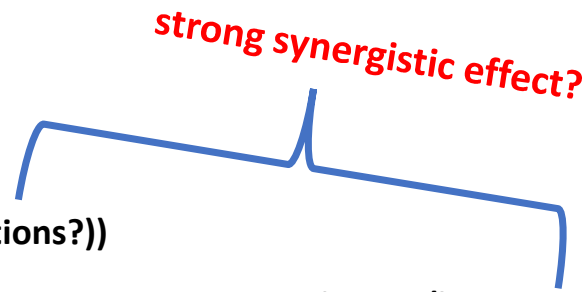

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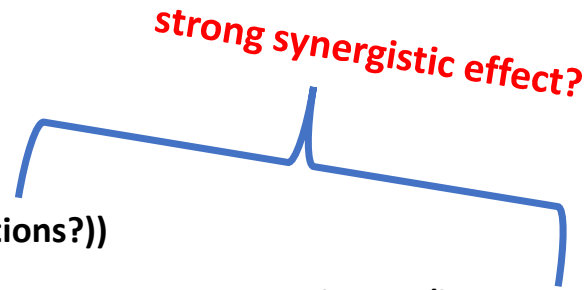

Consequences:

- Orthostatic dysregulation, intolerance (OI) and orthostatic stress
- CV maladaptation to exercise together with disturbed microcirculation (LC, ANCA-vasculitits)

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Energy Deficit in Skeletal Muscle is Caused by a Combined Effect of Hypoperfusion and Mitochondrial Dysfunction

Mitochondrial dysfunction

Muscle and brain blood flow ↘

ATP ↘, Fatigue

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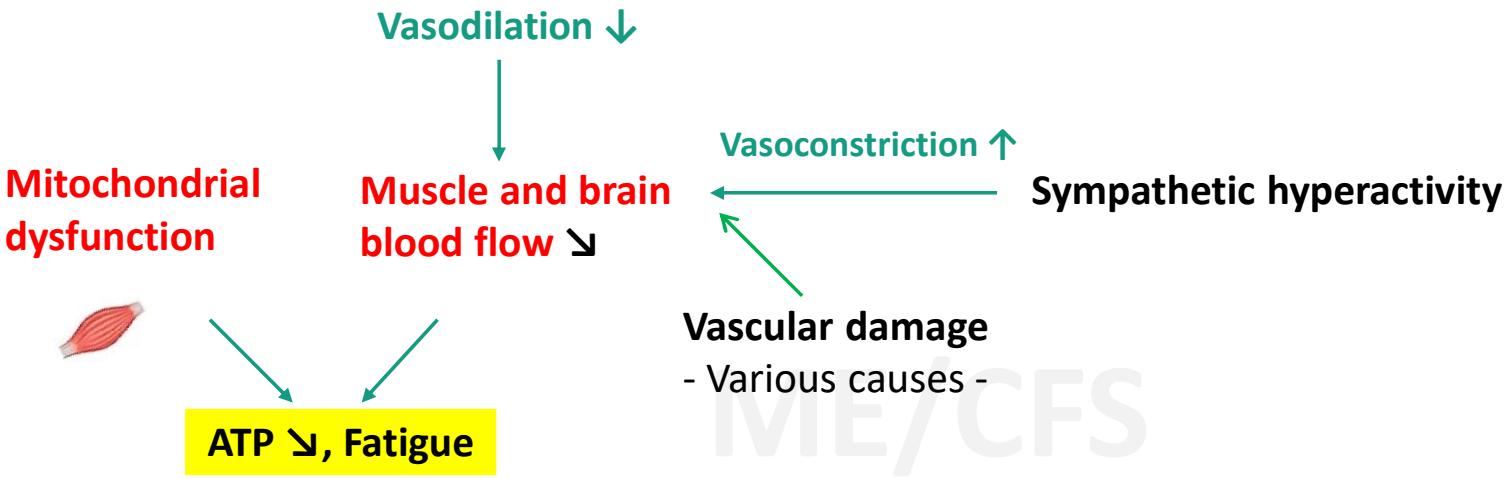

