

PROSTAGLANDIN (PG)

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October 21, 2025

RECOMMENDED CITATION

mohammad looti (2025). *PROSTAGLANDIN (PG)*. PSYCHOLOGICAL SCALES. Retrieved from <https://scales.arabpsychology.com/?p=54537>

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Primary Disciplinary Field(s): Biochemistry, Physiology, Pharmacology

1. Core Definition

Prostaglandins (PGs) constitute a crucial class of biologically active lipid compounds that function primarily as autocrine and paracrine signaling molecules. This means they generally exert their effects locally near the site of their synthesis rather than traveling long distances through the bloodstream like classical endocrine hormones. Chemically, they belong to the broader family of compounds known as eicosanoids, which are derived from 20-carbon essential fatty acids, most commonly arachidonic acid. They are fundamentally involved in mediating many complex physiological processes throughout the body, including regulating smooth muscle contraction, controlling body temperature, and profoundly modulating inflammatory and immune responses. Unlike typical hormones, PGs are not stored in cells; instead, they are synthesized rapidly, on demand, in response to specific chemical or mechanical stimuli, act immediately on local receptors, and are then quickly metabolized and inactivated. Their potent, localized action underscores their importance in maintaining cellular homeostasis and responding dynamically to internal disturbances, such as tissue damage or infection.

The core function of PGs is characterized by their ability to induce a wide array of physiological effects, often in a highly specific, tissue-dependent manner. For instance, within the vascular system, certain prostaglandins, such as PGI₂ (prostacyclin), are powerful vasodilators and potent inhibitors of platelet aggregation, functions that are critical for maintaining smooth and unobstructed blood flow. Conversely, in the reproductive system, PGF₂ α is essential for inducing labor and powerful uterine contractions. The source material correctly notes that prostaglandins are key players in influencing **blood pressure** and enhancing **inflammation**. This inherent duality--promoting both protective functions (such as inflammation to initiate healing) and necessary regulatory functions (such as maintaining vascular tone)--makes the prostaglandin system a vital and highly successful target for pharmacological intervention, particularly in the management of pain and inflammatory diseases.

2. Etymology and Historical Development

The initial discovery of prostaglandin activity dates back to the early 1930s when American gynecologist Raphael Kurzrok and pharmacologist M. H. Lieb observed that human seminal fluid contained substances capable of causing powerful contraction and relaxation of isolated uterine muscle strips. This observation suggested the presence of highly active biological agents within the fluid. However, the compound received its definitive name in 1935 from Swedish physiologist Ulf von Euler, who, alongside M. W. Goldblatt, successfully isolated the active lipid substance from

seminal fluid and prostatic glands in sheep and monkeys. Von Euler mistakenly believed that the substance originated exclusively from the prostate gland, leading him to coin the term **prostaglandin**. Despite the misnomer regarding its site of sole origin (it is produced ubiquitously in nearly all nucleated mammalian cells), this initial research established the fundamental understanding that these compounds acted as powerful, short-range local mediators.

The major breakthroughs in understanding the chemistry and metabolic pathways of PGs occurred decades later, beginning in the 1960s, primarily through the pioneering work of Swedish biochemists Sune K. Bergström and Bengt Samuelsson, and British pharmacologist John Vane. They were instrumental in isolating and purifying the various complex forms of prostaglandins and elucidating their chemical structures, confirming them to be fatty acids characterized by a unique five-membered ring structure. This research definitively showed that PGs were synthesized directly from arachidonic acid, an essential polyunsaturated fatty acid. Most critically, in the early 1970s, Vane identified the key enzyme responsible for the initial steps of prostaglandin synthesis--the cyclooxygenase (COX) enzyme--and demonstrated the groundbreaking mechanism by which traditional therapeutic agents like aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) exerted their anti-inflammatory and analgesic effects by inhibiting this very enzyme. This monumental collective body of work revolutionized biochemistry and pharmacology, culminating in the award of the Nobel Prize in Physiology or Medicine to Bergström, Samuelsson, and Vane in 1982.

3. Chemical Structure and Classification

All prostaglandins share a basic core chemical structure derived from prostanoic acid, which is a 20-carbon fatty acid containing a distinctive cyclopentane ring. The different classes of prostaglandins are designated by letters (A, B, C, D, E, F, G, H, I, J), with the specific letter indicating the nature of the functional groups and substitutions present on this five-membered ring structure. For example, E-type prostaglandins (PGE) contain a ketone group at carbon 9 and a hydroxyl group at carbon 11, whereas F-type prostaglandins (PGF) possess hydroxyl groups at both C9 and C11. Further structural specificity within these primary classes is meticulously denoted by subscripts (1, 2, or 3), which quantify the number of double bonds present in the two non-ring fatty acid side chains (e.g., PGE₂ is derived from arachidonic acid and contains two double bonds).

