



# A new wrinkle: Skin manifestations of aging may relate to autonomic dysfunction

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**Summary** Various mechanisms have been argued for skin wrinkling, one of the hallmarks of aging. We hypothesize that chronic sympathetic bias is a previously unrecognized mechanism for wrinkling. In the acute setting of water immersion, reversible skin wrinkling is a well-known reflex mediated by the autonomic nervous system. We postulate that skin wrinkling results as a local maladaptive manifestation of a global chronic sympathetic bias that emerges during aging. The persistence of such changes may induce additional compensatory remodeling to cause permanent alteration of the skin. Sympatholytic agents may prove beneficial for arresting or ameliorating the development of wrinkles. Conditions that amplify sympathetic bias such as stress, smoking, amphetamine abuse, HIV, heart failure, and transplantation may accelerate wrinkling. Other common diseases of the skin may also arise as particular manifestations of aberrant autonomic activity through induction of vascular and immune dysfunctions. The temporal and spatial distribution of these dermatologic conditions may reflect variation of autonomic balance, which also regulates T helper immune balance. For all of these dermatologic conditions, local and systemic administration of drugs and medical devices that pharmacologically or electrically modulate autonomic nervous system activity may yield benefits as well.

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## Introduction

The development of folds and creases in the skin – wrinkles – represents one of the hallmarks of aging. These changes have previously been largely ascribed to ultraviolet damage and collagen remodeling from sun exposure [1]. While photoaging clearly occurs, wrinkling eventually occurs in virtually all areas of the body, including those re-

gions which receive little or no sun exposure. Other explanations invoked to explain the development of wrinkles include induction of stretching and laxity from use of facial musculature [1]. As originally described by Glogau, wrinkles progress through a defined evolutionary sequence – they start out only identifiable at times of animated expression, but eventually culminate in wholesale appropriation of skin structure [1]. We propose that sympathetic bias may play a significant and underappreciated role in the formation of wrinkles – one which represents a previously unexploited opportunity for therapeutic intervention.

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## Evidence

We know that as the body undergoes chronologic aging, progressive sympathetic bias develops over time [2]. This imbalance may underlie dysfunction that arises in many physiologic systems [2]. Given the diffuse nature of autonomic innervation, tonic sympathetic drive should affect the behavior of the skin throughout the body. Indeed, the transient change in electrical potential evoked by various stimuli has become known as the skin sympathetic reflex, or SSR [3]. Abnormal SSR can also indicate the presence of autonomic dysfunction in diseases such as diabetes [4].

Numerous reports have described the phenomenon of reversible wrinkling of the skin in response to water immersion [5]. Although vasoconstriction appears to mediate this process [6], the presence of peripheral arterial disease does not interfere with this process, suggesting that this process does not involve hemodynamics per se [7]. However, disruption of sympathetic nerve fibers does inhibit this change, identifying the autonomic nervous system as a requisite mediator of this phenomenon [8]. This finding has enabled water immersion wrinkling to become a bedside test of sympathetic nerve function in the limbs [9]. The need for water to induce wrinkling may arise from the need for altered epidermal homeostasis to function as a trigger [10].

If so, sympathetic bias may also produce an overall bias towards sustained wrinkling. Smoking has a strong association with wrinkle formation [11], and chronic use of nicotine leads to the production of sympathomimetic effects [12]. One might expect to find accelerated skin wrinkling in other conditions that amplify sympathetic bias such as behavioral stress, physiologic stress, environmental stress, amphetamine abuse, AIDS, heart failure, and transplantation. The utility of botulinum toxin to diminish wrinkles may not entirely lie in its ability to paralyze underlying muscle – disabling sympathetic innervation to the targeted region of skin may also produce a benefit [13]. Indeed, the efficacy of botulinum toxin in treating hyperhidrosis arises from its ability to block the sympathetic innervation of eccrine sweat glands [14].

Although SSR involves the post-ganglionic, unmyelinated sympathetic fibers of the sudomotor pathway [15], as opposed to the vasoconstrictor sympathetic pathway which controls wrinkling [6], the presence of high levels of sympathetic activity may lower the threshold for generating a wrinkling response to any local changes in humidity, such as that produced by water immersion, or

to other environmental parameters. However, with sufficient escalation of activity, the increased sympathetic bias alone may prove sufficient to compel such changes without the need for environmental cofactors. If allowed to continue on an ongoing basis, the persistence of such changes may induce additional compensatory remodeling to cause permanent alteration of the skin.

## Implications

If the formation of wrinkles relies in part on the development of sympathetic bias, sympatholytic agents, ACE-inhibitors, pro-cholinergics, acetylcholinesterase inhibitors, anti-aldosterone agents, and renin-inhibitors may prove beneficial for arresting or ameliorating the development of wrinkles. Topical application of such agents in appropriate vehicles may limit the production of undesirable systemic side effects. Alternatively, systemic administration may provide ease of administration and simplify the beautification regimen. Retrospective studies comparing individuals on adrenergic antagonists for other conditions with their age-matched counterparts would provide evidence for this premise. Timely use of such interventions likely would prove critical, so as to abrogate any process prior to the development of more durable sequelae as a byproduct of remodeling.

These findings suggest that the structure and function of the skin may have closer ties to overall systemic health than one might suspect. Spatial variation in autonomic function may generate immunologic variation and thus play a significant role in many dermatologic diseases. Leprosy may exemplify this intertwining of immunity and autonomic activity – the bacteria responsible for its pathogenesis infect sympathetic nerves [21–24], which preferentially harbor a Th2 immune biased environment more conducive to their growth. The tendency towards involvement of the nose, ears, and distal extremities may stem from those regions harboring increased sympathetic activity because of greater environmental variability secondary to displacement from the homeostatic core of the body. In similar fashion, diseases such as psoriasis that demonstrate a characteristic pattern of involvement on the body may array their lesions according to regional variations in sympathetic bias. Indeed, psoriasis often worsens with use of beta-blockers [20], suggesting that autonomic regulation plays a significant role in this disease. The temporal variation of many dermatologic disease during menstrual, seasonal, and lifespan cycles as

well as during pregnancy may also relate to adaptive variation of autonomic balance, which also modulates Th balance.

Other diseases of the skin may also arise as particular manifestations of aberrant autonomic activity. The erythema associated with many eruptions may stem from manifestations of autonomic dysfunction such as hyperemia, endothelial cell dysfunction, vasomotor dysfunction, and inflammation. Conditions such as atopic dermatitis that typically worsen with stress [16] may involve provocation of local immunologic reactions via a systemic sympathetic response. Many indicators of autonomic dysfunction arise in the context of atopic dermatitis, including abnormal sweating patterns [17], abnormal adrenaline response to standing [18], as well as abnormal arteriolar function, pilomotor smooth muscle function, and sweat gland function [19]. For all of these dermatologic conditions, local and systemic administration of drugs and medical devices that pharmacologically and electrically modulate autonomic nervous system activity may yield benefits as well.

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