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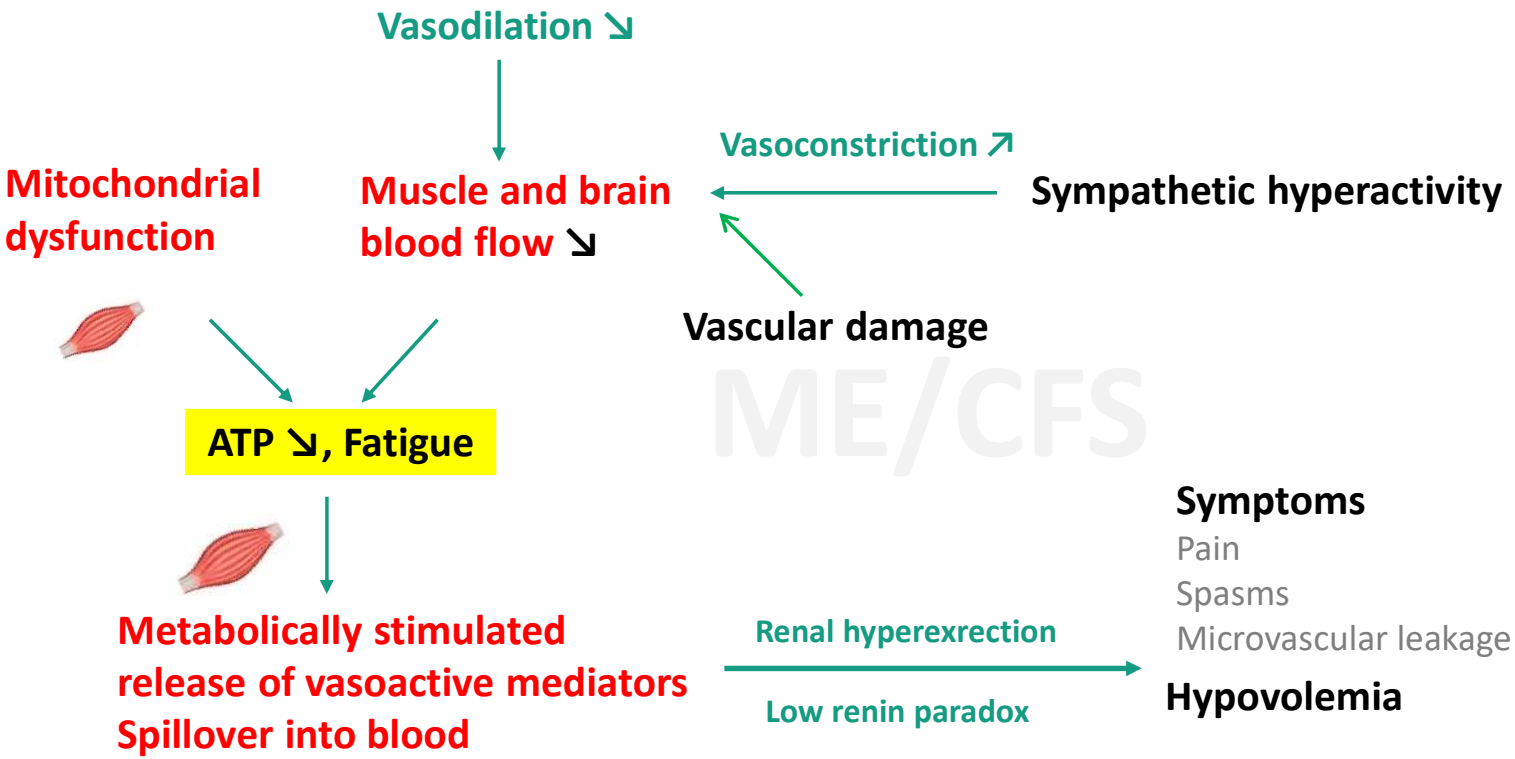

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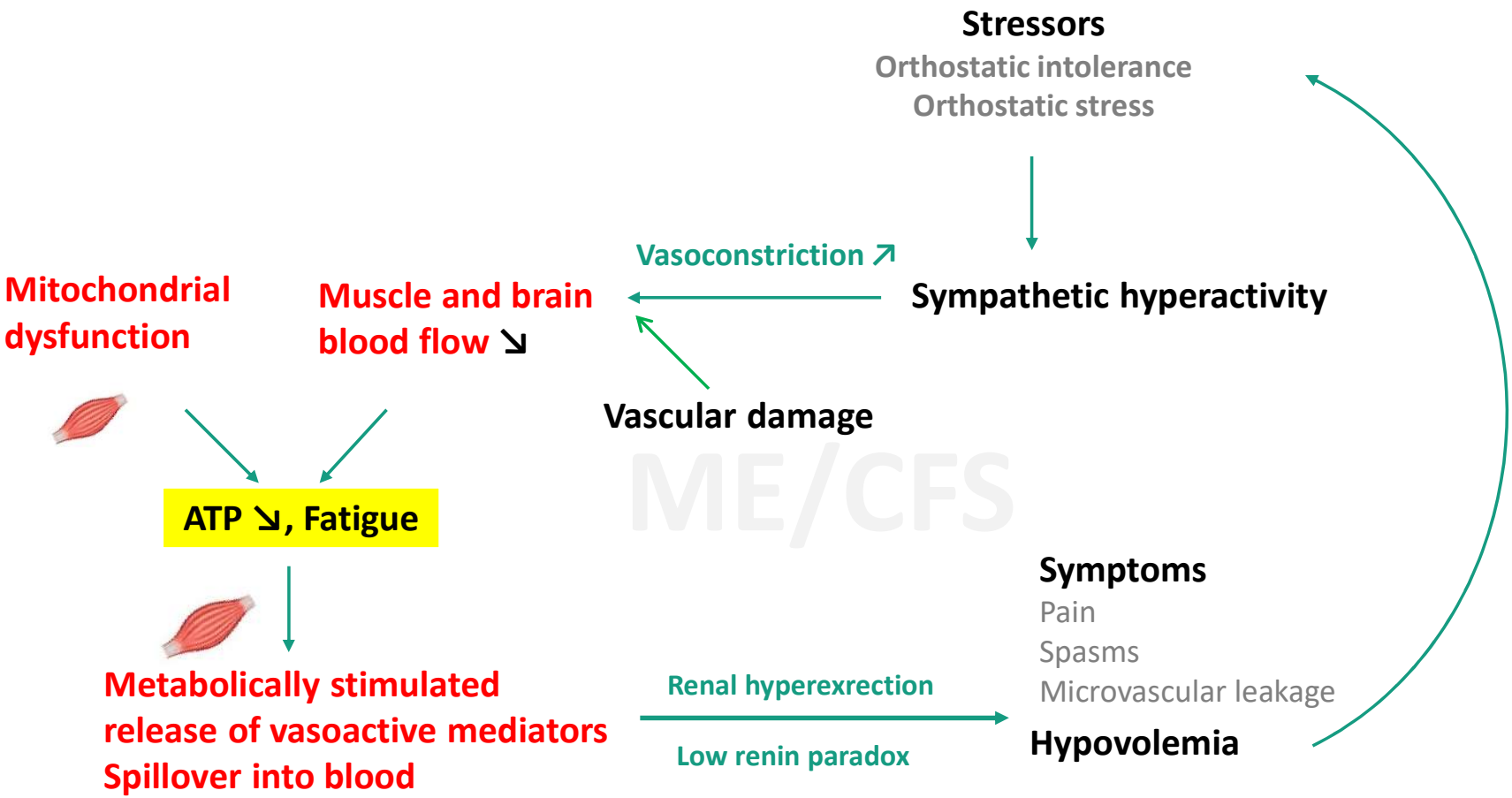

