EDITORIAL

Why fixing the furrow does not fix the flash: understanding hot flash biology with botulinum neurotoxin

Although best known for its use as a popular anti-wrinkle cure for forehead frowns, botulinum toxin A, the sympathetic cholinergic nerve blocker, has been Food and Drug Administration approved since 2004 as an effective treatment of hyperhidrosis or excessive sweating. The neurotoxin seems to abolish the sweating response primarily through its inhibition of acetylcholine effects on sweat gland secretion. According to the International Society for Hyperhidrosis, a patient education resource, treatment side effects are rare, and improvements can last for up to a year. Surgeons, airline pilots, and others in the public eye have embraced its use as a solution to a long-standing occupational hazard.

At the same time when excessive perspiration has become a curable “lifestyle” problem, the science of sweating has taken on important public health implications, given the serious consequences of hyperthermia in such diverse populations as military combat personnel and the elderly during summer heat waves. Using sophisticated space-laboratory technologies, including a tube-lined, water perfusion suit to simulate cold and heat stress in a controlled environment, researchers have tested an array of pharmacologic probes to better characterize the differential contributions of sympathetic vasoconstrictor and vasodilator mechanisms for temperature-induced changes in skin blood flow. The picture is far from clear, but most human studies conducted in the last 15 years support an important role for an active sympathetic cholinergic vasodilator system for heat loss, neuroregulated in part by acetylcholine, which is separate from the mere suppression of the sympathetic adrenergic vasoconstrictor system. Using botulinum toxin as the experimental challenge to inhibit cholinergic neurons, researchers have demonstrated a clear and consistent blockade of the expected elevations in skin blood flow and sweating responses in heat-stressed individuals. (For an excellent review of this field, see Kellogg.)

For the most part, these elegantly designed heat stress protocols have been conducted in young healthy men (although in some cases, the sex of the research participants is not reported). But recently, some of the same investigators studying the neuroregulation of sweating with botulinum toxin have discovered middle-aged women and the menopausal hot flash as a new study paradigm for the further testing of the “active cholinergic vasodilator” hypothesis. In so doing, they chart a new direction in hot flash research, which is likely to lead to further insights about the nature of night sweats.

A series of recent studies funded by the National Institute on Aging and conducted by physiologist Craig Crandall, PhD, and colleagues from the University of Texas Southwestern Medical Center is shedding light on the biochemical mediators of downstream hot flash effects in the skin. Using laser-Doppler flowmetry as a specific sensor of skin blood flow, their 2008 findings confirmed the long-held presumption that hot flashes are indeed accompanied by dramatic increases in local cutaneous blood flow. Now, in this issue of Menopause, the Crandall team extends these findings and reports for the first time on the effects of botulinum toxin type A (referred to here as BTX) as a hot flash probe.

Using the same heat stress procedures, measurement methods, and experimental drug regimen as in earlier work with young men, two groups of postmenopausal symptomatic women underwent monitoring after pretreatment with BTX either in the forearm (low-intensity responses) or glabelar (high-intensity responses) regions. Local changes in skin blood flow and sweat rates at the BTX-treated site and at adjacent, untreated control sites were compared before, during, and after hot flash episodes. To explore whether any BTX effect involved a neural origin, a third group of untreated volunteers were monitored during hot flashes solely for changes in postganglionic sympathetic nerve activity (recording from the nerve innervating the skin on the dorsal side of the foot). In support of the study hypothesis, BTX treatment dramatically attenuated the expected hot flash–induced increases in blood flow and sweating in both forearm and forehead compared with the adjacent control areas. Moreover, in the third group of untreated women, increased skin nerve activity was observed during hot flash episodes, pointing to an important neural link.

Taken together, these findings, though preliminary, provide breakthrough evidence for a key role for the sympathetic cholinergic nervous system as a mechanism for the heat dissipation skin responses to a hot flash, the same system involved in thermoregulation during heat stress.

It would have been ideal had all women undergone the same identical protocol with the full set of measures conducted simultaneously, or an asymptomatic group (premenopausal?) been monitored as a secondary control. However, given the participant burden, the extensive instrumentation required for the full protocol and related equipment costs, such an undertaking may not have been feasible. (A TV news video clip of a research volunteer undergoing the experimental protocol can...
be seen at the url referenced below.6) Another minor question relates to whether the high body mass index of the study sample (mean ± SD body mass index, 27 ± 6 kg/m²; range, 21-42 kg/m²) may have influenced the observed hot flash results or, for that matter, the generic sweating response itself. In view of the well-known relationship between obesity and hot flash incidence, presumed to be a function of thermogenic load, further studies controlling for this confound would seem warranted.

It is clear that the more we study the hot flash mechanism, the more questions we raise. With the experimental conditions described here, these investigators observed a significant dip in blood pressure with hot flashes, yet no preflash elevation in core temperature was observed, contrary to the findings of other teams.7,8 To what extent these differences were caused by the more extreme heating methods used here compared with the conventional hot flash induction methods used by others (heating pads worn in a warm room) awaits further study (As a neuroendocrine physiologist, I am tempted to suggest the addition of salivary cortisol measures as a marker of protocol stress.)

It may be too early to extrapolate from what is known about the thermoregulation of heat stress to the vasomotor symptoms of menopause, but these findings add to the evidence for some overlapping similarities as well as differences between the two sets of biology. In a 2010 study in Menopause, the Crandall team9 also demonstrated a role for nitric oxide, but not prostaglandin inhibition, in hot flash–triggered skin vasodilation, both known to contribute to neurally mediated vasodilatory responses to heat stress.

As we drill down further to the essence of the hot flash response, these granular insights will surely refine our thinking about potential new compounds to therapeutically exploit for minimizing hot flash discomforts. However, to their credit, the investigators of the current report provide the cautionary note that their findings do not support the use of BTX treatment to alleviate hot flashes. Such reasonable advice is likely to go unheeded, and the potential for distorted interpretations of these findings by the lay media is high. In the eyes of the public, it may not be a giant leap from the use of BTX for severe facial blushing or excessive axillary sweating to menopausal symptoms. There are already several media reports on the Internet6,10 that conflate these different phenomena (which I discovered by googling, “botox to prevent hot flashes”). As noted by Dr. Crandall himself in 2008 in response to a TV news reporter who wondered about the value of BTX as a hot flash remedy, he replied: “…perhaps we can find other agents that might…have similar effects (sic on hot flashes) without adverse effects, because clearly we’re not going to give Botox throughout the body.”

Only time will tell whether the public understands this important, emerging insight: a hot flash, though sensed most commonly in the upper chest and face, is a systemic, body-wide, heat dissipation response, regulated by a complex set of neural controls. It has been known for some time that a complication of regional sympathectomy (as well as BTX treatment) to block sweating in the axilla or face is the onset of compensatory sweating in other body regions. To borrow an analogy, it seems that Mother Nature (typically portrayed as a wise, postmenopausal woman) may not be so easily fooled by short-cut attempts to undermine her sophisticated suite of hemodynamic regulatory mechanisms. The hot flash may indeed be part of that armamentarium.

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REFERENCES