

Neuromodulation and Plasticity in the Respiratory Tract

Prini Jain and Alok S Shah*

Pulmonary Department, University of Chicago, USA

*Corresponding Author: Alok S Shah, Pulmonary Department, University of Chicago, USA.

Received: September 09, 2020; Published: September 28, 2020

Abstract

The respiratory system is constantly being modulated by numerous aminergic, and peptidergic substances like ligands and neurotransmitters that act at all levels of integration, from sensory level of central networks to motor nuclei. All of the processes leading to respiration involve the action of multiple neuromodulators through G- protein coupled receptors or metabotropic receptors and second messenger systems which amplify the action of microscopic ligand (protein) binding within the cell membrane. These neuromodulators include serotonin (5-HT), substance-p (SP), and cholecystokinin (CCK) which usually exert excitatory effects on respiratory activity. Neuromodulators, unlike neurotransmitters, have a widespread effect in our nervous system. In an area located in the medulla oblongata called the pre-botzinger complex (Pre-BotC) neuromodulators can modulate frequency and amplitude in different types of pacemaker neurons. The effect of these modulators are constantly changing in our respiratory system due to various different factors including genome type, age, gender, diseases etc. The long-term alteration of the effects of neuromodulators with prior experience and development is known as long term plasticity. On the contrary, plasticity on a shorter time scale is known as short term plasticity. Plasticity may induce structural or functional alterations at different sites in the respiratory control system which in further results in changes in our breathing pattern. Plasticity is vital for our survival and helps us adapt with our constantly changing environmental conditions. Although the neural system connected to respiratory control has been regarded as immutable, evidence has accumulated in recent years proving that the respiratory control system exhibits impressive plasticity, just as in other regions of the nervous system. Because of its recent discovery we have just brushed upon this concept and a lot is left to be unraveled.

Keywords: Respiratory System; Neuromodulators; G-Protein Coupled Receptors; Pre-BotC; Plasticity; Serotonin; Diseases

Introduction

Neuromodulators have multiple functions in controlling respiratory rhythmic activity. They regulate the amplitude and frequency of respiratory activity by acting on various neural networks within the ventral respiratory column (VRC) and the parafacial respiratory group (pFRG) present in the medulla oblongata of the brain stem, which are believed to be responsible for respiratory rhythm generation [1]. However, researchers are still uncertain how these regions interact to generate breathing rhythm and patterns, but it is now well established that a particular area within the ventral respiratory column (VRC) called the pre-Botzinger complex (pre-BotC) is involved in ventilatory (inspiratory) activity and pattern formation [2]. The pre-BotC is known to generate three distinct types of respiratory activity patterns that we know of today i.e. normal respiratory activity (eupneic inspiration), sighs and gasps [3]. This neural network exhibits a wide range of plasticity, but not much of it has been understood yet. Although we are far from understanding all aspects of neuromodulation, it is well established that neuromodulation is an integral part of the respiratory pattern and rhythm generation process.

In this review we will focus on only a few important neuromodulators that play an important role in orchestrating the respiratory network and the effects of various drugs, genetic mutations, age and gender on these modulators and how it induces long term changes in the respiratory system. Neuromodulation and plasticity are extremely complex processes that are crucial to acknowledge in order to develop a better understanding of the human brain and most other functions of our body that are yet to be discovered. This may provide us with useful insights to pathological states, thereby providing therapeutic interventions to ones who need it.

Respiratory rhythm generation in the brain

Rhythm generation for respiration is initiated in the medullary neurons of the brain that are responsible for inspiratory and expiratory activities of the lungs. Each different activity is initiated by various different regions of the brain stem such as the dorsal and ventral respiratory groups, pontine respiratory centers, pre-botC and parafacial respiratory group [4]. There are many other parts of the brain that may be involved in respiratory rhythm generation such as the Kolliker Fuse nucleus (KFn). However, it is still not fully understood how these regions interact with each other to produce a continuous inspiration- expiration pattern for breathing.

Dorsal respiratory group (DRG)

It is mainly composed of inspiratory neurons located bilaterally in the medulla oblongata. DRG controls the basic rhythm of breathing by triggering inspiratory impulses to the motor nerves of the diaphragm and external intercostal muscles. The nerves of the DRG extend into the ventral respiratory groups. The vagus and glossopharyngeal nerves transmit sensory impulses to the DRG from the lungs, peripheral chemoreceptors, joint proprioceptors, and airways [5]. These inputs modify the breathing pattern via the feedback mechanism with the aid of neuromodulators and transmitters [6].