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Wirth and Scheibenbogen, 2020, 2021, 2022

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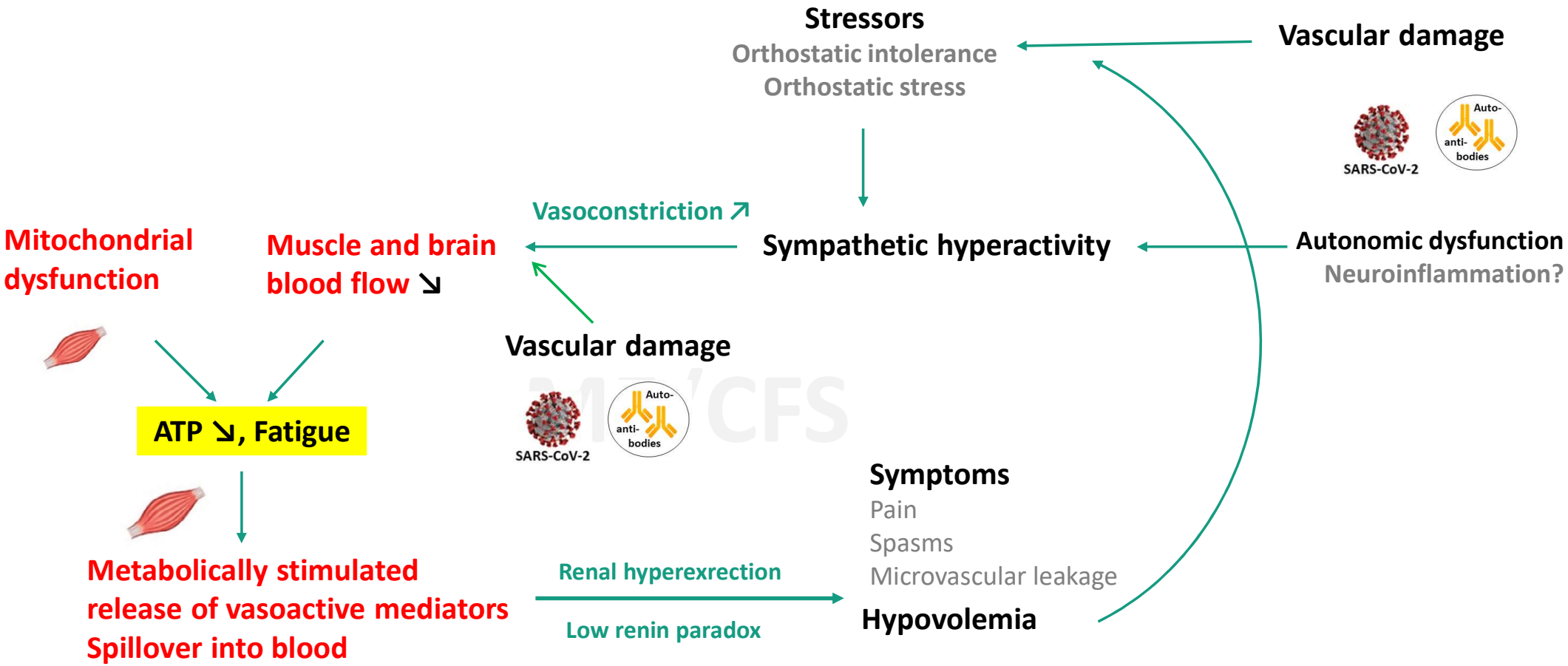

