The Bezold-Jarisch Reflex

A Historical Perspective of Cardiopulmonary Reflexes

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ABSTRACT: The Bezold-Jarisch reflex is an eponym for a triad of responses (apnea, bradycardia, and hypotension) following intravenous injection of veratrum alkaloids in experimental animals. The observation was first reported in 1867 by von Bezold and Hirt, and confirmed in 1938–1940 by Jarisch. The triad depends on intact vagi and is mediated through cranial nervous medullary centers controlling respiration, heart rate, and vasomotor tone. The respiratory effects are mediated through pulmonary vagal afferents and the bradycardia and vasodepression through cardiac vagal afferents. The veratrum alkaloids activate all known receptors in the carotid–aortic and cardiopulmonary areas. The cardiopulmonary receptors (baroreceptors, cough receptors, and parenchymal stretch receptors) also respond to other chemical substances: nicotine, capsaicin, venom, antihistaminics, halogenated anesthetics, diguanides, and serotonin (5-hydroxytryptamine). Derivatives of last-mentioned amine activate Type 1, 2, or 3 receptors and have potential therapeutic use. Since several types of cardiopulmonary receptors participate in the Bezold-Jarisch reflex, it has been difficult to develop a blockade to one type of receptor for therapeutic use (cough, bronchospasm, pulmonary hypertension, or coronary vasospasm). Axon reflexes influence pulmonary blood vessels, bronchial blood vessels, and bronchial smooth muscles. These intrapulmonary reflexes need further study as to how they relate to the Bezold-Jarisch reflex in health and disease. The cardiopulmonary and carotid–aortic reflexes can serve as defense mechanisms against chemical hazards that are likely to be inhaled in the workplace and in the environment.

KEYWORDS: Autonomic nervous system; Baroreceptors; Bezold-Jarisch reflex; Bronchopulmonary system; Cardiopulmonary control; Carotid–aortic receptors; Chemoreceptors; Nicotine; Respiratory control; Serotonin; Vasovagal syncope, Vagus; Veratrum alkaloids

I. INTRODUCTION

This article is a historical review of carotid-aortic and cardiopulmonary reflexes. The first international conferences on this subject were sponsored by the Section on Pharmacology (SEPHAR) of the International Union of Physiological Sciences during their First Congress (1961) held in Stockholm,[1] and the Second Congress (1963) held in Prague.[2] SEPHAR, which later became the International Union of Pharmacology, was organized by Carl F. Schmidt from the University of Pennsylvania and

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TABLE 1. Cardiopulmonary eponyms

Eponyms (year)	Location of receptors and afferent innervation (cranial nerve)
Carotid–aortic reflexes: baroreceptors and chemoreceptors	
Cyon-Ludwig's nerve (1866)	Aortic depressor (X)
Hering's nerve (1927)	Carotid sinus (IX)
Heymans and Heymans reflex (1927–1938)	Carotid body chemoreceptors (IX)
Cardiopulmonary reflexes: baroreceptors and other receptors	
Hering-Breuer reflex (1868)	Pulmonary stretch (X)
Kratschmer reflex (1870)	Upper respiratory cough (I, V, IX)
Bainbridge reflex (1914–1915)	Right atrium (X)
McDowall reflex (1924)	Right atrium (X)
Harrison reflex (1932)	Right atrium
von Bezold and Hirt reflex (1867)	Vagal receptors (X)
Jarisch effect (1938)	Vagal receptors (X)
Bezold-Jarisch reflex (1940)	Cardiac and pulmonary (X)
Starling's law of the heart (1927)	Heart–lung preparation

Corneille Heymans from the University of Ghent (Belgium), who trained pharmacologists and physiologists on reflex control of respiration and circulation.[3] It is comforting for basic scientists active during the 1940s to note that clinical researchers are currently interested in cardiopulmonary reflexes. The present conference was organized largely through the efforts of the Cardiovascular Center and Department of Internal Medicine at the University of Iowa and the American Physiological Society.

