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Series on Dyspnea. Part 3. Mechanisms, efferent copy or corollary discharge

Series en disnea. Parte 3. Mecanismos, copia eferente o descarga corolaria

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ABSTRACT

All the theories about the mechanisms of generation of dyspnea had defenders and detractors and, interestingly, with the development of sophisticated neurophysiological techniques and functional imaging, it has been possible to rank each one of them. All have survived the passage of time and none can singularly explain dyspnea in all clinical situations, showing the complex and multifactorial nature of the phenomenon. The concept of length-tension inappropriateness has found support in recent decades with new evidence in its favor. Specially with the discovery of the pathways involved and with the application of neurophysiological knowledge, the length-tension inappropriateness theory would be refined with the corollary discharge or efferent copy. This corollary discharge or efferent copy is a basic attribute of the nervous system found in the animal kingdom, from invertebrates to primates and in the human species. This article is dedicated to the history of the efferent copy and its incorporation as a hypothesis to explain dyspnea, which is currently the most accepted one.

Key words: Dyspnea; Breathing Mechanics; Corollary Discharge, Efferent Copy

RESUMEN

Todas las teorías sobre los mecanismos de generación de disnea tuvieron defensores y detractores e, interesantemente, con el desarrollo de sofisticadas técnicas neurofisiológicas y de imágenes funcionales ha sido posible jerarquizar cada uno de ellos. Todas han sobrevivido al paso del tiempo y ninguna puede explicar por sí sola la disnea en todas las situaciones clínicas, lo cual habla de la naturaleza compleja y multifactorial del fenómeno. El concepto de inadecuación tensión y longitud halló en las últimas décadas un sustento con nuevas evidencias a su favor. En particular, con el hallazgo de las vías involucradas y con la aplicación de conocimientos neurofisiológicos, la teoría de la inadecuación tensión y longitud se vería refinada con la descarga corolaria o copia eferente. Esta descarga corolaria o copia eferente es un atributo básico del sistema nervioso, que se encuentra en el reino animal, desde los invertebrados a los primates y en la especie humana. Este artículo está dedicado a la historia de la copia eferente y su incorporación como hipótesis para explicar la disnea, la más aceptada en la actualidad.

Palabras clave: Disnea; Mecánica respiratoria; Descarga corolaria; Copia eferente

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INTRODUCTION

Why can't we tickle ourselves? Why doesn't an electric fish electrocute itself? Why doesn't the strong vibration of a cricket's legs disturb it? Why don't bats confuse their sounds with those of others? and ultimately, why do we experience dyspnea? Because of the efferent copy (EC) or corollary discharge (CD).[1]

An EC or CD is a fundamental attribute of the nervous system found in the animal kingdom, from invertebrates to primates, and in the human species.[1] This article is dedicated to the history of the EC and its incorporation as a hypothesis to explain dyspnea, which is currently the most accepted one.

When the motor system sends a signal to a muscle, it also sends an internal copy of the signal that does not exit the central nervous system (CNS). This internal signal is called the "efferent copy" or "corollary discharge". This EC or CD is compared with the sensory input or reafferent, which comes from the moving muscle. If the EC/CD and the reafferent are equal, it means that the intended movement is the same as the executed movement. This prevents unnecessary self-induced perceptions (Figure 1).

The command sent from a motor region of the central nervous system (motor command) is copied and sent to other regions of the CNS before the movement occurs. Subsequently, the effector (e.g., muscle) sends afferent information to the CNS, where both signals are compared. If both signals are equal (intended movement = executed movement), there are no unnecessary self-induced perceptions.

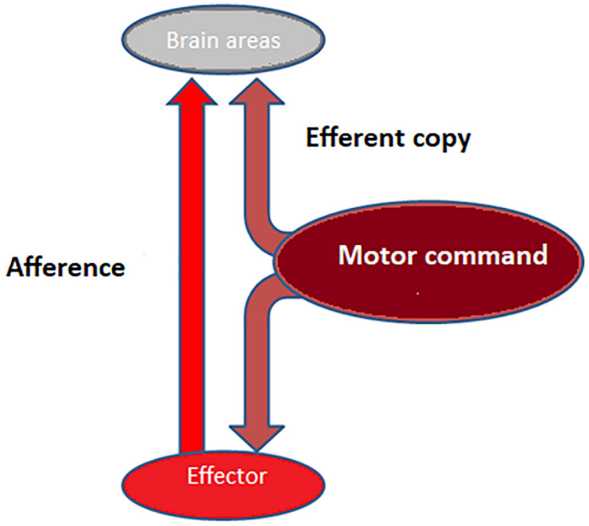

Figure 1. Basic scheme of efferent copies.