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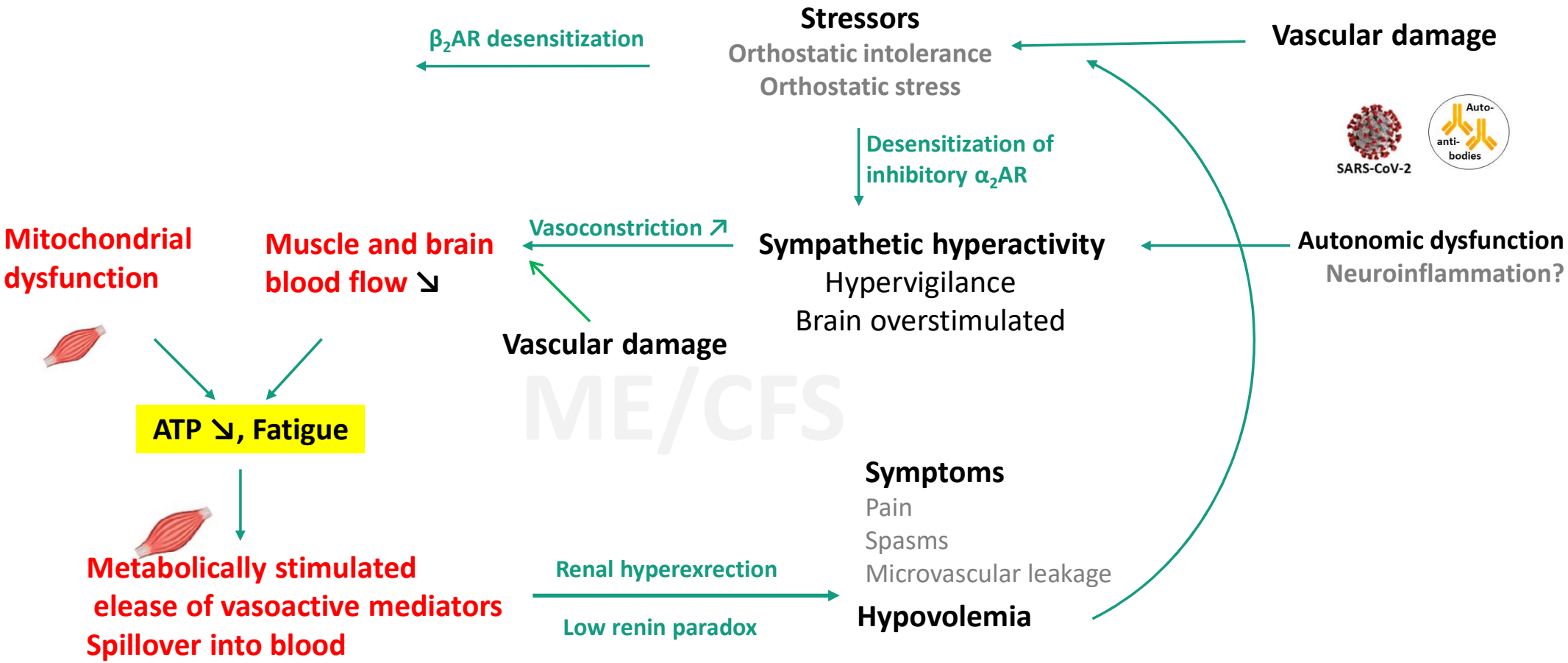

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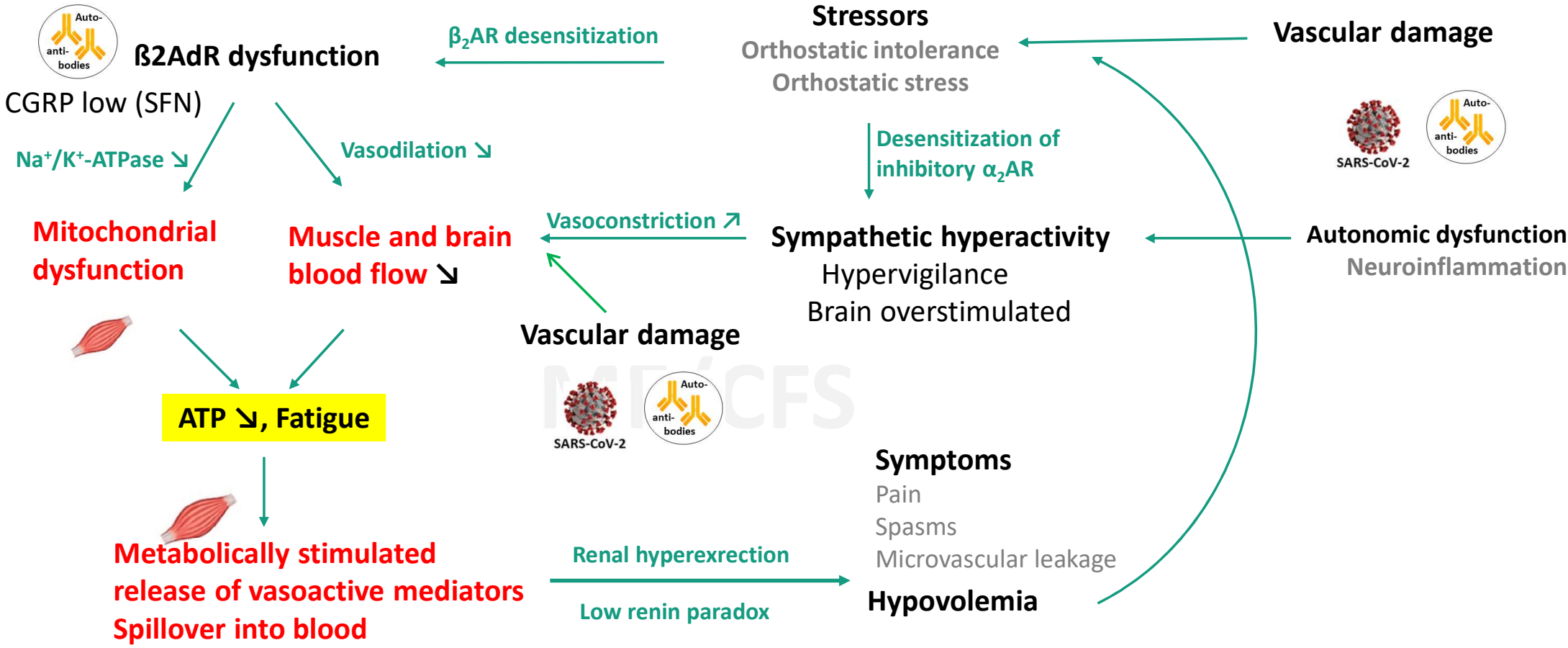