The senior author of this article, Domingo M. Aviado (DMA), was born in the Philippines and migrated to the United States in 1946 as a transfer medical student from the University of the Philippines to the University of Pennsylvania, where he obtained his medical degree in 1948. Dr. Carl F. Schmidt, then head of the Department of Pharmacology, selected cardiopulmonary reflexes as DMA's first research project,[4] which dictated his interest in the search of new therapeutic agents. DMA later became interested in developing new drugs for the treatment of cardiopulmonary diseases and wrote the first monographs devoted to lung circulation,[5] antitussive agents,[6] sympathomimetic drugs,[7] and propellants to dispense bronchodilators.[8] These monographs, as well as a pharmacology textbook,[9] were written primarily to improve the contents of lectures for medical students. Carl F. Schmidt often reminded his younger associates that their primary function at Penn was teaching and that pharmacologic research should be directed so that students can understand the mechanism of drug action.

As a Penn medical student, DMA was aware that William Bennett Bean, the Professor of Internal Medicine at the University of Iowa, was also born in the Philippines. In 1950 Professor Bean edited a small handbook that was required reading for Penn students: *Sir William Osler: Aphorisms from Bedside Teachings and Writings*.[10]

Sir William Osler was a Professor of Clinical Medicine at Penn from 1884 to 1889 before moving to Johns Hopkins Medical School and Oxford University. The *Aphorisms* were collected by Professor Bean's father, Robert Bennett Bean, who founded the Department of Anatomy at the University of the Philippines. Shortly after Professor William Bennett Bean was born in Manila, his father returned to the United States to become the Professor of Anatomy at the University of Virginia.[11]

Dr. William Bennett Bean was Professor of Internal Medicine at Iowa Medical School and wrote several articles on medical history relating to fingernail growth.[12] During the centennial celebration of Iowa Medical School (founded in 1879), Bean recalled events leading to the formation as the first continually existing coeducational medical school in the United States.[13] There were six physician-founders, including one on Materia Medica, who undoubtedly discussed U.S. pharmacopeia remedies such as *Veratrum* plant alkaloids used in the treatment of hypertension.[14] There was no chair in Physiology, although the respiratory and circulatory reflexes had already been discovered by professors at European medical schools (see TABLE 1).

II. CARDIOPULMONARY REFLEXES

Cardiopulmonary reflexes belong to the autonomic or involuntary nervous system and consist of the following: (a) sensory receptors in the heart and lungs; (b) the sensory or afferent fibers in the parasympathetic X cranial nerves, including nodose ganglia of vagus; (c) medullary centers regulating visceral function by reciprocal activity on parasympathetic, and sympathetic innervations; (d) preganglionic synapses to thoracic ganglia for sympathetic efferent innervation, and to intravisceral ganglia for parasympathetic efferent innervation; (e) postganglionic fibers from sympathetic thoracic ganglia, anatomically longer than postganglionic fibers from parasympathetic intravisceral ganglia; and (f) neuroeffector junctions for parasympathetic mediated by acetylcholine, and for sympathetic mediated by norepinephrine. The Bezold-Jarisch reflex is interrupted by cervical vagotomy, indicating that the parasympathetic innervation of the cardiopulmonary area is essential in the transmission of the afferent and/or efferent groups of nerve impulses.

Definition of Bezold-Jarisch Reflex

In 1867, von Bezold and Hirt[15] described in experimental animals the triad of responses (bradycardia, hypotension, and apnea) as a result of intravenous injection of an alkaloidal extract of *Veratrum viride* or *Viscum album*. The response was eliminated by cutting both cervical vagi (X cranial). The 1867 publication was forgotten until, when Jarisch reported the results of veratrum alkaloidal injections in animal experiments, revealing that the responses were reflex in nature and introduced the eponym of *Bezold reflex*.[16,17] Subsequent investigators, mostly pharmacologists and physiologists, referred to the triad of responses as *Bezold-Jarisch reflex* or Bezold-Jarisch effect, the latter, to emphasize that veratrum alkaloids have multiple actions on several groups of reflexes and also directly on the medullary centers.

