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The mysterious role of prostaglandin E₂ in the medullary raphé: a hot topic or not?

Joseph A. DiMicco and Dmitry V. Zaretsky
Department of Pharmacology and Toxicology, Indiana University School of Medicine, Indianapolis, Indiana

THE STUDY BY TANAKA AND MCALENN published in this issue of American Journal of Physiology—Regulatory Integrative and Comparative Physiology (32) addresses a subject of considerable interest in the field of thermoregulation and one that for many years has been central to our understanding of fever, the regulated increase in body temperature evoked by immune challenge. The notion that prostaglandin E₂ (PGE₂) plays a key role in the signaling that translates a peripheral immune challenge into changes in the activity of specific thermoregulatory circuits is well established, but exactly where (and how) this signaling occurs is not entirely clear. The median preoptic area of the hypothalamus is certainly one such site (for review, see Ref. 2). However, PGE₂ may reach other regions of the brain after being synthesized either locally, e.g., in the vascular endothelium of blood vessels throughout the central nervous system (35), or peripherally (9) so that relatively high levels appear in the cerebrospinal fluid in fever (8, 10). This and the fact that receptors for PGE₂ are found elsewhere in the brain (19) invites the possibility that the action of PGE₂ at other sites may well contribute to the febrile response.

In this regard, it is somewhat surprising that the specific hypothesis examined—i.e., one such site might be the medullary raphé—had not been tested previously. The evidence in support of such a suggestion represents convergent findings from several investigative directions over the past decade and makes a compelling case. First, neurons in the region of the raphé pallidus (RP) have emerged as key regulators of sympathetic activity responsible for both metabolic activation of interscapular brown adipose tissue (IBAT), the major thermogenic organ in rats, and cutaneous vasoconstriction in the tail, a peripheral brown adipose tissue (IBAT), the major thermogenic organ in rats, and cutaneous vasoconstriction in the tail, a principal means of conservation (and, conversely, dissipation) of heat in this species (13, 14, 22, 23, 31). Second, central administration of PGE₂ results in increased fos expression, a marker for neuronal activation, in the region of the RP (17, 18). Third, neurons in the RP that are polysynaptically connected to IBAT express EP3 receptors (36), a prostaglandin E receptor subtype shown to be important in fever (20, 34). Finally, microinjection of the neuronal inhibitor muscimol into the RP blocks the increases in IBAT sympathetic nerve activity and fever evoked by central administration of PGE₂ in anesthetized rats (15, 17). Taken together, these data point to neurons in the RP as obvious additional potential sites of action for the central febrigenic actions of PGE₂.

Nevertheless, as is often the case for attractive ideas that are solidly rooted in previous experimental findings, the data of Tanaka and McAllen (32) that are relevant to this point are decidedly negative. Microinjection of PGE₂ directly into the region of the medullary RP failed to increase either IBAT or tail vasoconstrictor sympathetic nerve activity, thus appearing to preclude the possibility of a contribution for this mechanism to the febrile response in rats. However, several caveats are in order before the results of this potentially important study can be put into proper perspective.

One issue relates to the doses of PGE₂ and the volumes of injectate tested and the inherent difficulty involved in proving a negative. The authors employed doses ranging from 150–500 ng (i.e., 0.43–1.4 nmol) injected in volumes ranging from 300 nl to 1 μl. These doses are higher, in some cases by orders of magnitude, than those employed in similar microinjection studies to evoke febrile responses elsewhere in the central nervous system (1, 11, 12, 27, 37). In fact, the minimal dose injected (150 ng) is 15 times the dose shown to increase body temperature when injected intracerebroventricularly in unanesthetized rats (30). In addition, the doses used span a relatively narrow range in pharmacologic terms—less than a log. The inverted U-shaped dose response curve is not uncommon in the realm of pharmacology, and it is to basic principles of this discipline we must always attend when any substance, endogenous or not, is used as a drug as is PGE₂ here. Simply put, if a little is sufficient to elicit an effect, more may not always be better (see Refs. 7, 28, 33), and it is not inconceivable that the authors may have missed a response that would have been apparent at a lower dose.

Among the potential mechanisms through which microinjection of large doses could fail to elicit an effect might be spread or diffusion of the injected agent to other sites of action in adjacent regions, a potential complication of any microinjection study. In this case, this possibility is enhanced not only by the high doses injected but also by the facts that PGE₂ is highly lipid soluble and is not catabolized in the mammalian brain (19). These attributes, combined with the relatively large volumes of injectate used in the study, should translate into the ability of high doses of microinjected PGE₂ to reach and act at relatively distant sites in the brain. For example, EP3 and perhaps other subtypes of PGE receptors are detectable on neurons in the nearby ventrolateral medulla (16, 39), a site where, according to a preliminary report by Cao and Morrison (6), chemical disinhibition can suppress any increases in sympathetic nerve activity to IBAT evoked through the RP. Thus, it is not unreasonable to propose that hyperthermic effects of PGE₂ acting at the RP may have been obscured by its action at this or other brainstem sites and that a careful dose response analysis might unmask them.
While these caveats leave room for refinement and confirmation, the core finding of Tanaka and McAllen (32) that PGE₂ acting in the region of the medullary raphe appears not to contribute significantly to the hyperthermia that characterizes the febrile response will likely stand. This conclusion invites an intriguing question. If not as contributors to the hyperthermia seen in fever, then in what setting might these strategically located receptors play into the fast emerging panorama of central thermoregulatory circuitry?

One possibility, acknowledged by Tanaka and McAllen (32) in their discussion, but nonetheless left open by their results, is that PGE₂ might act in the RP not to excite but to suppress the activity of neurons in the region linked to the generation and conservation of body heat in the rat. The present study, like many that employ sophisticated, but technically complex, preparations to monitor endpoints related to specific thermoregulatory mechanisms, examined these endpoints in an anesthetized preparation. Because of this, core temperature was supported and maintained by external means, a standard approach in such experiments. Under these circumstances, an effect of microinjected PGE₂ to lower body temperature would be difficult to detect because, as these authors and others have shown, neither cutaneous tail vasococontractor nerves nor sympathetic nerves to IBAT exhibit significant levels of basal activity. Thus, the local microinjection of neuronal inhibitors, such as muscimol or glycine, under baseline conditions has no effect in anesthetized preparations (e.g., 3, 5, 13, 21). In contrast, microinjection of muscimol into the RP in conscious rats profoundly lowers body temperature (38), suggesting that under physiological conditions (i.e., in conscious rats at room temperature), these same neurons are active and play an important role in maintaining normothermia. It may be of interest, then, that systemic administration of LPS, a widely used model for fever, at typical (i.e., subneutral) ambient room temperatures (24, 25, 26). Like LPS-induced hyperthermia, these decreases in body temperature are likely mediated through the generation and actions of PGE₂ (see Ref. 9). If so, then could this hyperthermia, apparently absent in anesthetized rats (4), represent an action of PGE₂ at the mysterious EP₃ receptors in the RP, an action to inhibit active thermoregulatory neurons in the RP that was missed by Tanaka and McAllen?

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