HISTORY OF THE EFFERENT COPY

The first to propose the existence of the EC was Hermann von Helmholtz in the mid-19th century: *the CNS needed to create an EC from the motor command that controls the eye muscles in order to help the brain determine the location of an object in relation to the head*. He coined the term "psychophysics" and established a precise and non-linear relationship between the magnitude of physical stimuli and the perceived intensity. Helmholtz paved the way for the development of the psychophysical laws of Weber and Stevens.

The initial concept of EC was disregarded for 75 years after Sir Charles Scott Sherrington (Nobel Prize in Medicine in 1932) strongly criticized Hermann von Helmholtz's ideas in 1920.[2] It was not until the mid-20th century that Erich von Holst and Horst Mittelstaedt, in 1950, described the principle of reafference to explain how an organism is able to distinguish between a reafferent (self-generated) sensory stimulus and an exafferent (externally generated) stimulus.[3] This concept contributed to the understanding of interactive processes between the CNS and its periphery and received a total of 2973 citations.

It was Roger Wolcott Sperry (Nobel Prize in Physiology in 1981) who, thanks to his research on the optokinetic nystagmus reflex, introduced the concept of the CD and is considered the creator of that term.[4] His article has been cited 1636 times. The EC has been implicated in the lack of dyspnea in patients with COVID-19,[5] a hypothesis that deserves to be explored in greater detail.

Differences between efferent copy and corollary discharge

Through different experimental lines, Von Holst and Mittelstaedt[3] primarily referred to the concept of "efferent copy" while their contemporary Sperry[4] coined the concept of "corollary discharge". The first concept involves a real copy of the motor command (the efference) directed to the muscles. This term seemed appropriate for the questions that Von Holtz and Mittelstaedt addressed in invertebrates and for the general analysis of sensory processing that takes place in relation to motor

discharge. However, it has become evident that the connection between motor and sensory areas can be produced at several levels of motor control.

Through studies on fish, Sperry[4] used the second concept, "corollary discharge" to denote motor signals that influence sensory processing. However, his conception was less specific as regards the location where the motor discharge to the sensory pathways should arise. *So, the terms have a different history and some differences regarding the level of complexity, but they are often used interchangeably.* For the purposes of this article, they will be mentioned interchangeably.

In the coming decades, the concept of "efferent copy" will expand significantly. Poulet et al suggested the use of CD as a broad concept to encompass neural signals generated in motor centers that are not directly used to generate ongoing motor activity but often act to modulate sensory processing.[6]

TAXONOMIC CLASSIFICATION OF EFFERENT COPIES OR COROLLARY DISCHARGE

How is sensory processing connected in invertebrates and dyspnea in humans? What taxonomic type of internal copy produces dyspnea? Crapse and Sommer suggested a functional taxonomic classification of efferent copies for the entire animal kingdom. [1] Corollary discharge can be globally classified into categories of lower and higher order based on the function and operational impact of the signal.

The **lower-order** signaling is ubiquitous, as it is necessary for any animal equipped with sensory and motor systems. In this context, corollary discharge is a discriminatory mechanism that prevents maladaptive responses and sensory overload by restricting or filtering information. The cricket doesn't stun itself (and it can hear other environmental noises), and the electric fish doesn't electrocute itself.

When Titi monkeys howl, they face the same problem as crickets: initially, the sounds they emit should affect their hearing. A protective mechanism can be observed in the primary auditory cortex of the Titi monkey, where many neurons are suppressed during self-vocalization. Suppression begins about 200 ms before vocalization and continues throughout its duration. This could be a case where the CD interconnects motor and sensory areas that occupy comparable spaces of a sensorimotor pathway.[1]

Higher-order signaling plays a role in two types of functions. On the **perceptual** side, it facilitates the contextual interpretation of sensory information (analysis) and the construction and maintenance of an internal representation of this information (stability). On the **sensorimotor** side, it facilitates the acquisition of new motor patterns (learning) and the execution of sequences of rapid movements (planning). This type of corollary discharge allows specific brain structures to make appropriate adjustments in anticipation of the sensory input. Each bat only hears its own sound and not the sound of others, enabling them to build a cohesive representation of the world. *So far, the higher-order CD has only been identified in vertebrates.*

There isn't a single type of CD, but rather numerous subtypes that correspond to both the anatomical levels of the source and the target, as well as functional utilities.[1] As can be observed, this taxonomy illustrates the crucial point that, although Sperry's original concept[4] of CD aligns with the general flow of information from motor systems to sensory systems throughout the animal kingdom, it appears inappropriately simplistic to use a single concept to describe the signal.