Cardiopulmonary Eponyms

After Jarisch confirmed and elaborated on the 1867 report of von Bezold and Hirt, there was considerable effort made to identify the mechanism of action of veratrum alkaloids. Since several cardiopulmonary reflexes had been discovered prior to 1940, it was necessary to compare the veratrum response to each known reflex, most of them with eponyms commemorating the discoverer. TABLE 1 lists two groups of eponyms: carotid–aortic reflexes and cardiopulmonary reflexes. The last entry is *Starling's law of the heart* derived from heart–lung preparation, without any functional connection to the medulla, and refers to the nonvagal or automatic response of ventricular stroke volume to atrial venous return. Cardiac rate is dependent on intact autonomic innervation; an increase in venous return accelerated the heart rate (Bainbridge reflex) and also influenced respiration (Harrison reflex) and blood pressure (McDowall reflex). The right atrial receptors, which are presumed to be responsible for these three reflexes, are diametrically opposed to the triad of responses composing the Bezold-Jarisch reflex.

A Catalogue of Cardiopulmonary Reflexes

During the 1950s, the growing literature on cardiopulmonary reflexes was reviewed by Heymans and Neil,[18] Dawes and Comroe,[19] and Aviado and Schmidt.[20] These reviews identified the areas for further research, and a more complete catalogue of reflexes was compiled by DMA in a 1965 monograph entitled *The Lung Circulation.*[5] This monograph included a discussion of reflex control of pulmonary circulation, bronchial circulation, and cross influences from bronchopulmonary anastomoses and bronchial muscles. These areas are influenced not only by cardiopulmonary reflexes involving the medullary centers of the brain but also by bronchopulmonary axon reflexes that extend only to autonomic ganglia of the peripheral nerve.

At the present time, the catalogue of reflexes remains essentially unchanged from the 1965 list, and is summarized in TABLE 2. The four types of reflexes refer to the nature of influences on vasoconstrictor, cardioaccelerator and respiratory centers in the medulla: Type 1, perfect inhibition; Type 2, imperfect inhibition; Type 3, perfect stimulation; Type 4, mixed stimulation or inhibition of medullary centers. The type of reflexes depend on the intramedullary connections of the afferent nerves: X cranial or vagus, with distinct branches from heart, lungs, and aortic nerves (Cyon and Ludwig's); IX cranial or glossopharyngeal, limited to carotid sinus nerve (Hering's); I, V, and IX cranial nerves mediating afferent impulses from the upper respiratory tract (Kratschmer reflex); and somatic sensory nerves from extremities responsible for hyperpnea of muscular exercise. Each type of cardiopulmonary and carotid–aortic receptors has been identified by histological examination, recording of nerve impulses and functional separation for chemostimulation (sodium cyanide or hypoxemia), baroreceptor stimulation (elevation of intravascular or intracardiac blood pressure), lung-volume stretch receptor (inflation and deflation), and chemical or physical irritation (upper and lower respiratory tract cough receptors).

The types of respiratory and circulatory reflexes reported in the literature[5] are listed in TABLE 2. The baroreceptor types are activated by distension of the heart chamber or vascular lumen by balloon distension or by innervated organ perfusion

TABLE 2. Classification of reflexes based on nature of medullary central effects

Type	Location of receptors	Afferents in cranial nerves
Type 1.	Reflexes from baroreceptors producing *perfect inhibition* of vasoconstrictor, cardioaccelerator and respiratory centers	
	Carotid sinuses	IX (Hering's nerve)
	Aortic arch	X (aortic depressor or Cyon and Ludwig's nerve)
	Pulmonary conus	X (pulmonary branch)
	Left ventricle	X (cardiac branch)
Type 2.	Reflexes from baroreceptors and stretch receptors producing *imperfect inhibition*	
Type 2a.	Lacking only respiratory inhibition.	
	Right atrium	X (cardiac branch)
Type 2b.	Lacking only cardiac inhibition	
	Pulmonary veins	X (pulmonary branch)
Type 2c.	Cardiac inhibition only	
	Left atrium	X (cardiac branch)
Type 2d.	Respiratory inhibition only	
	Lung parenchyma	X (pulmonary branch: Hering-Breuer inflation reflex)
Type 3.	Reflexes from chemoreceptor producing *pure stimulation*.	
	Carotid bodies	IX (Heymans and Heymans' reflex)
	Aortic bodies	X (aortic depressor or Cyon and Ludwig's nerve)
	Glomus pulmonale	X (pulmonary branch)
Type 4.	Reflexes from various receptor types producing *stimulation or inhibition*.	
	Great veins and right atrium	X (cardiac branch: Bainbridge, McDowall, and Harrison reflexes)
	Lung parenchyma	X (pulmonary branch: Hering-Breuer deflation reflex)
	Lower respiratory tract	X (pulmonary branch for cough reflex)
	Upper respiratory tract	I, V, IX (Kratschmer reflex)
	Limbs during muscular exercise	Somatic noncranial (stretch receptors in tendon and joints)