Ventral respiratory group (VRG)

The VRG consists of both inspiratory and expiratory neurons located bilaterally in the medulla oblongata and is primarily active during exercise and while under stress. Inspiratory VRG neurons transmit inspiratory impulses from neurons located in the nucleus ambiguus to laryngeal and pharyngeal muscles and from neurons located in the rostral area of the nucleus retroambigialis to the diaphragm and external intercostal muscles [7]. The other VRG neurons transmit expiratory signals from neurons in the caudal area to abdominal muscles and internal intercostal muscles.

Pontine respiratory centres

The pons present in the brainstem modify the output of the medullary centres by either stimulating or inhibiting their impulses. The two respiratory pontine centres are the apneustic and pneumotaxic.

Apneustic center

It stimulates the inspiratory neurons of the DRG and VRG. its over stimulation results in apneustic breathing which is characterized by long gasping inspirations interrupted by occasional expirations [8]. This is due to the delay of the 'off' signal of the inspiratory ramp provided by the pneumotaxic center of the pons.

Pneumotaxic center

It is located in the upper portion of the pons [9]. It transmits inhibitory impulses to the inspiratory center of the medulla and is said to control the 'off-switch' of inspiration, thus controlling inspiratory time.

Parafacial respiratory group (pFRG)

The pFRG plays a vital role in the rhythm generation of active respiration and stimulates expiratory abdominal muscles in order to increase ventilation [10]. They are mainly under GABAergic (gamma aminobutyric acid) and cholinergic control. The activity of the pFRG is inhibited by GABAergic inputs which are the main inhibitory neuromodulators/neurotransmitters of the brain and activated by cholinergic systems (e.g. acetylcholine). Some research suggests that active expiration is evoked during hypercapnia, while during hypoxia it is elicited through activation of catecholaminergic C1 neurons.

Pre-Botzinger complex (pre-BotC)

The pre-botC is a cluster of interneurons in the VRG of the medulla oblongata. This region of the brain produces two types of breathing rhythms under normal oxygen levels in the body. In eupnea (normal breathing), the pre-botC generates a rhythm which is fast and has a low amplitude. On the other hand, in a sigh it generates a rhythm that is slow and large in amplitude [11]. These mechanisms are generated through the actions of different neurotransmitters and their receptors which depends on the surrounding environment, activities or propensity of the organism [12]. Under low levels of oxygen (hypoxia), the pre-botC generates a gasp which has a fast rise, short burst and low frequencies. Each type of rhythmic activity is dependent on different mechanisms (ion channels, neuromodulators etc.) [13]. A sigh relies on synaptic mechanisms that involve the action of P/Q type calcium channels which are voltage-gated calcium selective ion channels that mediate calcium influx and are activated by a strong membrane depolarization since it's a high threshold ion channel [14]. Sighs also depend on the metabotropic glutamate receptor- mGluR8 activation. On the other hand, eupneic activity is dependent on NMDA (N-methyl-D-aspartate) receptor mechanisms which is a type of ionotropic glutamate receptor activated by ligand binding as well as membrane depolarization. The brain derived neurotrophic factor (BDNF) is a neurotransmitter/neuromodulator which plays a crucial role in neuronal growth and survival. It's mainly found in the central nervous system, gut and other tissues. BDNF produces excitatory effects on the generation of respiratory rhythm by increasing the frequency of rhythmic activity in the pre-BotC. It activates the tyrosine receptor kinase B (TrkB) present in the pre-BotC which is both a target and a source of BDNF. Some of the neurons in the pre-BotC express the neurokinin-1 receptor (NK1R), which binds to substance-p and some express somatostatin which is a neuropeptide involved in modulating respiration [15]. The pre-BotC also contains subpopulations of glycinergic (inhibitory), GABAergic (inhibitory) and glutamatergic (main excitatory neurotransmitter in the brain) neurons [16]. There are two types of neurons that can be found in the pre-BotC, namely pacemaker (constant bursting potential) and non-pacemaker neurons (subtle firing state) There are two types of inward currents that play an important role in respiratory rhythm generation in pacemakers, the sodium current (INaP) and the calcium activated non-specific cation current (ICAN) [17,18]. Some pacemakers continue to display action potential bursts after all voltage dependent calcium channels are blocked using cadmium as an antagonist. These neurons are known as cadmium -insensitive pacemaker neurons (CI) and they are modulated by InaP [19]. The second type of pacemaker neurons are inhibited or cease to burst with exposure to cadmium. These are cadmium sensitive (CS) pacemaker neurons and are mediated by ICAN [20,21]. ATP (adenosine triphosphate)-dependent potassium channels aid neurons to detect energy changes or changes in oxygen levels in order to modify breathing patterns. These ion channels are activated with a decrease in ATP, which means that they provide the necessary hyperpolarization during hypoxia [22].