Physiologically, the most significant subgroups for human biology are typically those derived from arachidonic acid (the '2' series), as arachidonic acid is the most abundant precursor stored within human cell membranes. Within the overall eicosanoid family, PGs exist in a critical functional balance with related molecules such as thromboxanes (like TXA₂), which primarily promote clotting and vasoconstriction, and leukotrienes, which are potent mediators in asthma and allergic reactions. The intricate structural variations among these lipid compounds are directly responsible for the vast diversity in their biological activities; even a minor modification in a side chain can

fundamentally switch a PG's function from causing potent vasodilation to inducing severe vasoconstriction, or from relaxing smooth muscle to forcefully contracting it. Understanding these precise structural nuances is absolutely paramount for rational drug design and developing highly selective pharmacological therapies.

4. Biological Synthesis (The COX Pathway)

Prostaglandins are biosynthesized from membrane phospholipids through a highly regulated, enzyme-catalyzed sequence known as the arachidonic acid cascade. The initiating step requires the mobilization of arachidonic acid from the lipid bilayer of the cell membrane, a process typically catalyzed by the enzyme phospholipase A2 (PLA2), which is rapidly activated in response to various cellular stresses, mechanical damage, or humoral signals. Once liberated, the arachidonic acid substrate is rapidly channeled into the committed pathway for prostaglandin generation.

The central and defining step in PG synthesis is performed by the enzyme cyclooxygenase (COX), which is also systemically known as prostaglandin endoperoxide synthase (PTGS). COX executes two sequential enzymatic tasks: first, it introduces two molecules of oxygen into arachidonic acid, cyclizing the chain and forming an unstable intermediate called PGG2 (prostaglandin G2); second, it immediately reduces PGG2 to PGH2 (prostaglandin H2). PGH2 is the crucial, short-lived precursor molecule from which all other primary PGs and thromboxanes are ultimately derived. The subsequent conversion of PGH2 into specific terminal prostaglandins (such as PGE2, PGD2, PGF2 α , or PGI2) is catalyzed by various tissue-specific isomerases and synthases, such as microsomal prostaglandin E synthase, which dictate the final biologically active product produced by that specific cell type.

The discovery of two major isoforms of the COX enzyme--COX-1 and COX-2--is fundamental to both the physiology and pharmacology of prostaglandins. **COX-1** is generally recognized as the constitutive, "housekeeping" enzyme, which is active in nearly all tissues under normal conditions, where it produces PGs necessary for routine physiological functions, such as protecting the integrity of the stomach lining (PGE2) and regulating platelet aggregation necessary for clotting (TXA2). Conversely, **COX-2** is typically inducible; its expression is rapidly and dramatically increased in response to powerful inflammatory stimuli, such as cytokines and growth factors, at sites of injury or infection, mediating the massive production of inflammatory prostaglandins. This functional distinction became the critical basis for developing selective COX-2 inhibitors (coxibs), which were intended to reduce pain and inflammation effectively without the significant gastrointestinal and bleeding side effects commonly associated with non-selective NSAIDs that inhibit both isoforms.

5. Key Physiological Roles

Prostaglandins mediate an extraordinarily vast and diverse spectrum of biological processes, firmly establishing their role as ubiquitous and essential local regulators. One of their most recognized and clinically significant roles is in the initiation and resolution of **inflammation**. PGs, particularly PGE₂, are potent mediators of the four classic cardinal signs of inflammation: pain, redness (rubor), swelling (tumor), and heat (calor). They achieve this by increasing local blood flow through powerful vasodilation, increasing vascular permeability which facilitates the leakage of fluid and immune cells (leading to swelling), and sensitizing peripheral nerve endings to painful stimuli, often synergizing powerfully with other inflammatory mediators like histamine and bradykinin. While often perceived negatively due to the discomfort they cause, this inflammatory response is a critical and protective mechanism that facilitates wound healing, tissue repair, and the necessary clearance of pathogens.

Beyond the immune response, PGs are essential regulators of the circulatory, respiratory, and renal systems. PGI₂ (Prostacyclin), which is synthesized predominantly by endothelial cells lining blood vessels, acts as a powerful vasodilator and is the most potent endogenous inhibitor of platelet aggregation, thus providing crucial protection against the formation of dangerous thrombi (blood clots). This anti-clotting action is precisely balanced by Thromboxane A₂ (TXA₂), produced by activated platelets, which promotes powerful vasoconstriction and aggregation. In the kidneys, PGs help modulate renal blood flow, maintain the glomerular filtration rate, and regulate the precise balance of water and electrolytes. Furthermore, in the gastrointestinal tract, PGs (specifically PGE₂ and PGI₂) fulfill a vital cytoprotective role by inhibiting gastric acid secretion, stimulating the secretion of a protective layer of mucus, and maintaining robust mucosal blood flow, thereby shielding the stomach and intestinal lining from severe ulceration caused by acid and digestive enzymes.