IDENTIFICATION OF COROLLARY DISCHARGE PATHWAYS

The neurons mediating these signals have been hard to identify. The first evidence came from a single multisegmental interneuron of CD responsible for presynaptic and postsynaptic inhibition of auditory neurons in cricket singing (*Gryllus bimaculatus*).[6] Similar structures were found in the tadpole, the river crab, and the sea slug *Aplysia*. Studies in these species contribute to the classical understanding of CD: they project and target regions involved in the processing of reafferent information.

However, sensory processing is highly dynamic, taking into account the behavioral state of the animal. Therefore, analyzing sensory pathways in preparations under anesthesia or at rest may not provide a complete picture of sensory processing. Perhaps, in evolutionary terms, the CD initially modulated real activity, and then, in more complex brains, also targeted the regions involved in sensorimotor integration or motor planning.[7]

Our muscles are sensitive; this includes the respiratory muscles. In other words, we receive

sensory signals from muscles that reach our consciousness and inform us about what is happening in those muscles, similar to how sensory signals from the skin tell us what is happening there. *Studies in animals showed that a copy of the respiratory motor impulse is transmitted to the midbrain and thalamus.*[1-8]

DYSPNEA AND COROLLARY DISCHARGE

In 1978, with an article that got more than 1000 citations, McClosky et al suggested that *corollary discharge signals, or ECs originating from the respiratory centers in the brainstem can be transmitted to higher brain centers and give rise to a conscious awareness of the output motor command. This may play a significant role in the formation of the sensation of dyspnea*.[11]

The concept of CD is the most widely accepted to explain the origin of the sensation of inspiratory effort and dyspnea.[12-14] The proposed scheme for the respiratory system is essentially the same as the one described in Figure 1. Unlike pain receptors, the afferents projecting to the higher brain centers to compare with the EC are diverse.[15] Additionally, the respiratory system has an automatic (brainstem) and voluntary (motor cortex) motor command. This CD from different sources most likely gives rise to different sensations.[15] Therefore, in our opinion, dyspnea is not merely a carbon copy of pain.

Figure 2 depicts the CD in the respiratory system, with its dual involuntary and voluntary innervation. During involuntary breathing, respiratory centers send an EC to the sensory cortex, whereas during voluntary respiratory efforts, it is the motor cortex that sends the copy. Simultaneously, the respiratory muscles send afferents to the sensory cortex. When there is proper correspondence between the motor command and incoming afferent information from sensory receptors, there shouldn't be any sensation of dyspnea (Figure 2). On the contrary, when there is no correspondence, the resulting neuromechanical uncoupling contributes to the genesis of dyspnea. *This exchange between the motor command and the sensory cortex is currently the most accepted mechanism by which awareness of respiratory effort is achieved.*

If both copies (efferent and reafferent) are equivalent (same color), there is no dyspnea;

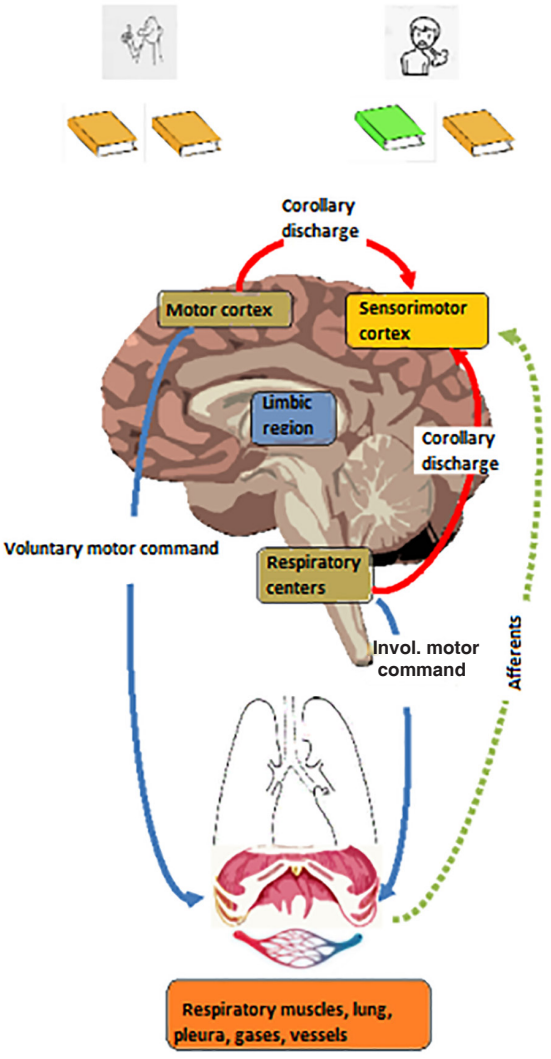

Figure 2. Corollary discharge in the respiratory system with its dual involuntary and voluntary innervation.

if the copies differ (different color), dyspnea occurs.