Neuromodulators and their effects on respiration

Neuromodulatory neurons are those which release neuroactive substances like peptides and proteins that either alter the rate of synaptic transmission to the postsynaptic neuron or change the properties of other neurons in the nervous system. In this case we will consider the neurons which actively participate in respiration. Neuromodulators have a widespread effect in the nervous system unlike neurotransmitters which only bind to the postsynaptic neuron. However, some neurotransmitters may also act as neuromodulators such as serotonin, acetylcholine, dopamine, norepinephrine etc [23]. Neuromodulators alter the synaptic strength of a neuron in three main

ways and at multiple time scales (from long term persistent modulation, to short-term or temporary modulation). This change in synaptic strength may occur presynaptically, by altering the number of neurotransmitters released (modulating calcium influx). Or it may occur postsynaptically, by altering the response of the receptors to the neurotransmitters. However, the action that the neuron takes depends on which postsynaptic receptor molecule receives that signal, whether it is excitatory or inhibitory and this affects its synaptic strength [24]. Synaptic strength may even be modulated by glial cells which release neurotransmitters in the synaptic cleft which in turn changes the way the postsynaptic neuron conducts the signal. A number of recent studies have shown that neuromodulators play an important role in long term potentiation or facilitation (LTP) and long-term depression (LTD). It isn't possible to cover all the possible neuromodulators of the respiratory system as the complications are endless. Therefore, we will be going through a few of the main neuromodulators of the respiratory system in this review. However even the mentioned mechanisms of the human body aren't fully understood yet.

Serotonin (5-HT) modulation

Serotonin also called 5-hydroxytryptamine (5-HT) is a monoamine neurotransmitter that also operates as a neuromodulator in the mammalian central nervous system [25]. It is produced in the central nervous system, in the Raphe nuclei located in the midline of the brainstem and it is stored in blood platelets and is released during vasoconstriction or agitation, where it acts as an agonist to other platelets [26,27]. 5-HT modulation in the respiratory system may be excitatory, inhibitory or sometimes have no effect mostly dependent on the type of postsynaptic receptor. Experiments were carried out to test the effect of 5-HT on the respiratory system by using a drug called para-chlorophenylalanine (PCPA) which inhibits the production of 5-HT. This led to an increase in respiratory output which made a conclusion that 5-HT neurons inhibit breathing [28]. However, simultaneously, if there is an extreme reduction in cytosolic 5-HT levels, then it would lead to a decrease in the somatodendritic 5-HT release. This would in turn lead to a decrease in 5-HT 1A (inhibitory GPCRs) receptor-dependent autoinhibition and a greater release of substance-p (SP) and the thyrotropin-releasing hormone (TRH), both of which have influential impacts on respiratory output. Therefore, a decrease in 5-HT synthesis may cause an increase in postsynaptic stimulation by 5-HT neurons [29]. This is an indirect inhibitory effect of 5-HT, however direct inhibitory connections have not been demonstrated yet. Recent research has revealed that 5-HT, SP, and TRH facilitate eupneic breathing. Except for 5-HT₃ receptors which are ligand gated ionotropic receptors, all 5-HT, SP and TRH (1 and 2) receptors are G protein-coupled receptors [30]. The activation of these GPCRs by means of G-proteins, modifies the excitability of their target neurons through the second messenger system, which in turn provides access to ligand gated ion channels to affect the membranes excitability. Another example of indirect excitatory motor output is observed in the hypoglossal motor neurons that depolarize in response to the activation of 5-HT₂, neurokinin-1 (NK-1) and TRH receptors [31]. This is due to part inhibition of TWIK (tandem of P domains in a weak inwardly rectifying K⁺ channels) -related acid-sensitive (TASK) channels [32]. In some pre-BotC neurons, 5-HT_{2A} and NK-1 receptor activation causes depolarization via the modulation of cation leak channels. These channels may include non-selective Na⁺ leak channels (NALCN) which are critical for the generation of normal respiratory motor output [33]. 5-HT induces intrinsic bursting in pre-BotC pacemaker inspiratory neurons. Coming to the various receptor types, each receptor has a different effect on the respiratory system. All 5-HT₁ (1A, 1B, 1D, 1E, 1F) receptors and 5-HT₅ receptors couple with the G_{i/o} protein family inhibit adenylate cyclase (AC) activity (catalyzes conversion of adenosine triphosphate to cAMP), thus decreasing the level of intracellular cyclic adenosine monophosphate (cAMP) and increase K⁺ membrane conductance. 5-HT₄, 5-HT₆ and 5-HT₇ receptors are linked to G_s proteins and they trigger a pathway that leads to AC activation and cAMP production [34]. The 5-HT₂ (2A, 2B, 2C) receptor family couple with the G_{q/11} protein type [35] and induce the action of phospholipase C (PLC) increasing the intracellular inositol triphosphate (IP₃), diacylglycerol (DAG) and Ca²⁺ levels [36]. This protein may also indirectly alter cAMP synthesis, by decreasing G_s protein abundance or by activating adenylate cyclase 8 (ADCY8) by the PLC, Ca²⁺, calmodulin pathway. However, these mechanisms are poorly understood and yet to be studied [37].

