Reversal and Prevention of Opioid-induced Respiratory Depression

An Essay Submitted for the Partial Fulfillment of Master Degree in Anesthesiology

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List of Abbreviations

5HT	5-Hydroxytryptamine
8-OH-DPAT	8-hydroxy-2-(di-n-propylamino) tetralin
ACTH	Adrenocorticotropic Hormone
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole-proprionic acid
APSF	Anesthesia Patient Safety Foundation
ASA	American Society of Anesthesiology
cAMP	Cyclic Adenosine Monophosphate
CNS	Central Nervous System
COX	Cyclooxygenase
CTZ	Chemoreceptor Trigger Zone
CYP450	Cytochrome P450
DOR	Delta Opioid Receptors
$ETCO_2$	End-Tidal Carbon Dioxide
GABA	Gamma-Amino Butyric Acid
GPCRs	G-protein coupled receptors
HCVR	Hypercapnic Ventilatory Response
HVR	Hypoxic Ventilatory Response
ICU	Intensive Care Unit
IL-1	Interleukin-1
KOR	Kappa Opioid Receptors
LOX	Lipoxygenase
M3G	Morphine 3-Glurcuronide
MOR	Morphine Opioid Receptors
MSA	Multiple Systems Atrophy
MSH	Melanocyte-Stimulating hormone
N/OFQ	Nociceptin/Orphanin FQ
NK	Natural Killer
NMDA	N methyl D-aspartate
NSAIDs	Non-Steroidal Anti-Inflammatory drugs

NTS	Nucleus of the Tractus Solitarius
OR	Operating Room
ORL	Opioid Receptor Like
PACU	Post Anesthetic Care Unit
PCA	Patient Controlled Analgesia
PCO2	Partial pressure of Carbon Dioxide
PCP	Phencyclidine
PG	Prostaglandin
PO2	Partial pressure of Oxygen
PTcCO_2	Transcutaneous Carbon Dioxide
RR	Respiratory Rate
SPO_2	Oxygen Saturation
SSRIs	Selective Serotonin Reuptake Inhibitors
TCA	Tricyclic Antidepressants
TENS	Transcutaneous Electrical Nerve Stimulation

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Introduction

Respiratory drive is mainly generated in the brainstem and is affected by inputs from various sources including conscious inputs from the cortex, as well as inputs from chemoreceptors which gauge the changes in the blood's chemical components. There are two types of chemoreceptors: Central chemoreceptors in the brainstem and Peripheral chemoreceptors in the carotid and aortic bodies ***(Feldman and Del Negro, 2006).***

It's generally agreed upon that opioid receptors can be classified into four classes which are; MOP (μ), KOP (κ), DOP (δ), and the nociceptin/orphanin FQ peptide receptor (NOP). These receptors are mainly present on pain neurons in the central nervous system. However, they are also distributed in various sites all over the body. These sites include sites affecting respiration where opioid receptors have a strong presence in the brainstem as well as higher centers such as the insula, anterior cingulate cortex and thalamus ***(Baumgartner et al., 2006).***

Opioid receptors are also present in carotid bodies and vagi. Additionally, mechanosensory receptors responsible for the relay of mechanical and sensory input from the epithelial, submucosal and muscular layers of the airways and lungs also show presence of opioid receptors ***(Kubin et al., 2006).***

Opioid drugs have long been administered for the relief of pain as well as other uses including the reduction of diarrhea, anxiety and coughing. There are many side effects that have long been associated with opioid use. These include nausea, vomiting, drowsiness, hypotension, constipation and others. The opioid-induced complication often treated with the most apprehension is

respiratory depression which also happens to be the main focus of this essay.

While the most reliable and therefore, most commonly used medication for the reversal of opioid-induced respiratory depression is naloxone, it may possibly be associated with the reversal of opioids' analgesic effects. Fortunately, there are several recent medications which appear to be quite promising regarding the reversal of respiratory depression resulting from opioids, while at the same time preserving their analgesic effects. Advanced monitoring of oxygenation and ventilation has also been considered essential for preventing opioid-induced respiratory depression from occurring in the first place ***(Van Dorp et al., 2007).***

Aim of the work

The aim of this work is to discuss and review the efficacy of recent methods used for the reversal and prevention of opioid-induced respiratory depression, as well as their advantages and disadvantages.