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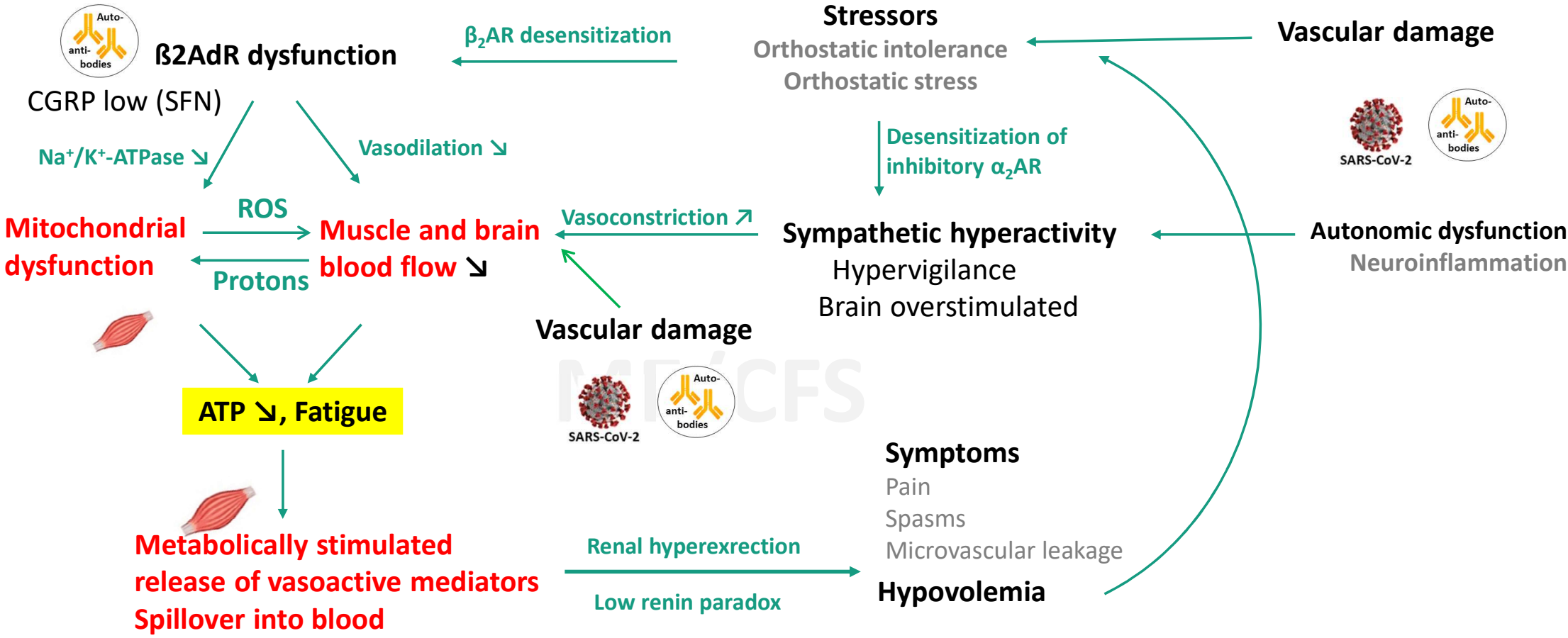

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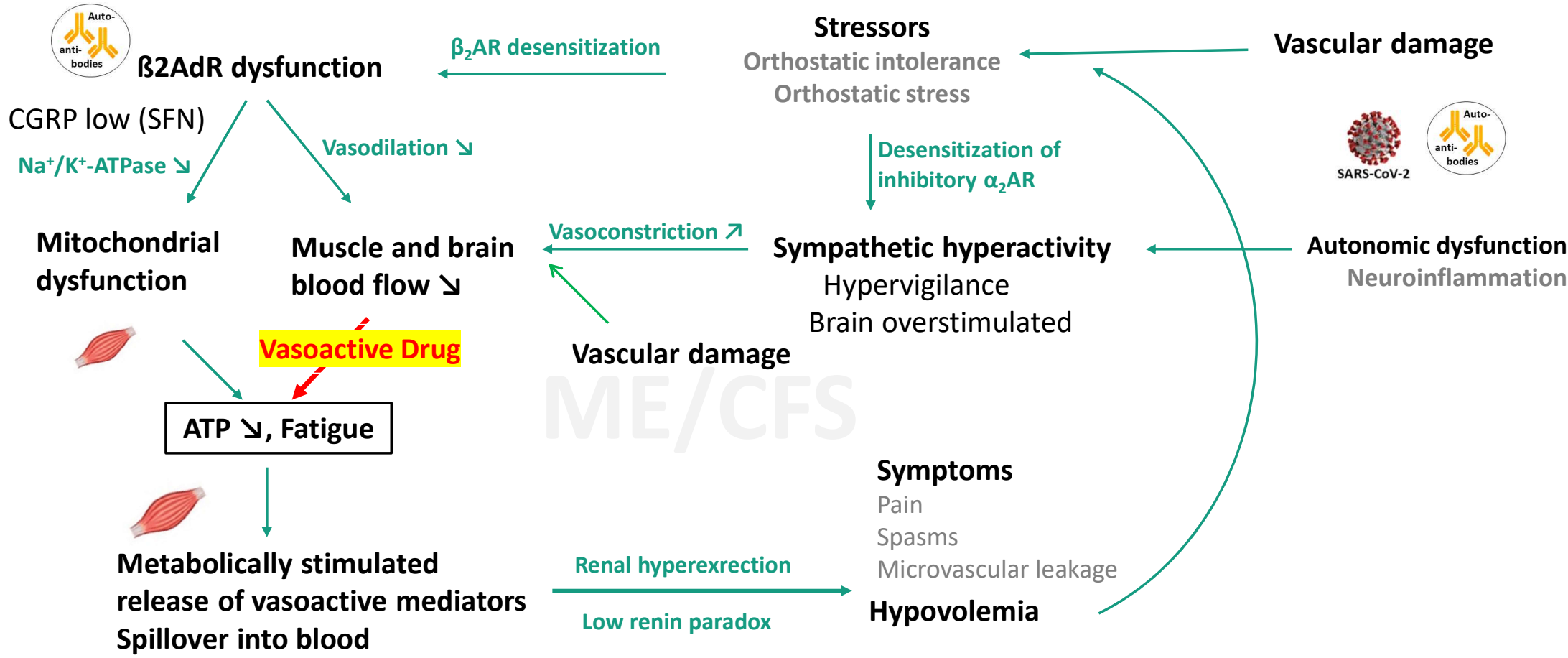