Substance-p (SP) modulation

SP is a peptide composed of a chain of 11 amino acid residues (undecapeptide). It is a member of the tachykinin neuropeptide family. Although it is a neurotransmitter, it also acts as a neuromodulator [38,39]. Substance-p and neurokinin A (NKA) are closely related and

are both produced from a polyprotein precursor. It is mainly associated with inflammatory processes and pain. Neurokinin 1 receptor (NK1R) is the endogenous receptor for substance-p which belongs to the tachykinin receptor sub-family of G-protein-coupled-receptors (GPCRs) [40]. When SP binds to NK1R, it results in internalization by the clathrin-dependent mechanisms (coat protein used to build small vesicles in order to transport molecules within cells) to the acidified endosomes where the complex dissociates after which SP is degraded and NK1R is re-expressed on the cell's surface [41]. Substance-p is the first to respond to extreme stimuli (immediate defense system). Since it acts as a vasodilator it is also associated with bronchoconstrictive properties (constriction of the airways in lungs) resulting in coughing, wheezing, and even shortness in breath. The BotC contains glutamatergic NK1R expressing neurons which are strongly modulated by SP. However, its exact effect in the other brain regions of the respiratory system have not been explored in detail yet. Recent data reveals that selective activation of NK1R in the BotC of the VRG evoked bradypnea (slow breathing rate) by the lengthening of the expiratory period. Endogenous activation of NK1R in the BotC initiates the expiratory lengthening effect of the Hering-Breuer reflex (induced by lung expansion, which excites pulmonary stretch receptors in airways. Stimulation of these receptors shortens inspiratory time as the tidal volume increases, thus increasing the frequency of breathing. When lung expansion is prevented, this reflex lengthens the inspiratory time, thus helping to preserve tidal volume), thus maintaining the respiratory rhythm and frequency [42].

Cholecystokinin (CCK) modulation

Cholecystokinin, is the primary excitatory neuromodulator and naturally occurring neuropeptide in the central nervous system, originally identified in the gut where it is involved in secretion of pancreatic enzymes etc. [43] Cholecystokinin receptors are present within the nucleus of the solitary tract (NTS), VRG, the Kolliker Fuse nucleus (the subparabrachial nuclei, one of the three parabrachial nuclei in the brainstem), and in neurons projecting to these areas, which provide an input to respiratory system [44,45]. Minute amounts of CCK precursor messenger RNA (mRNA) were expressed in the lungs and pulmonary neuroendocrine cells (specialized airway epithelial cells) of mammals. CCK1 and CCK2 receptors genes may be found in pulmonary vascular endothelial cells, macrophages, bronchial and alveolar epithelial cells [46]. When CCK ligands bind to its receptors, it transmits a cascade of signals across the membrane by inducing GPCR activity which amplifies the signal via the second messenger system and produces a long-lasting effect in the nervous system. In this case an enzyme known as phospholipase C (PLC) is activated by the alpha subunit of the G- protein which catalyzes phospholipids within the cell into two molecules - DAG (activates enzymatic pathways) and IP₃ (stimulates release of Ca²⁺ which binds proteins together) similar to the serotonin pathways discussed above. Various different types of CCK receptors produce different effects on the respiratory system. Some produce excitatory effects while some exert inhibitory effects. CCK-4 receptor subtype results in subjective dyspnea (reduction in vital capacity of the lungs without any effect on the respiratory resistance- shortness of breath). CCK-4 along with the CCK-2 receptor causes an increase in the tidal volume and minute ventilation. However, it has no effect on the respiration frequency. These observations suggest that the CCK-2 receptor agonist might be acting as an excitatory ligand, thus a respiratory stimulant which exerts its effect on anxiety via a direct modulation of respiration. It was observed that CCK-8 decreased the respiratory rate while sleeping. CCK-8 receptor agonists modulate the slowing down of respiratory rhythm through the CCK-1 receptors and depresses the tidal volume via central CCK-1 dependent mechanisms. There are many other subtypes of CCK receptors expressed in humans, however their exact functions in the respiratory system haven't been well explained yet [47].