Respiratory Control

The automatic activity of the respiratory system is modified via the respiratory center, which is present in the nervous system so that it can meet the body's changing requirements. The activity of this respiratory center is affected by certain receptors ***(West, 2003).***

Respiratory Centers

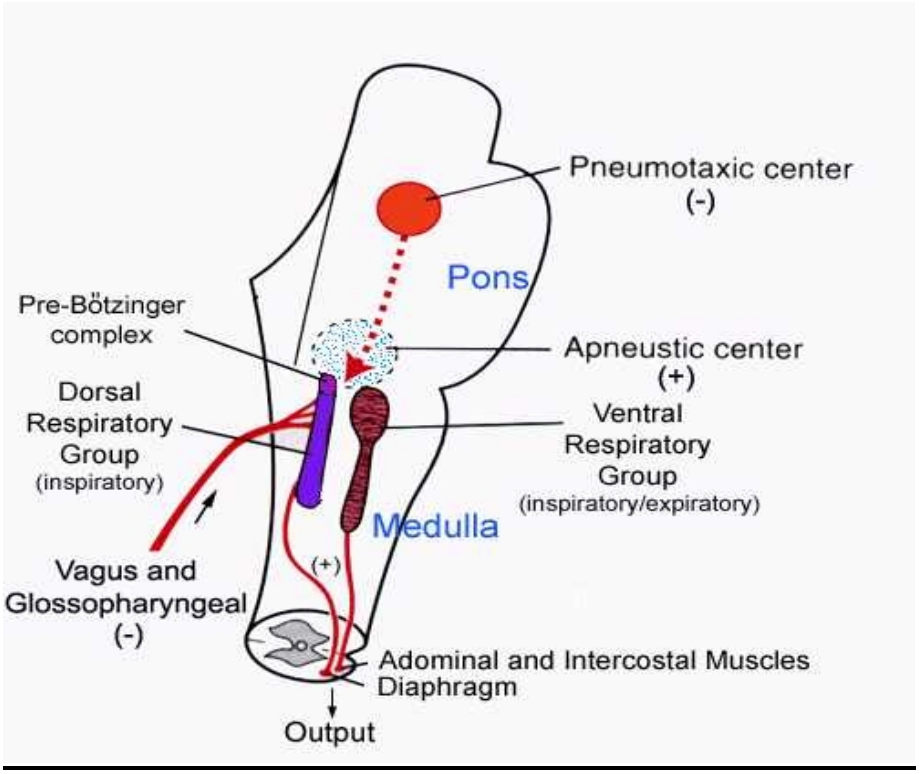

Figure (1): Organization of the Respiratory Center (Guyton and Hall, 2011).

The respiratory center consists of a group of neurons located bilaterally in the brain stem, specifically the medulla oblongata and the pons. These neurons are distributed in the form of 3 main groups ***(Kara et al, 2003).***

These groups are:

a) The dorsal group of neurons located in the dorsal portion of the medulla, which is mainly concerned with inspiration.

b) The ventral group located in the ventrolateral area of the medulla, which is responsible for expiration.

c) Finally, the pneumotaxic center which falls in the dorsal area of the upper portion of the pons. This center is mainly concerned with the rate and the depth of respiration.

a) The dorsal group; role in the inspiratory control and respiratory rhythm regulation:

It would be fair to say that this group plays the principal role in respiratory control. Neurons are located mainly within the *nucleus of the tractus solitarius (NTS),* in addition to other neurons which lie within the adjacent reticular substance. The NTS is the site of termination of the vagal and glossopharyngeal nerves. These nerves transmit signals to the respiratory center from various receptors; 1) the peripheral chemoreceptors, 2) the baroreceptors and also; 3) different receptors located within the lungs themselves ***(West, 2003).***