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Wirth and Scheibenbogen, 2020, 2021, 2022

Postural Tachycardia in ME/CFS Teaches What Goes Wrong

- **Characteristics of POTS**
  - Symptomatic OI, no fall in BP, but rise in heart rate
  - Decrease in CBF (van Campen et al., 2021)
- **Recognitions:**
  - **Overshooting sympathetic activity causes cerebral vasoconstriction** to reduce CBF and most likely skeletal muscle blood flow
  - **Symptoms of OI and impaired cognition are mainly due to a decrease in CBF to further raise sympathetic activity (vicious circle)**
  - A certain rise in sympathetic tone is necessary to constrict capacitance vessels for orthostatic regulation, but sympathetic activity is **excessive** causing even cerebral vasoconstriction
- **Possible therapeutic interventions:**
  - Decrease sympathetic tone to a reasonable level, but maintain what is necessary:
    → **Antisympathotonic drugs like guanfacin and clonidine in moderate doses**
  - **Vasodilation** of brain and skeletal muscle blood vessels

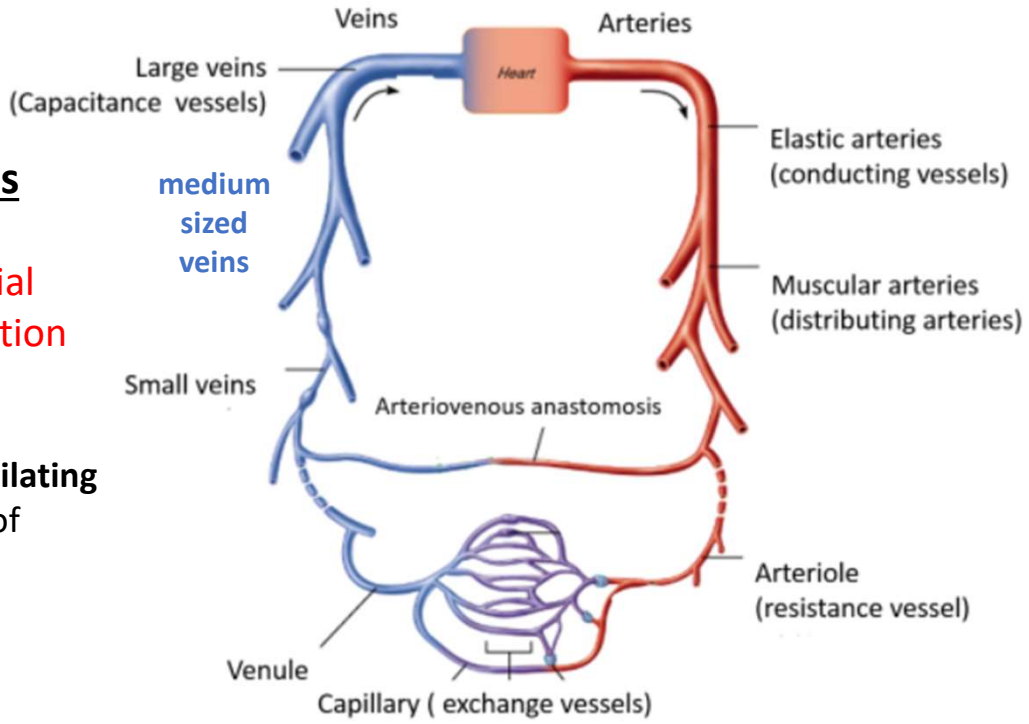
The Ideal Vascular Profile of a Vasodilator Drug for the Treatment of ME/CFS: Selective Vasodilation

Capacitance vessels

No dilation !

Contraction is essential for orthostatic regulation (MoA of Midrodine)

Histamine is strong in dilating veins: Beneficial effect of antihistamines?



Brain and skeletal muscle blood vessels

Dilation !

Intestinal blood vessels

No or little dilation to maintain BP as the perfusion pressure and to avoid diversion of blood away from brain and muscles (steal efffects)

Selective vasodilation of brain and skeletal blood vessels is not possible with current drugs

Is at least preferential vasodilation possible?