Acetylcholine (ACh) modulation

Acetylcholine (ACh) is a primary neuromuscular transmitter that functions in the brain and the rest of the body. It even operates as a neuromodulator in the central nervous system. Its main function is muscle activation and initiating movement [48]. However, it also affects the respiratory system. Its two receptors, nicotinic (found in tobacco) [49] and muscarinic (found in mushrooms), can be found throughout the brain, but the muscarinic receptors are more common in the human brain. In mammals such as humans, 5 subtypes of muscarinic receptors have been discovered, namely M₁, M₃, M₄ and M₅ [50]. All of them function as GPCRs which is, they exert their effect via the second messenger system. The M₁, M₃ and M₅ receptor subtypes are G_q coupled (they increase intracellular levels of IP₃ and

calcium via activation of PLC. they usually exert an excitatory effect on their target cells [51]. On the other hand, the M2 and M4 subtypes Gi/Go coupled receptors (they decrease intracellular levels of cyclic AMP by inhibiting adenylate cyclase, thus producing an inhibitory effect on target cells. There are muscarinic receptors on preBotC inspiratory neurons and the excitatory effect of preBotC is primarily mediated by these receptors, primarily the M3 receptor subtype. In the preBotC inspiratory neurons, ACh operates via the M3 receptors on the postsynaptic terminal of neurons to open cationic channels which are permeable to sodium and potassium. This resultant inward cation current depolarizes the inspiratory neurons including pacemaker neurons present within the preBotC [52]. This action conduces an influential effect because pacemaker- like neurons in the preBotCare the center for respiratory rhythm generation and the voltage dependent bursting properties of the pacemaker neurons are the basis of respiratory frequency regulation [53]. Therefore, we may conclude that acetylcholine exerts an excitatory effect on the respiratory system.

Neuronal plasticity in the respiratory system

Plasticity is a permanent alteration in the neuronal circuitry based on prior experience. It's the neurological term for the brain's way of learning or processing new information and developing set actions based on that exposure or consequence. These experiences include exposure to certain drugs, injury, aging, diseases etc. Our breathing pattern must constantly adapt in accordance to our life's circumstances. Plasticity is expressed in all segments of the respiratory system in different forms. In this review we will briefly highlight a few aspects of plasticity observed in the respiratory system. It may involve structural or functional changes at different sites within the respiratory network. Plasticity is usually initiated by neuromodulatory influence on the respiratory control system. Neuromodulators promote plasticity in their target cells by initiating particular synaptic events that leach to plasticity and may even alter the capacity of neuromodulation (plasticity due to metamodulation) [54].

Mechanisms involved in plasticity

Neuromodulator-induced synaptic plasticity

In this case synaptic plasticity is introduced by neuromodulators which tend to activate intracellular signaling cascades, which in turn alters the strength of other synaptic inputs such as the effect of the GABAergic or glutamatergic signals. An example of such a neuro-modulator would be serotonin. Its release into the presynaptic terminal initiates intracellular cascades which result in an increase in the neuron's synaptic strength for a short or long term. Serotonin -dependent plasticity plays a crucial role in respiratory motor control [55]. Other neuromodulators such as noradrenaline may also initiate synaptic plasticity, but may produce a different effect [56].

Activity-dependent plasticity

In activity-dependent plasticity the change in the efficacy of a synapse is caused by the previous activity at that synapse. In areas of the brain where there is a lot of high frequency activity going on, the synaptic transmission would enhance at multiple time domains [57]. This phenomenon is termed short/long term potentiation (STP/LTP) [58,59]. On the contrary, areas performing low frequency activity would undergo a decrease in synaptic efficacy known as short/long term depression [60] (STD/LTD) [61]. These mechanisms may indirectly rely on the activation of particular neuromodulators and their effect on the synapse, whether they have an inhibitory or an excitatory effect.