in experimental animals, usually the anesthetized dog. The responses are uniformly similar to the triad of responses composing the Bezold-Jarisch reflex.

Chemical Sensitivity of Cardiopulmonary Receptors

Veratrum alkaloids activate all receptors listed in TABLE 2. It is for this reason that the Bezold-Jarisch reflex has been referred to as *chemoreflexes,*[19] defined as responses to nonspecific irritation by veratrum alkaloids and other chemical agents.

The term is not applicable to chemoreceptor reflexes (sensitive to cyanide and hypoxia), but to other forms of reflexes, including baroreceptor and stretch reflexes. The reflex elicited by intracoronary injection of veratrum alkaloids is caused by chemical excitation of baroreceptors in the cardiac wall supplied by coronary arteries. Although there are respiratory effects from left ventricular baroreceptors, this is not included in the Bezold-Jarisch reflex evoked when veratrum alkaloids are administered by pulmonary artery injection or by inhalation. The pulmonary venous receptors are activated by inhalation, although the inhalation also influences the Hering-Breuer receptors that may contribute to the apnea component of the Bezold-Jarisch reflex.

The triad of response can be elicited by chemical agents that can be grouped into the following: (a) plant alkaloids, including other veratrum alkaloids identified by Krayer.[17] Veriloid and protoveratrine were used for the treatment of systemic hypertension, but were discarded during the 1960s because of the narrow safety margin between depressor dose and dose that caused medullary effects such as vomiting and gastrointestinal hyperactivity. (b) Nicotine and capsaicin also elicit the triad of responses, but are not used for therapeutics. (c) Venoms from snake, insects (bee, scorpion), and marine animals elicit the Bezold-Jarisch reflex that contributes to their lethality. (d) Tissue constituents, such as potassium chloride, histamine, and serotonin, also elicit the Bezold-Jarisch reflex. Some antihistaminic agents have been reported to cause the reflex that is independent of their therapeutic use as antiallergen. Some derivatives of serotonin have selective actions on Type 1, Type 2, or Type 3 receptors and are being tested for therapy of gastrointestinal diseases. (e) Synthetic organic compounds, such as phenyldiguanide, ethylacetoacetate, thioureas, and halogenated anesthetics, also elicit the Bezold-Jarisch reflex, but these observations have not been applied to the development of selective antagonistic agents.

III. CARDIOPULMONARY RECEPTORS IN HEALTH AND DISEASE

The interest of physiologists and pharmacologists in the Bezold-Jarisch reflex is based on the premise that the reflex is more than an experimental curiosity for researchers to test chemical agents for treatment of diseases yet to be identified. It is anticipated that scientists now will be encouraged to explore this research so that new preventive and therapeutic agents can be developed. The 1965 review of cardiopulmonary baroreceptors[5] is a starting point for the study of physiology and pathologic physiology of cardiopulmonary receptors. The National Library of Medicine, which started Medline in 1965, introduced *Bezold-Jarisch Reflex* as a Mesh Heading in 1972. Publications of original research articles are readily available from Medline, as is the 1965 monograph. This section summarizes current concepts of the role of reflexes in the pathogenesis of cardiopulmonary diseases.