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Vasoactive Drugs Having no Effect on Cerebral and Skeletal Muscle Blood Flow in the Healthy Situation

- Calcium channel blockers (CCBs)
- Angiotensin-receptor blockers (ARB)
- ACE-inhibitors

} Renin low in ME/CFS (paradox)

- Nitrates, molsidomin
- Endothelin-antagonists
- Alpha1 adrenergic-blockers (slight rise) ↔ Agonist Midrodine for orthostatic hypotension

These drugs may have some vasodilator efficacy in highly vasoconstricted areas in patients (vascular spasms) or in pathophysiology where these mediators might be generated (e.g. endothelin elevated in ME/CFS)

Drugs like ARBs or ACEi may show chronic beneficial effects on vascular remodeling and on damage as in PCS

The Vasoactive Drugs that Remain Showing a Rise in CBF

Soluble guanylate cyclase (sGC) stimulation: Rise in CBF even with falling BP

- Vericiguat (confirmed in older patients with an sGC activator from Cyclerion)

PDE5-inhibitors: good efficacy on cerebrovascular resistance but inconsistent on CBF due of BP fall

- Similar to sCG-inhibition, still dependency on NO. Avoid those with a short duration of action like Silfenadil

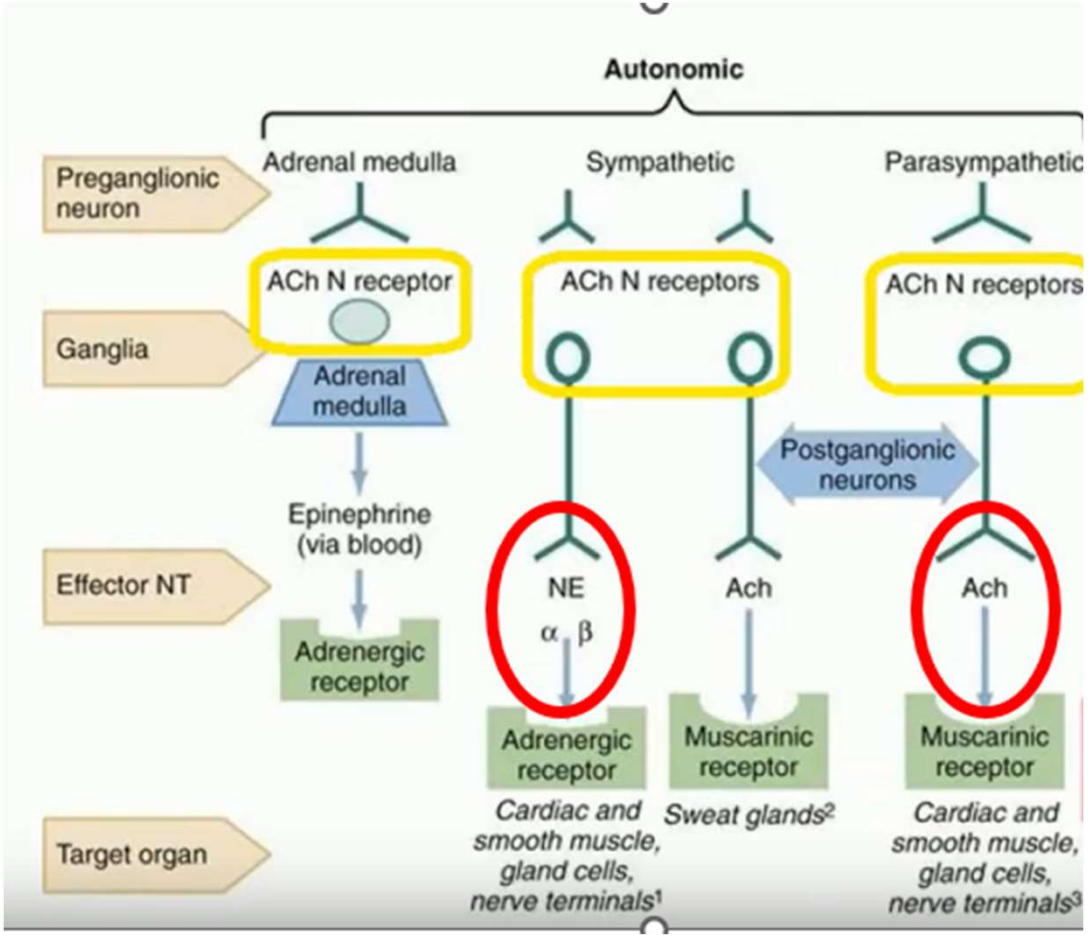
Stimulation of receptors on endothelial cells to release NO: ß3AdR, AChR

- ß3-adrenergic agonism: ß1-receptor antagonist Nebivolol with additional ß3-adrenergic agonistic properties
- Stimulation of endothelial acetylcholine receptors: two different types
  - Muscarinergic M3 receptor agonism (pyridostigmine (Mestinon))
  - Nicotinic receptor agonism via the "beneficial" **α7nAChR** (nicotine patches for LC [1] , Mestinon)
    - α7nAchR gains importance vs muscarinergic receptors in experimental hypertension
- Arginine as a supplement to fully exploit NO-formation? Slightly raises CBF in animals

These drugs raise CBF, but not skeletal muscle blood in the healthy situation. Nevertheless, they may oppose excessive vasoconstrictor influences in skeletal muscle

[1] Leitzke. Bioelectronic Medicine 2023, 9:2

Cholinesterase-Inhibition and Nicotine: Transmission in the Ganglion of Sympathetic and Vagal Nerves is Nicotinergic



Pyridostigmine and Nicotine:

- The effect of nAChR stimulation in the first sympathetic ganglion is predominant over the vagal ganglion to raise sympathetic tone in healthy situation
- **May be suited for patients with orthostatic hypotension and patients with alpha1-adrenergic AAB to improve orthostatic regulation**
- **Risk**: Excessive sympathetic stimulation by nicotine?

Choice of Drug May Depend on the Type of Associated OI

OI is present in at least 90% of ME/CFS, associated with a decrease in CBF

POTS and symptomatic OI (no tachycardia, no hypotension, but symptoms of OI and fall in CBF (van Campen et al.))