Alterations in neuromodulation

Breathing is a process which requires the influence of multiple neuromodulators, excitatory along with inhibitory working in unison. Each of them is capable of expressing synaptic plasticity by influencing the involved neurons in their respective ways. A change in concentration of neuromodulators near their target cells may be a result of changes in the activity of the neuromodulatory neuron, the reuptake of a neuromodulator once released into the synaptic cleft, its synthesis degradation, the number and size of neuromodulatory terminals, the density and type of receptors on the presynaptic and postsynaptic terminals of the target neuron and even their intracellular signaling

mechanisms. The change in concentration of neuromodulators due to any of the above-mentioned factors may lead to neuronal plasticity in the form of metamodulation.

Alterations in neuronal properties (Morphological)

A neuron can alter its functions via a phenomenon termed morphological plasticity through which a neuron changes the shape and size of its soma and dendrites (its physical properties). By changing the distribution of membrane channels or postsynaptic receptors, neurons can alter their membrane potential, membrane capacitance, membrane resistance, action potential threshold voltage etc. in this manner the contribution of a neuronal circuit in the respiratory system can be altered which in turn provides an altered output [62].

Growth of new synapses

The strength of an inhibitory or excitatory synapse might increase due to the formation of new synaptic connections between pre-existing neurons. This is more prominent during early stages of development. Strengthened synaptic connectivity may be the result of the arrival of an increased number of growth cones (facilitate axon growth) or sprouting of existing nerve terminals (branching) [63]. The growth of new synapses is usually triggered by deafferentation (the freeing of a motor nerve from sensory components by severing the dorsal root central to the dorsal ganglion), synaptic activation and even due to the increased concentration of neurotrophic factors (peptides which induce the growth of neurons) [64]. During developmental stages or after tissue transplants, synaptic pruning is an important factor which leads to plasticity by affecting synapses in the brain. It is a process by which the brain eliminates excess synapses.

Neuromodulatory imbalance

The balance of influence of neuromodulators on the respiratory system results in a steady respiratory output. Once this balance is disrupted by a strengthened or weakened influence of a particular neuromodulator for various reasons, it may cause respiratory plasticity. This plasticity may be short term potentiation/depression (STP/STD) or long-term potentiation/depression (LTP/LTD) depending on the influence of the neuromodulator on the synapse. These variations in the neuromodulatory balance are a plausible explanation for varied responses of the respiratory system towards intermittent hypoxia (alternating periods of normoxia - normal oxygen levels and hypoxia - lower than normal oxygen levels) as compared to hypercapnia (elevated carbon dioxide levels in blood) [65], expressed by an imbalance between the opposing effects of serotonin neuromodulation and noradrenaline neuromodulation [66].

Respiratory neuromodulation disorders

Since neuromodulators play such an important role in the functioning of the respiratory system, any disturbance in any aspect of neuromodulatory control might lead to an adverse effect on the body, thus causing unwanted symptoms and breathing disorders.

Rett syndrome

One such neurological condition that has been directly linked to a disturbance in neuromodulatory control is the Rett syndrome [67]. People diagnosed with this disorder typically suffer from severe breathing abnormalities including respiratory dysrhythmia, hyperventilation and breath - holding [68]. These respiratory disturbances are analogous to deficiencies in SP [69], serotonin, noradrenaline and dopamine and the patients have X - linked mutations in the methyl - CpG binding protein 2 gene (Mecp2).

Prader-Willi syndrome

The Prader-Willi syndrome is another disorder which is closely associated with a disturbance in the aminergic neuromodulatory control system. People suffering from this disorder have mutations in the neclin gene which is linked to severe irregularities in breathing and

abnormalities in the 5-HT modulation [70]. Due to the complexity and interconnected network of the functioning of the neuromodulatory system, it is probable that many other modulators are also disturbed in such patients. However, how these modulators are altered is yet to be understood.

Concluding Remarks

The aspects of neuromodulation and neuronal plasticity highlighted in this review paper indicate that neuromodulators play a crucial role in day to day functions such as respiration and an imbalance or disturbance in this system is capable of causing exaggerated effects in other organ systems of the body due to its highly interconnected network. In spite of all the extensive research done towards interpreting how exactly these neuromodulators affect certain aspects of respiration, it is still challenging to predict how a given neuromodulator acting at various levels of the respiratory system will affect the final output. This would be difficult to predict especially due to the fact that our brain and body has many feedback mechanisms in place, which tend to compensate for the change in concentration of a neuromodulator. There are also many neuromodulators that could potentially compensate for a defect in one modulatory system that a small disturbance in a neuromodulatory system would have only a limited number of consequences in the concerned system, which are usually not very severe. Understanding the underlying mechanisms of neuromodulators is incumbent for further research and development in the field of neuroscience and even finding possible cures to various medical conditions.