Why is our breathing not usually self-perceived?

The sensory cortex also receives afferents from events that occur in the chest and respiratory muscles and processes the information.[14] When it receives the EC, the sensory cortex adjusts accordingly to minimize, eliminate, or compensate for the sensory consequences of movement. Due to this general strategy, breathing under normal conditions is an unconscious process[1] (and within certain ventilation limits).

What is the relationship between the length-tension inappropriateness of Campbell and the efferent copy?

In fact, a dissociation between the motor command and the mechanical response of the respiratory system recalls the theory of length-tension inappropriateness by Campbell and Howell in the 1960s.[15] The theory has been generalized to include not only information arising in the respiratory muscles but also the one emanating from receptors throughout the entire respiratory system, and has been named with various terms.[15-19]

- Neuromechanical dissociation.
- Efferent-reafferent dissociation.
- Length-tension inappropriateness.
- Neuroventilatory dissociation.
- Afferent discordance (mismatch).
- Neuromechanical decoupling.
- Neuromuscular dissociation.

What respiratory conditions can have a dissociation between efferent and afferent information and result in dyspnea?

In addition to the mentioned neurophysiological findings, various experimental data and clinical observations are consistent with the concept of efferent-afferent inappropriateness.[20-25]

In both patients and healthy individuals, temporary suppression of ventilation during speech or eating causes a mismatch between the respiratory motor command and the expected movement.

When normal subjects breathe CO_2, their ventilation increases, and most experience dyspnea. However, if ventilation is reduced while CO_2 remains constant, subjects report a marked increase in the intensity of breathlessness, even though the chemical drive to breathe has not changed.

When normal subjects are forced to breathe at an inspiratory flow that is different from what they have chosen as the most comfortable, they experience a sensation of air hunger.

A similar phenomenon can occur in patients receiving mechanical ventilation and showing unsuitability for the respirator.

All of this suggests that, under a given set of conditions, the brain "expects" a certain ventilation pattern and associated afferent feedback, and deviations from this pattern cause or intensify the sensation of dyspnea.

Is there any relationship between corollary discharge and the lack of dyspnea in patients with COVID-19?

COVID-19 is surprising and intriguing in various aspects. One of its relevant characteristics is the ability to recognize the absence of dyspnea in the majority of cases. If the physiopathological mechanisms of dyspnea development are not yet well understood, we shouldn't be surprised, since we have limited knowledge of the dyspnea mechanisms in COVID-19.[5] In some series, intubated and ventilated subjects exhibited tachypnea and tachycardia.[26-28] In a retrospective study, dyspnea and chest tightness were much more common in deceased patients.[29] Dyspnea was one of the associated predictors of severe illness and death.[30] To understand the absence of dyspnea in COVID-19, the main focus is on phenotypes that show severe hypoxia and almost normal respiratory system distensibility. In respiratory distress due to COVID-19 pneumonia, the respiratory system (transpulmonary distensibility and driving pressure) was reported to be pseudonormal.[31, 32] From a physiopathological perspective, which does not exclude the direct neurotoxic effect of the virus and a systemic response in the infectious context but rather encompasses it, the lack of dyspnea in COVID-19 can be explained by an adaptation in the sensory cortex of the brain of the two signals coming from the motor command and the periphery via CD.[5]

CONCLUSIONS AND THERAPEUTIC PROJECTIONS

All animals, from the humble nematode to the cognitively advanced primate require the type of signaling that allows the CD which protects against unnecessary self-induced perceptions. We are still in an embryonic stage of CD research in the animal kingdom. However, *the exchange between the motor command and the sensory cortex is currently the most accepted mechanism by which awareness of respiratory effort is achieved.* Neuronal pathways have been identified. Indeed, a dissociation between the motor command and the mechanical response of the respiratory system recalls the Campbell and Howell's "length-tension inappropriateness" theory from the 1960s. The future goal will be to discover how

the CD influences perception. Experiments so far have shown that inactivation of CD pathways can alter behavior, and subtle perceptual changes may justify these behavioral alterations. This knowledge may be highly relevant for the relief of refractory dyspnea.

KEY POINTS

- Clinical, experimental, neurophysiological data, and clinical observations support the concept of a lack of tension-length adequacy, neuromechanical dissociation, or efferent-reafferent dissociation (EC/CD) as the central core in the genesis of dyspnea.
- The central concept is that, under a given set of conditions, the brain 'expects' a certain ventilation pattern and associated afferent feedback; deviations from this pattern cause or intensify the sensation of dyspnea.
- It is necessary to go deeper into the role of CD in the absence of dyspnea in COVID-19 as well as in other conditions.

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