The dorsal group of neurons is considered as the main site of the basic rhythmic control of respiration. This group has been observed to continue discharge of rhythmic inspiratory action potentials, even after transection of peripheral nerves entering the medulla and transection of the brain stem both above and below the medulla. This action is attributed by physiologists to the

presence of a network of neurons where one set of neurons excites another, which in turn inhibits the first one ***(Albert et al., 2002).***

This neuronal network is present entirely within the medulla consisting mainly of the dorsal group in addition to adjacent areas of the medulla, and that this is where the basic control of respiratory rhythm occurs ***(Gaultier and Gallego, 2008).***

The inspiratory "Ramp" signal

The nervous signal that is transmitted from the dorsal group of neurons to the inspiratory muscles does not occur in the form of a sudden burst of action potentials. Instead, the signal starts slowly and weakly, as if gradually going up a ramp for about 2 seconds during the normal breathing process. The signal is then cut off for about 3 seconds allowing excitation and therefore, contraction of the diaphragm to stop followed by the elastic recoil of the lungs and chest wall so that expiration may occur ***(Albert et al., 2002).***

The ramp form of this signal allows the following:

- During heavy inspiration, the rate of the ramp signal may be increased therefore allowing the lungs to fill rapidly.
- The rate of respiration can be controlled by varying the cessation point of the ramp.

This means, that the earlier the ramp ceases, the shorter the duration of inspiration becomes. The duration of expiration will also be decreased. Naturally, the rate of respiration will then be increased ***(Ben-Tal and Smith, 2007).***

b) The ventral group; inspiratory and expiratory functions:

This group is located in the medulla on either side. It lies rostrally in the *nucleus ambiguus* and caudally in the *nucleus retroambiguus*. The functions of this group of neurons differ from that of the dorsal group in the following manner:

i) During normal quiet breathing, this group of neurons is nearly inactive. Therefore the main group of neurons that functions under these circumstances is the dorsal group which transmits repetitive inspiratory signals to the diaphragm followed by elastic recoil of the lungs and thoracic cage, which then result in expiration ***(Hilaire and Pasara, 2003).***

ii) This group does not appear to play a role in the basic underlying rhythm that controls respiration.

iii) When there are demands for increased pulmonary ventilation, respiratory signals exceed the capacity of the basic rhythmic discharge from the dorsal group causing the ventral group to begin contributing with additional respiratory drive ***(Gray, 2008).***

iv) It has been discovered through electrical stimulation of the ventral group of the neurons that some of them when stimulated result in inspiration, while others result in expiration. Therefore, this group is responsible for contributions to both inspiration and expiration, especially during heavy breathing as in exercise. Thus, it can be viewed as an "overdrive" respiratory center where it contributes additional respiratory drive when increased pulmonary ventilation demands arise ***(Hilaire and Pasaro, 2003)***

c) The pneumotaxic center's effects on the duration of inspiration and respiratory rate:

The pneumotaxic center lies dorsally within the *nucleus parabrachialis* in the upper pons. It transmits signals to the inspiratory center which result in the "switching-off" of the previously mentioned ramp signal. It therefore controls the filling of the lungs during the breathing cycle. As a result, the duration of inspiration varies according to the strength of the signal from the pneumotaxic center ***(Costanzo, 2006).***

This limitation of inspiration caused by signals from the pneumotaxic center will result secondarily in the increase of the respiratory rate because of the shortening of expiration and thus the entire period of each breath. Therefore, the respiratory rate also varies according to the strength of the signal from the pneumotaxic center ***(Song et al., 2006).***

Control of the respiratory center via signals from the lungs:

The central nervous system mechanisms for control of respiration aren't limited to operations within the brainstem. There are contributions to the central nervous system's control of respiration made by sensory nerve signals that are transmitted from the lungs themselves ***(Morris et al, 2003).***

The most important group of sensory nerve signals that are transmitted from the lungs are those created by the stretch receptors present in the muscular portions of bronchi and bronchioles, which transmit their signals via the vagi to the dorsal group of respiratory neurons whenever the lungs become inflated to the extent of being overstretched. The effects of the nerve signals initiated by these receptors are similar to those discharged from the pneumotaxic center; meaning that when the lungs