Reproductive physiology is also profoundly dependent on intricate prostaglandin signaling. PGF₂ α is critical in the process of luteolysis (the programmed regression of the corpus luteum) in many mammalian species and is frequently utilized clinically in veterinary medicine to synchronize estrus cycles. In human obstetrics, PGs are absolutely crucial for initiating and facilitating the final stages of term pregnancy; they are responsible for cervical ripening (softening and effacement) and initiating the rhythmic, powerful uterine contractions necessary for labor. The broad, indispensable spectrum of physiological effects mediated by PGs clearly highlights why the therapeutic or pathological disruption of PG synthesis has widespread and often complex systemic consequences throughout the body.

6. Pharmacological Significance and Clinical Applications

The potent and remarkably varied biological activities of prostaglandins make them highly significant molecules in clinical medicine, where they serve both as direct therapeutic agents themselves and, more frequently, as primary targets for drug action. The most common

pharmacological interaction with the prostaglandin system involves inhibition, primarily achieved through the ubiquitous use of non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, and naproxen. These drugs act by inhibiting COX enzyme activity, which significantly reduces the production of inflammatory PGs (chiefly PGE₂), resulting in their characteristic anti-inflammatory, analgesic (pain relief), and antipyretic (fever reduction) effects. However, the non-selective inhibition of COX-1 is directly responsible for the common and serious side effects associated with traditional NSAIDs, including the risk of gastrointestinal ulcers and increased bleeding tendencies.

Conversely, synthetic analogs of naturally occurring prostaglandins are used directly as therapeutic medicines for treating highly specific conditions. For example, Misoprostol (a synthetic PGE₁ analog) is routinely prescribed to prevent NSAID-induced stomach ulcers and, crucially, is used in obstetrics to induce labor or facilitate medical abortions due to its strong uterine contractile properties. Alprostadil (another potent PGE₁ analog) is used in neonatology to temporarily maintain the patency of the ductus arteriosus in newborns with certain life-threatening congenital heart defects and is also administered to treat severe erectile dysfunction due to its powerful local vasodilatory action. Furthermore, Latanoprost (a PGF₂ α derivative) is widely and successfully used in ophthalmology to treat glaucoma by increasing the outflow of aqueous humor, effectively lowering dangerously elevated intraocular pressure. The highly precise clinical manipulation of PG pathways continues to represent one of the most therapeutically successful and active areas of modern pharmacological research and treatment.

7. Debates and Criticisms

While the systematic inhibition of prostaglandin synthesis by NSAIDs has remained a cornerstone of pain and inflammation management for well over a century, the development and subsequent use of selective COX-2 inhibitors (coxibs) generated intense and prolonged international debate regarding their potential cardiovascular safety profile. Drugs like Rofecoxib (Vioxx) were specifically engineered to spare the protective, constitutive COX-1 enzyme in the gastric tract while exclusively targeting and inhibiting the inducible, inflammatory COX-2. However, detailed clinical studies revealed that the selective inhibition of COX-2 inadvertently disrupted the essential homeostatic balance between pro-thrombotic TXA₂ (produced via constitutive COX-1 in platelets) and the vital anti-thrombotic PGI₂ (produced primarily via constitutive and inducible COX-2 in the vascular endothelium).

By selectively blocking the synthesis of PGI₂, these drugs shifted the delicate cardiovascular balance toward a state of increased platelet aggregation and potent vasoconstriction (the unopposed TXA₂ effect). This critical imbalance led to a confirmed, increased risk of serious adverse cardiovascular events, including acute myocardial infarction (heart attack) and ischemic stroke, particularly in susceptible patients. This devastating observation led to the mandated

withdrawal of several major COX-2 selective drugs from the global market and profoundly highlighted the complexity and potential dangers of therapeutic targeting within the intricate eicosanoid system. Ongoing criticism and research efforts are now intensely focused on the necessity of considering the full systemic consequences of inhibiting these localized signaling molecules, especially concerning the critical equilibrium required for long-term vascular health. The future direction of PG-related drug development is trending toward developing agents that can target specific downstream PG receptors rather than inhibiting the upstream synthesis enzyme, aiming to achieve far greater therapeutic specificity with fewer major systemic side effects.

Further Reading

[Prostaglandin - Wikipedia](#)

[Eicosanoids: Prostaglandins, Thromboxanes, Leukotrienes, and Related Compounds - NCBI Bookshelf](#)

[Cyclooxygenase \(COX\) - ScienceDirect Topics](#)