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Editorial Focus: *Prostaglandin riddles in energy metabolism: E is for excess, D is for depletion.* Focus on "Food deprivation alters thermoregulatory responses to lipopolysaccharide by enhancing cryogenic inflammatory signaling via prostaglandin D_2"

Andrej A. Romanovsky and Andras Garami

Systemic Inflammation Laboratory, Trauma Research, St. Joseph's Hospital and Medical Center, Phoenix, Arizona

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THIS EDITORIAL FOCUS FEATURES A paper by Krall et al. (12) from the laboratories of two young investigators at Albany (New York) College of Pharmacy: Alex Steiner and Carlos Feleder. Both have already published their first independent studies (32, 37, 38), and their collaborative work highlighted herein continues this series of exciting projects and expands it to study the central mechanisms of the effect of food deprivation on the thermoregulatory response to systemic inflammation. The spotlight in this work is on PGE_2 and PGD_2. Whereas the role of the former in energy metabolism and inflammation is well established, particularly as a mediator of fever, the role of the latter is less clear.

The study by Krall et al. (12) reports, among other findings, that administration of PGD_2 into the lateral cerebral ventricle of the rat produces a weak hypothermic response. This observation finds support in several studies (Table 1), including an early study from the group of Osamu Hayaishi (36), author of many discoveries in the biology of PGD_2 (15, 17, 22). By the same token, the hypothermic activity of PGD_2 contradicts multiple reports in rats, rabbits, and cats, showing that PGD_2 either does not affect body temperature or causes hyperthermia (Table 1). One such report (5) is coauthored by Anthony Milton, a pioneer in studying thermoregulatory effects of prostanoids and discoverer of the pyrogenic activity of PGs of the E and F series (16). Is it possible that PGD_2 possesses a dual thermoregulatory action and can either decrease or increase body temperature?

The complex biology of PGD_2 makes such a proposition plausible and provides plenty of potential mechanisms, including dose-dependent (6, 11, 22) and species-specific (13) ones. The instability of PGD_2, due to its rapid enzymatic and nonenzymatic metabolism via multiple pathways, can also be a contributing factor. Some PGD_2 metabolites are thought to be biologically inactive, and the authors of the highlighted paper (12) observed that the hypothermic activity disappeared when stock solutions of PGD_2 were stored for $>$ 3 wk at -80°C. Other metabolites, including several PGs of the J series with a cyclopentenone structure, are biologically active and, moreover, can affect body temperature. For example, 15-deoxy-$\Delta^{12,14}$-PGJ_2 has been reported to be both antipyretic (18) and pyrogenic (A. A. Steiner, A. S. Dragic, J. Pan, A. A. Romanovsky; unpublished observation; cited from Ref. 30) in rats. It has also been shown that the thermoregulatory action of PGD_2 can depend on the route of administration (29) and be site specific within the brain (36), even though the current knowledge about specific sites and mechanisms of the central action of PGD_2 is sketchy. It was thought originally that its receptor (DP, presently known as DP1) is widely distributed throughout the brain, as mentioned in the highlighted paper (12). However, more recent studies with a specific antibody have shown that DP1 immunoreactivity is concentrated in the limited area of leptomeninges of the basal forebrain, where it is often colocalized with lipocalin PGD synthase (17). This area is in close proximity to the ventrolateral preoptic area (a "sleep center"), and the DP1 receptor in the subarachnoid space of the basal forebrain is thought to trigger the effects of PGD_2 on sleep (8). In addition to DP1, PGD_2 can also act through a distinct receptor type, DP2 (also known as the chemoattractant receptor-homologous molecule expressed on T-helper type 2 cells, or CRTH2) and through several other prostanoid receptors, perhaps different receptors in different species (34), as well as via a non-receptor-mediated mechanism.