Bibliography

1. Jack L Feldman., *et al.* "Looking for inspiration: new perspectives on respiratory rhythm". *Nature Reviews Neuroscience* 7.3 (2006): 232.
2. P A Gray., *et al.* "Normal breathing requires preBötzing complex neurokinin-1 receptor-expressing neurons". *Nature Neuroscience* 4.9 (2001): 927-930.
3. S P Lieske., *et al.* "Reconfiguration of the neural network controlling multiple breathing patterns: eupnea, sighs and gasps". *Nature Neuroscience* (2000): 600-607.
4. Diethelm W Richter and Jeffrey C Smith. "Respiratory Rhythm Generation *In Vivo*". *The National Center for Biotechnology Information* 29.1 (2014): 58-71.
5. "Regulation of Breathing".
6. Joseph Feher. "Dorsal Respiratory Group - an overview". ScienceDirect Topics. *Quantitative Human Physiology* (2017).
7. JA Neubauer. "Ventral Respiratory Group - an overview". ScienceDirect Topics. *Encyclopedia of Respiratory Medicine* (2006).
8. Steven D Waldman MD JD. "Apneustic Center - an overview | ScienceDirect Topics". *Pain Review* (2009).
9. Chi-Sang Poon and Gang Song. "Pneumotaxic Center - an overview | ScienceDirect Topics". *Progress in Brain Research* (2014).
10. Annette Pisanskiab and. "The parafacial respiratory group and the control of active expiration".
11. "Pre-Bötzing complex". Wikipedia.
12. Jeffrey C Smith., *et al.* "Pre-Bötzing Complex: A Brainstem Region That May Generate Respiratory Rhythm in Mammals". *The National Center for Biotechnology Information* 254.5034 (2011): 726-729.
13. SP Lieske., *et al.* "Reconfiguration of the neural network controlling multiple breathing patterns: eupnea, sighs and gasps". *Nature Neuroscience* (2000).

14. Richard J Van Dam., *et al.* "Rhythm generation by the pre-Bötzinger Complex in medullary slice and island preparations: Effects of adenosine A1receptor activation". *BMC Neuroscience* 9 (2008).
15. F Chigr., *et al.* "Anatomical distribution of somatostatin immunoreactivity in the infant brainstem". *Science Direct* 29.3 (1989): 615-628.
16. Ying-Ying Liu., *et al.* "Substance P and Enkephalinergic Synapses Ontoneurokinin-1 receptor-immunoreactive neurons in the pre-Bötzinger complex of rats". *European Journal of Neuroscience* (2004): 65-67.
17. Hidehiko Koizumi and Jeffrey C Smith. "Persistent Na⁺ and K⁺-Dominated Leak Currents Contribute to Respiratory Rhythm Generation in the Pre-Bötzinger Complex *In Vitro*". *The Journal of Neuroscience* (2008).
18. Marino Ramirez., *et al.* "The role of spiking and bursting pacemakers in the neuronal control of breathing". *Journal of Biological Physics* (2011).
19. Christopher A Del Negro., *et al.* "Persistent sodium current, membrane properties and bursting behavior of pre-bötzinger complex inspiratory neurons *In vitro*". *Journal of Neurophysiology* 88.5 (2002): 2242-2250.
20. Muriel Thoby-Brisson. "Identification of Two Types of Inspiratory Pacemaker Neurons in the Isolated Respiratory Neural Network of Mice". *Journal of Neurophysiology* (2001).
21. Fernando Peña., *et al.* "Differential contribution of pacemaker properties to the generation of respiratory rhythms during normoxia and hypoxia". *Neuron* 43.1 (2004): 105-117.
22. Atsushi Doi and Jan-Marino Ramirez. "Neuromodulation And The Orchestration Of The Respiratory Rhythm". *Respiratory Physiology and Neurobiology* 164.1-2 (2008): 96-104.
23. Atsushi Doi., *et al.* "Neuromodulation and the orchestration of the respiratory rhythm". *Respiratory Physiology and Neurobiology* 164 (2008): 96-104.
24. Scott Rich., *et al.* "Effects of Neuromodulation on Excitatory–Inhibitory Neural Network Dynamics Depend on Network Connectivity Structure". *Journal of Nonlinear Science* (2018).
25. "Serotonin". Wikipedia.
26. Francisco J de Abajo. "Effects of selective serotonin reuptake inhibitors on platelet function: mechanisms, clinical outcomes and implications for use in elderly patients". *Drugs Aging* (2011).
27. Simon N. "Young "How to increase serotonin in the human brain without drugs". *Journal of Psychiatry and Neuroscience* (2007).
28. E B Olson., *et al.* "Serotonin and the control of ventilation in awake rats". *Journal of Clinical Investigation* (1979).
29. Fernando Peña and Jan-Marino Ramirez "Substance P-Mediated Modulation of Pacemaker Properties in the Mammalian Respiratory Network". *Journal of Neuroscience* (2004).
30. Matthew R. "Hodges and George B Richerson. "Contributions of 5-HT Neurons to Respiratory Control - NCBI". *Respiratory Physiology and Neurobiology* (2008).
31. Brandes Edward J., *et al.* "Serotonergic modulation of inspiratory hypoglossal motoneurons in decerebrate dogs". *Ivo F* 95.6 (2006): 3449-3459.
32. E M Talley., *et al.* "TASK-1, a two-pore domain K⁺ channel, is modulated by multiple neurotransmitters in motoneurons". *Neuron* 25.2 (2000): 399-410.