- sGC-activator (Vericiguat), PDE5-inhibitors, Nebivolol
- Guanfacin and clonidin (antisympathotonic drugs to cut the sympathetic overshoot with moderate doses)

Orthostatic hypotension

- Physostigmine; nicotine patches (if AAB against M3-AChR as nicotine acts via α7nAChR)
- Antihistamines? Vascular actions of histamine involve both H1- and H2-receptors
- Alpha1-adrenergic agonist Midrodine

Expected benefits: Improved organ perfusion

- CBF: Improvement of neurological symptoms, cognition, brain fog and OI (!), decrease in sympathetic tone
- Skeletal muscle: improved exercise tolerance, less symptoms

Precautions:

- Vascular therapy under coverage of volume therapy, compression stockings, salt, mineralcorticoids.
- Moderate doses only, dose escalation, careful monitoring

Outlook: A More Effective Treatment with a New Drug Principle from a Rationale, Pathophysiologically Driven Approach?

Deficit of current vasoactive drugs

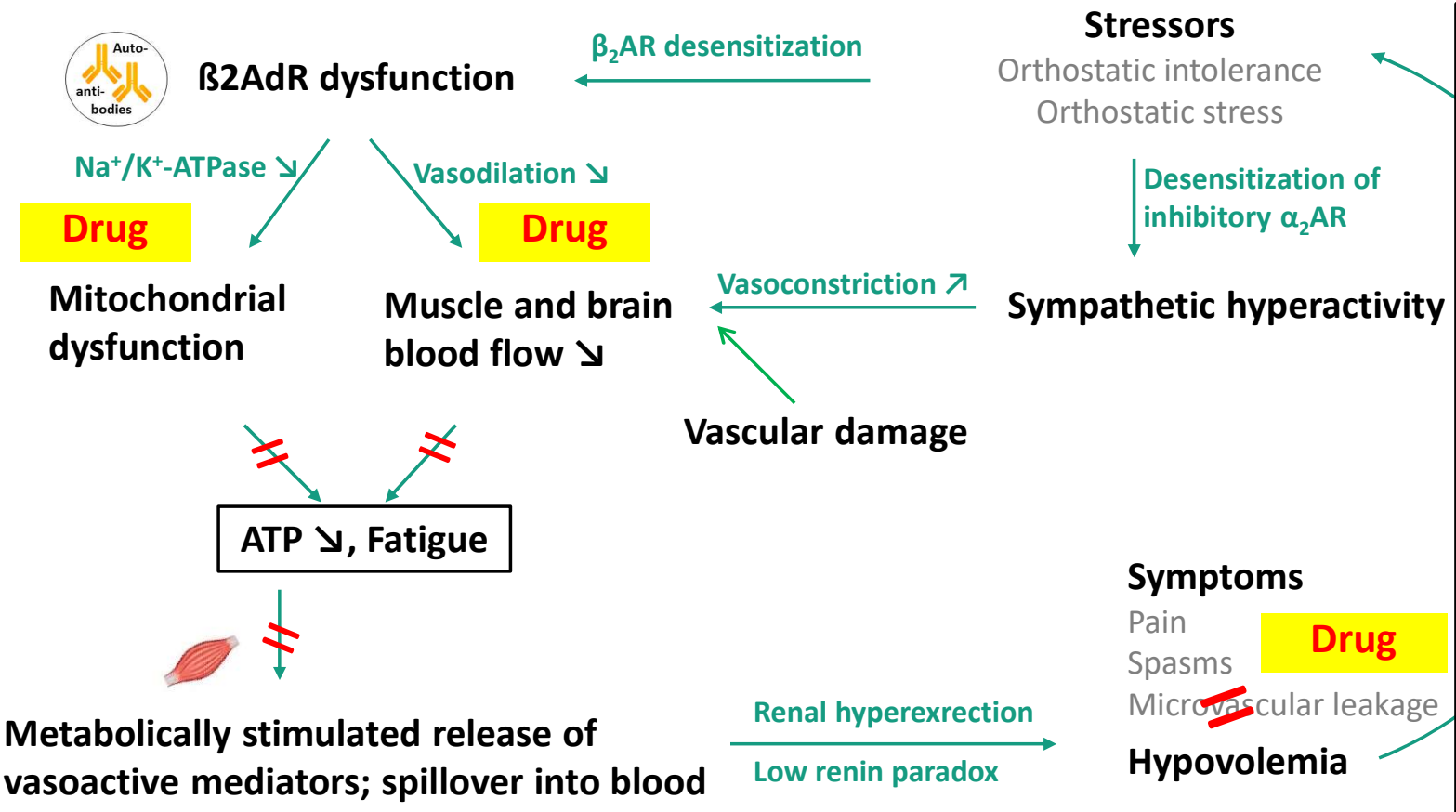
- No stimulation of Na^+/K^+-ATPase in skeletal muscle (related to mitochondrial dysfunction)
- No direct effect on skeletal muscle blood flow
- A number of precautions to avoid worsening of orthostatic function

New drug principle

- Stimulation of Na^+/K^+-ATPase in skeletal muscle
- Moderate stimulation of both cerebral and skeletal muscle blood flow. No fall in BP
- Inhibition of microvascular leakage

Derived from the unifying working hypothesis (Wirth and Scheibenbogen, 2020,2021,2022)

Outlook: A More Effective Treatment with a New Drug Principle with Multiple Beneficial Effects against Key Pathomechnisms of ME/CFS?



Outlook:

- **Human proof-of-concept in 3 years (phase 2)**
- **Novel first-in-class approach, no drug repurposing**
- **Development by Mitodicure GmbH, a biotech startup**
- **Critical step: > €10m seed financing needed**