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The Sympathetic Arterial Innervation and Body Stress

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The sympathetic nervous system (SNS) is the anatomic conduit for the body's physiologic responses to various forms of physical and mental stress. Largely for this reason SNS relationships to the ancient Vedic philosophy of mind/body balance continue to attract attention. For example, recent studies of murine disease models have elucidated mechanisms by which stressful SNS excitations and ablations can alter the body's immune system responses to uveitis and encephalitis(1).

Similarly, current studies of the SNS arterial innervation have revealed a new aspect of the body's response to stress; namely, the stimulated release of tissue plasminogen activator (t-PA), the body's principal fibrinolytic system enzyme, from SNS nerve endings embedded in artery walls. Previously known to exist in CNS neurons and pathways, as reviewed (2), we later observed its presence in the arterial innervation(3). Subsequently, a vast peripheral SNS axon network was shown to distribute active t-PA throughout the murine organism (4), and to abruptly release t-PA in vitro and in vivo in response to SNS stimulations (5). The importance of the t-PA presence in artery walls relates to its ability to cleave plasminogen and thereby activate plasmin, the aggressive and versatile protease that lyses fibrin clots, degrades and remodels extracellular matrices, activates cytokines and regulates cell migrations (6). In addition, both t-PA and plasmin can degrade fibrinogen, a major determinant of blood viscosity(7). Stressors have long been known to increase blood fibrinolysis and t-PA activity but the vessel wall t-PA source was not identified, or thought to be vascular endothelium (8). We therefore surmise that the acute releases of t-PA with Norepinephrine(9) into the bloodstream during stressful SNS excitations serves to prevent capillary clotting and stasis during periods of arteriolar constriction. This new link between the body's sympathetic and fibrinolytic systems now suggests that these multiple t-PA and plasmin proteolytic effects in artery walls and the blood are autonomically regulated, and play a wider role in cardiovascular responses to chronic stress than previously recognized(5).

Crucial to an understanding of this new process is the seldom studied unique anatomy of the arterial innervation. For example, its design points to a high capacity for the continuous production and storage of large amounts of the t-PA enzyme needed to fill a vast peripheral network of SNS axons. T-PA is synthesized and packaged in vesicles within the cell bodies of paravertebral SNS ganglion neurons. The active enzyme is then transported for long distances in fine (0.5-3.0 μ m wide) axons that extend to multiple artery walls. On leaving the heart these innervated arteries divide and subdivide into ever smaller tubes having progressively thinner walls. But here is the point: as these arteries narrow down to become arterioles the plexus of t-PA-bearing sympathetic nerve terminals embedded in the outer wall adventitia fails to diminish in proportion to the thinning wall and narrowing lumen (3,10). Consequently, the walls of small resistance arteries and arterioles that control blood pressure and capillary perfusion receive more t-PA-bearing sympathetic nerve endings per unit of surface area than larger arteries

Further, these fine t-PA bearing axons persist down to the 1 μ m thin walls of 20 μ m wide precapillary arterioles (3). Because these microarteries connect to and regulate perfusion in an estimated ten billion capillaries in the adult human (11) the need for an ongoing high production of t-PA becomes evident. Indeed, in vitro studies of t-PA release from isolated arterial segments have confirmed an interesting mathematical relationship between artery size and t-PA release: i.e. arterial segment t-PA release per milligram is directly proportional to the immunostained SNS innervation density, and inversely related to the luminal endothelial surface and the vessel diameter(3).

Within the artery wall t-PA is released from bulging varicosities found in all SNS nerve terminals embedded in the adventitia(10). Sympathoadrenal stressors trigger an acute burst release of active t-PA from vesicles closely packed within these varicosities embedded in the outer artery walls (Fig 1). This exocytosis is accompanied by norepinephrine release from similar or the same vesicles.(9) In turn, these observations have raised the possibility that t-PA released from adventitial nerve terminals in thin arteriole walls may cross the wall and enter the microcirculation. Indirect evidence for such a passage in vivo includes i) an abrupt rise in rodent plasma t-PA fibrinolytic activity level following SNS stimulations; and ii) reductions of over 60% that following a systemic chemical

sympathectomy.(8) In addition recent unpublished data from transgenic mouse models have confirmed that bio-marked t-PA confined to the SNS enters the bloodstream . Interestingly, these observations now provide a new explanation for the long historic association of stressful violent deaths with a persistant post –mortem fibrinolysis and bleeding from small vessels, as well as similar autopsy observations in England during WW2 (8). Together, these findings underscore that the sympathetic t-PA release during stress is most prominent in the vast innervated microvasculature, rather than larger arteries . In mental health research the long known association of chronic and recurrent stress with premature ageing and its disorders has also been hypothesized to reflect the role of t-PA as an effector agent of artery wall damage (5).