An important methodological issue that cannot be neglected is that the thermoregulatory effect of a compound often strongly depends on the ambient temperature, especially in small rodents. Many adrenergic compounds (39), drugs of abuse (19), LPS (33), platelet-activating factor (10), and other substances cause hyperthermia in a thermoneutral environment but cause hypothermia under subneutral conditions. It is, therefore, critical to conduct thermophysiological experiments in rats and mice at a tightly controlled ambient temperature. It is also important to determine whether this temperature is neutral, subneutral, or supraneutral in each experimental setup, because the thermoneutral zone for the same animal in different setups varies widely, depending on several physical factors that affect heat exchange between the animal and its environment (25). One way to determine whether the conditions in a given setup are thermally neutral, subneutral, or supraneutral is by assessing tail skin blood flow, e.g., by thermometry or thermography (25), and several laboratories now use this approach for experiments in rats (1, 4) and mice (27). From this point of view, the work of Krall et al. (12) is impeccable. In addition to determining the thermoneutral zone in their setup and using properly characterized thermal conditions, the authors also took an important precautionary step in making all injections through preimplanted cannulas, without touching the animals, thus minimizing the associated stress and avoiding stress hyperthermia. Stress hyperthermia due to drug administration has been shown to strongly affect thermal responses. For example, it can

Address for reprint requests and other correspondence: A. A. Romanovsky, Systemic Inflammation Laboratory, Trauma Research, St. Joseph's Hospital and Medical Center, 350 W. Thomas Rd., Phoenix, AZ 85013 (e-mail: aromano@chw.edu).

Table 1. *Effects of PGD_2 on deep body temperature*

Species	Site of Administration	Dose, μg	Effect	Reference No.
Rat	Preoptic area	~0.9*	↓	36
	3rd ventricle	~0.02–0.8*	↓	36
	Lateral ventricle	0.001–10	↑	29
		0.01–0.03	↓	11
		0.1	↓	12
		~1–3*	↓	36
		1–50	↔	3
		2	↓	6
		20	↑	6
	Cisterna magna	0.05–0.5	↑	7
	Subarachnoid space	13†	↑/↓	15
	Femoral vein	0.1–10	↔	29
	Vena cava	16–102	↓	Unpublished‡
		85	↓	Unpublished§
Rabbit	Lateral ventricle	0.09–18	↔	13
		176	↑	13
Monkey	Lateral ventricle	2–285†	↔	22
		190†	↑	22
Cat	3rd ventricle	0.4–64	↔	5

Effects on deep body temperature are marked as: ↓, decrease; ↑, increase; ↔, no change; ↑/↓, inconsistent. *Dose was recalculated based on the body mass reported; †total amount administered over a 6-h infusion; ‡A. Garami, E. Pakai, A. A. Romanovsky, unpublished data, cited from Ref. 30; §A. A. Steiner, A. S. Dragic, J. Pan, A. A. Romanovsky; unpublished data, cited from Ref. 30.

mask the early febrile phase and modify the later phases of LPS fever (24). Because the physiological experiments of Krall et al. (12) were conducted expertly, their study leaves little doubt that PGD_2 can decrease body temperature in rats, at least under some conditions.