Cardiovascular Regulation

The most widely accepted theory for function of cardiopulmonary baroreceptors is as follows: regulation of right ventricular and left ventricular outputs to compensate for changes in systemic venous return, with optimum levels of pulmonary cir-

culatory parameters: pulmonary arterial pressure, pulmonary venous pressure, and pulmonary capillary blood flow. The baroreceptors in the systemic vena cava, right atrium, pulmonary conus, pulmonary veins, left atrium, and left ventricle are sensing elements that regulate heart rate, systemic vasomotor tone, and respiration.[5,22]

Vasovagal Syncope

The syndrome of cardiac slowing with hypotension or vasodepression (vasovagal syncope) has been attributed to activation of the Bezold-Jarisch reflex. The reports that appeared prior to 1965[5] are confirmed in more recent case studies of vasovagal syncope associated with deglutition syncope,[23] shoulder arthroscopy in supine position,[24] and orthostatic intolerance among astronauts.[25] Vasovagal syncope has also been reported in the following cardiac procedures: coronary arteriography,[26] coronary injection of thrombolytic agents,[27] and radio frequency catheter ablation of accessory pathway in patients with Wolff-Parkinson White syndrome.[28] Vasovagal syncope has been attributed to the Bezold-Jarisch reflex in the following situations: sudden death among athletes,[29] syncope in patients with Chagas myocarditis,[30] hemolyses-related syncope,[31] microwave hyperthemia syncope,[32] high-altitude syncope,[33] and fainting after closure of arteriovenous fistula.[34] The last mentioned occurring of vasovagal syncope has been referred to as Branham's sign,[34] for diagnosis of arteriovenous fistula in the extremities. Vasovagal syncope is a common emergency room diagnosis.

Bronchopulmonary Axon Reflexes

This review of the Bezold-Jarisch reflex that is dependent on intact vagus and participation of medullary centers, requires a consideration of bronchopulmonary axon reflexes that are not mediated through the medulla. After acute denervation of canine lung, the smooth muscle components of the airways, pulmonary blood vessels, and bronchial blood vessels still respond to chemical irritants. Chronic denervation to allow degeneration of preganglionic and postganglionic nerve fibers eliminates the responses, referred to as *bronchopulmonary axon reflexes* (see references cited in *The Lung Circulation*, pp. 171–173, and the Index page, 1345).

In the somatic nervous system, the axon reflex is as follows: dermal pain is accompanied by vasodilation, which is simulated by intradermal application of histamine, or by electrical stimulation of the dorsal (sensory) root of the spinal nerve. Cutaneous injection of histamine transmits nerve impulses through a sensory nerve antidromically to another sensory branch to initiate vasodilation. This form of somatic axon reflex cannot be elicited if the sensory afferent fibers undergo degeneration by severing its connections to dorsal root ganglia.

A pulmonary vascular axon reflex has been postulated to occur in pulmonary embolism. Embolism in one lobe causes pulmonary vasoconstriction in another lobe, provided the sympathetic innervation is intact. Thoracic sympathectomy eliminates postembolism vasoconstriction and reduces the intensity of sulfur-dioxide-induced pulmonary venous spasm. Definitive studies consisting of recording of action potentials in the sympathetic nerves are lacking.

A pulmonary bronchoconstrictor response triggered by bronchial irritation has been postulated as a vagal axon reflex. The vagal ganglia in the lung parenchyma

TABLE 3. A unified concept of cardiopulmonary receptors as defense mechanism in response to inhalation of atmospheric pollutants

Receptor areas	Defense mechanisms
Upper respiratory tract	Apnea to reduce lower respiratory tract absorption
Bronchial mucosa, blood vessels and smooth muscles	Bronchial vasoconstriction and bronchoconstriction to reduce airway absorption and alveolar concentration
Lower respiratory tract	Inspiratory gasp followed by expiratory blast (cough reflex)
Atria and ventricles	Asystole and bradycardia to reduce systemic blood distribution of absorbed chemical inhalant
Cardiopulmonary receptor areas	Depressor reflex to reduce cerebral blood flow
Extracardiopulmonary areas	Other mechanisms to promote excretion and metabolism of absorbed chemical

mediate the bronchospasm through the short ganglionic axon branches to bronchial mucosa and bronchial smooth muscles. Irritation of bronchial mucosa can send antidromic nerve impulses to bronchial smooth muscle, resulting in bronchospasm. This response is part of the defense mechanism discussed in the next and final section.