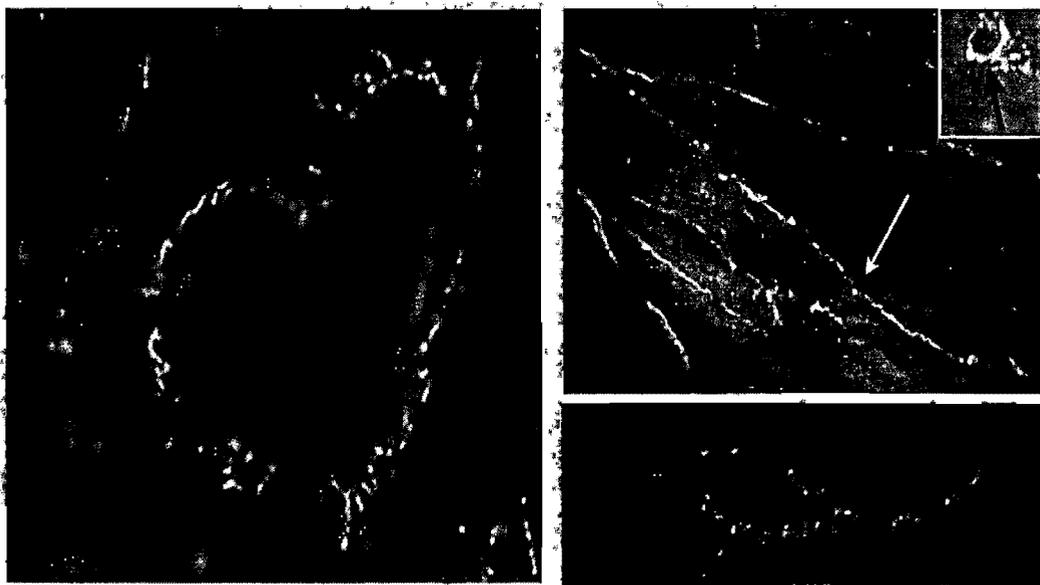


FIGURE: Artery walls immunostained for t-PA show the enzyme (white fibers) within SNS axons in the outer wall adventitia. (Left) large coronary artery h section shows t-PA- bearing axons confined to adventitia of a thick wall without t-PA presence in the media. (Right) Pericardial surface shows SNS axon terminals with tiny varicosities embedded in arteriole walls. Arteriolar section (arrows & inset) shows thin wall permeated by released t-PA.

We therefore conclude that, new anatomic and functional observations of the arterial innervation verify the concentration of an autonomically regulated t-PA release in the innervated microvasculature, and that the enzyme passes through arteriole walls and enters the bloodstream. These effects are additional to, and do not contest, the ongoing constitutive release of t-PA from vascular endothelium. Further studies of the SNS autonomic regulation of microvascular fibrinolysis as physiologic and pathophysiologic mechanisms are therefore recommended.

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References

1. Cone RE. 2006. Neuroimmune interactions: a bidirectional flow that leads to health and disease. *neuroImmune interactions: a bidirectional flow that leads to health and disease.elements*,4(2),7-9,2006
2. Sttckland S. 2001. Tissue plasminogen activator in nervous system function and dysfunction. *Thromb Haemost* 86: 138-143

3. Jiang X, Wang Y, Hand AR, Cone RE and O'Rourke J. 2000. Presence of tissue plasminogen activator(t-PA) in the adventitial sympathetic nerves that innervate small arteries: morphologic evidence for a neural fibrinolysis. *Fibrinolysis and Proteolysis*. 14:35-46
4. Hao Z, Guo C, Jiang X, Krueger S, Pietri T, Dufour S, Cone RE and O'Rourke J. 2006. New transgenic evidence for a system of sympathetic axons able to express tissue plasminogen activator(t-PA) within arterial/arteriolar walls. *Blood* 108:200-202.
5. Hao Z, Jiang X, Sharafieh R, Shen S, Hand AR, Cone RE and O'Rourke J. 2005. Stimulated release of tissue plasminogen activator from artery wall sympathetic nerves: Implications for stress-associated wall damage. *Stress* 8:141-149
6. Syrovets T, Šimmet T. 2004. Novel aspects and new roles for the serine protease plasmin. *Cell Mol Life Sci* 61:873-885
7. Hitosugi M, Omura K, Yufu T, Kido M, Niwa M, Nagai T, Tokudome S. 2007. Changes in blood viscosity with the recombinant tissue plasminogen activator alteplase. *Thrombosis Research* 120:447-450
8. O'Rourke J, Jiang X, Hao Z, Cone RE, Hand AR. 2005. Distribution of sympathetic tissue plasminogen activator to the distant microvasculature. *J Neurosci Res* 79:727-733
9. Parmer RJ, Mahata S, Sebald MT, O'Connor DT, Miles LA. 1997. Tissue plasminogen activator(t-PA) is targeted to the regulated secretory pathway. Catecholamine storage vesicles as a reservoir for the regulated release of t-PA. *J Biol Chem* 272: 1976-1962
10. Burnstock G. 1975. Innervation of vascular smooth muscle: histochemistry and electron microscopy. *Clinical and Experimental Pharmacology and Physiology Suppl.* 2:7-20
11. Guyton AC, Hall JE. 2000. The microcirculation and the lymphatic system in: Guyton, AC, Hall JE, editors. *Textbook of medical physiology*. Philadelphia: Saunders. 183-197

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8. Dwivedi S, Pachori S.B. Amrita, Medicinal plants with hypotensive activity. *The Ind. Pract.* 1994; XLVII (2) 117-134.
9. F. Ahumada et. al. *Phytochemical research*, vol.-5, issue-3, 111-114.
10. Anwar H: Gilani et. al. *Journal of ethnopharmacology*, vol. -100, issue-3, 14 sept. 2005, 347-352.
11. Publication and information Directorate, CSIR, the wealth of India, 1996; VII: 3-4.
12. Mishra A.S., Verma J. Nirupama K.: *Studies on medicinal properties of Convolvulus pleuricaulis and Boerhaavia diffusa*. *Biojournal* 1995; 6(1-2): 87-94.
13. Prof. Ajay Kumar Sharma: *Heart Disorders and Their Care in Ayurveda*; Sri Satguru Publications, Delhi, 1st Edition 2005.

**Soul : As in the body the embodied self passes through childhood,
youth and old age, so is its passage into another body;
—the wise thereat are not disturbed**

Gita, chapter 2, verse 13

**No weapon can pierce it;
no fire can burn it;
no water can moisten it;
nor can any wind wither it**

Gita, chapter 2, verse 23