Besides decreasing body temperature, PGD_2 is thought to induce sleep (8), increase food intake (21), and cause analgesia (23) (Fig. 1). Interestingly, these effects are the exact opposite of those produced by the fever mediator, PGE_2, which is generally thought to cause wakefulness (8), decrease food intake (20), and induce hyperalgesia (28). Remarkably, these PGE_2- and PGD_2-mediated responses form distinct patterns that can be seen, respectively, during the first phase of LPS fever, which is mediated by PGE_2 (2, 31), and during LPS hypothermia, which is thought to be mediated by PGD_2 (36). We have called these two patterns the early and the late sickness syndromes, respectively, and proposed that they represent two different, sequential stages of the sickness syndrome (26). As a general rule, the early phase syndrome develops in a previously healthy organism, at the onset of its response to an infection. The late phase syndrome occurs when the organism is already exhausted by the preceding early phase syndrome, weakened by a preexisting pathology, or exposed to a severe, damaging homeostatic challenge. The biological significance of the early phase syndrome is the signaling of the pathogenic challenge (hyperalgesia), recruiting active defense mechanisms (fever), and securing the means (wakefulness, hypertension, generalized motor agitation) for the active search of the optimal environment (conditions for behavioral thermoregulation, sufficient water supply, protection from predators, etc.) for fighting the beginning malady. Manifestations of sickness during the late phase syndrome change drastically. The pain associated with damage loses its signaling function and starts to contribute to morbidity; consequently, hyperalgesia changes to hypoalgesia. Costly energy consumption during the early phase syndrome, decreased energy supply (e.g., due to the development of adaptive anorexia), and pathological energy expenditure (inefficient functioning of damaged tissues) make the threat of energy deficiency real. Hence, the energy-intensive responses (wakefulness, motor agitation, and arterial hypertension) change into sleep, motor depression, and normo- or hypotension, respectively. An elevated body temperature remains potentially beneficial, but its benefits could now be easily offset by the harmfully high energetic cost. Responding to this delicate balance, threshold dissociation develops, thus allowing body temperature to be maintained at either an elevated level or, if the cost-benefit ratio is especially unfavorable (e.g., in a cold environment), at a lowered level. Several energy-saving symptoms of the late phase syndrome, including sleep and motor depression, have been either proposed or directly shown to be beneficial during infection, and the conservation of energy is probably the primary role of this syndrome (26). Consistent with such a role, Krall et al. (12) report that the hypothermic effect of PGD_2 is enhanced following food deprivation. This is a new observation, which may be important for understanding mechanisms of thermoregulatory and other physiological responses to decreased food supply. Such mechanisms are currently being studied in several laboratories (9, 35), and the involvement of central PGD_2 proposed by Krall et al. (12) identifies a new lead for this research.

In conclusion, whereas the effects of PGE_2 are those occurring when energy is readily available, the highlighted study from the laboratories of Alex Steiner and Carlos Feleder (12) shows that PGD_2 may mediate responses occurring when

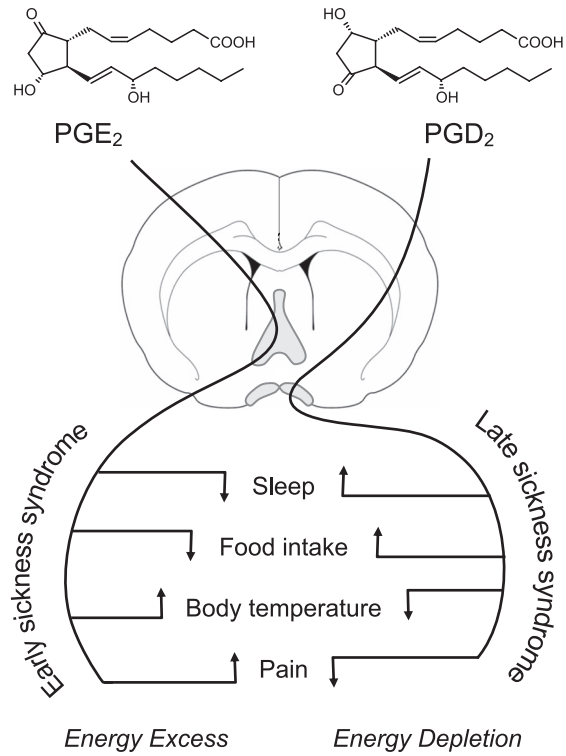

Fig. 1. The chemical structures and some physiological, brain-mediated effects of PGE_2 and PGD_2. PGE_2 causes fever by acting on EP3 receptors in the median preoptic nucleus (14). PGD_2 causes sleep by acting on DP1 receptors in the leptomeninges of the basal forebrain (17). Both sites are schematically shown.

energy resources are threatened or depleted. E is for excess; D is for depletion. There is also an A in this story: it goes to the Albany College of Pharmacy for establishing the young, vibrant, and highly promising program in the physiology and pharmacology of systemic inflammation.

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DISCLOSURES

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