IV. CARDIOPULMONARY REFLEXES AS A DEFENSE MECHANISM AGAINST TOXIC CHEMICAL HAZARDS

A more recent hypothesis is being proposed in this article, centered on a unified concept that cardiopulmonary reflexes are defense mechanisms against chemical inhalants. We are suggesting that the cardiopulmonary reflexes serve initially to reduce the degree of inspired pollutant absorbed in the blood, then protect the vital organs from the potential toxicity of absorbed pollutant, and finally facilitate the elimination and deactivation of pollutant. The six defense mechanisms against atmospheric pollutants are summarized in TABLE 3 and listed as receptor areas in the following order.

(1) *Upper Respiratory Tract Receptors:* When irritated by chemical substances or dust particles, these receptors send impulses via olfactory, trigeminal for taste, and pharyngeal nerves (I, V, IX cranials). The end result is apnea or breath-holding, which reduces the amount of inhalant reaching the lower respiratory tract. This is the Kratschmer reflex that is accompanied by bradycardia and vasodepressor response followed by a vasopressor response from systemic vasoconstriction. This sequence of events from irritation of the upper respiratory tract has been confirmed to occur in human subjects. The practice of using spirit of ammonia to arouse a patient who has fainted is explained by chemical irritation of receptors in the upper respiratory tract.

(2) *Bronchial Mucosal Receptors:* Bronchial mucosal blood flow is reduced, based on thermocouple recordings derived in intact, as well as in denervated or excised lungs of experimental animals. Bronchopulmonary axon reflexes responsi-

ble for reduction of bronchial blood flow are difficult to differentiate from a direct effect on bronchial vascular smooth muscle or vasoconstriction. There is also immediate bronchospasm, which can be explained by axon reflexes or local effect on bronchial smooth muscle. Both bronchial vasoconstriction and bronchospasm serve, respectively, to reduce absorption of pollutant in bronchial passages and decrease pollutant concentration in pulmonary alveoli.

(3) *Lower Respiratory Tract Cough Receptors:* Chemical or physical irritation initiates inspiratory gasp, followed by expiratory blast. The act of coughing serves the purpose of immediate expulsion of the inspired pollutant. The components of the cough reflex and evolution of antitussive drugs are reviewed in a monograph published under SEPHAR sponsorship.[6] A search for drugs to selectively block cough receptors without influencing other bronchopulmonary receptors has failed.

(4) *Atria and Ventricles:* The atria and ventricles can be influenced if the chemical inhalant activates the cardiac component of the Bezold-Jarisch reflex (asystole and bradycardia). This chemoreflex response retards systemic distribution of the absorbed chemical pollutant, after escaping constriction of pulmonary veins that are more reactive than the proximal arterioles.

(5) *Cardiopulmonary Receptor Areas:* The baroreceptors in the pulmonary circulation and coronary circulation can respond to chemical irritants. The reflex depressor response caused by systemic vasodilation results in reduction in cerebral blood flow and syncope. Any chemical pollutant absorbed in the blood is less likely to reduce blood flow to the brain, since cerebral blood vessels are less likely to constrict than other vascular beds (splanchnic, renal, and extremities).

(6) *Systemic Circulation and Carotid–Aortic Chemoreceptors:* Carotid–aortic chemoreceptor activation would initiate opposite effects to those originating from cardiopulmonary baroreceptors. Chemoreceptor activation by absorbed chemical inhalant initiates tachycardia and hyperpnea that accelerate respiratory tract elimination. As blood flows through abdominal organs, the pollutant can be excreted through renal and intestinal circulation. Hepatic distribution of blood ultimately can metabolize or inactivate the foreign substance if susceptible to hepatic enzymes.

Summary of Defense Mechanisms

The preceding six defense mechanisms are not applicable to all inhaled pollutants. The extent of participation depends on the chemical and physical properties of the pollutant. It should be noted that inhaled chemical substances do not introduce new mechanisms in the lungs, heart, systemic circulation, and visceral organs. Like pharmaceutical agents, chemical toxic pollutants do not introduce new mechanisms, but simply activate existing cardiopulmonary reflexes that serve as defense mechanisms. If these defense mechanisms fail, the end result is disease of the heart and lung that are initially reversible, and later, irreversible and fatal. Chemical hazards in the workplace and in the environment have been classified according to the nature of predominant diseases associated with inhalation exposure.[37]

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