33. Boxun Lu Yanhua Su., *et al.* "The Neuronal Channel NALCN Contributes Resting Sodium Permeability and Is Required for Normal Respiratory Rhythm". *Cell* (2007).
34. Gérard Hilaire., *et al.* "The Role Of Serotonin In Respiratory Function And Dysfunction". *Respiratory Physiology and Neurobiology* 174.1-2 (2010): 76-88.
35. Matteo Giulietti., *et al.* "How much do we know about the coupling of G-proteins to serotonin receptors?". *Molecular Brain* (2014).
36. Aaron Mullally. "Secondary Messenger System: Phospholipase C Mechanism".
37. Atsushi Doi., *et al.* "Neuromodulation and the orchestration of the respiratory rhythm". *Respiratory Physiology and Neurobiology* (2008).
38. James E Krause and Andrew D Hershey. "Structure, Functions, and Mechanisms of Substance P Receptor Action". *Science Direct* (1992).
39. "Substance P". Wikipedia.
40. C A Maggi., *et al.* "The mammalian tachykinin receptors". *General Pharmacology* (1995).
41. E F Grady., *et al.* "Delineation of the endocytic pathway of substance P and its seven-transmembrane domain NK1 receptor". *Molecular Biology of the Cell* (1995).
42. Angelina Y Fong and Jeffrey T Potts. "Neurokinin-1 receptor activation in Bötzinger complex evokes bradypnoea". *The Journal of Physiology* 575.3 (2006): 869-885.
43. "Cholecystokinin". Wikipedia.
44. Beinfeld M., *et al.* "Cholecystokinin receptors | Introduction | BPS/IUPHAR Guide".
45. S A Wank. Am., *et al.* "Cholecystokinin receptors". *The Journal of Physiology* (1995).
46. Katarzyna Kaczyńska., *et al.* "Contribution of CCK1 receptors to cardiovascular and respiratory effects of cholecystokinin in anesthetized rats". 54 (2015): 29-34.
47. Katarzyna Kaczyńska., *et al.* "Neuropeptides and breathing in health and disease". *Pulmonary Pharmacology and Therapeutics* (2017).
48. XM Shao and JL Feldman. "Acetylcholine Modulates Respiratory Pattern: Effects Mediated by M3-Like Receptors in PreBötzinger Complex Inspiratory Neurons - NCBI". *Journal of Neurophysiology* (2000): 1243-1252.
49. Xuesi M Shao., *et al.* " $\alpha 4^*$ Nicotinic Receptors in preBötzinger Complex Mediate Cholinergic/Nicotinic Modulation of Respiratory Rhythm - NCBI". *The Journal of Neuroscience* 28.2 (2008): 519-528.
50. "Acetylcholine". Wikipedia.
51. L Quartara and CA Maggi. "Ligands and mechanisms of cellular activation". *Science Direct* 31.6 (1997): 537-563.
52. Aaron Mullally., *et al.* "Secondary Messenger System: Phospholipase C Mechanism".
53. Atsushi Doi and Jan-Marino Ramirez. "Neuromodulation And The Orchestration Of The Respiratory Rhythm". *Respiratory Physiology and Neurobiology* 164 (2008): 96-104.
54. Gordon S Mitchell., *et al.* "Neuroplasticity in respiratory motor control - NIH". *Journal of Applied Physiology* (2003).

55. Jason H Mateika, *et al.* "Intermittent hypoxia and respiratory plasticity in humans and other animals: does exposure to intermittent hypoxia promote or mitigate sleep apnoea?" *Experimental Physiology* 94.3 (2009): 279-296.
56. Gordon S Mitchell, *et al.* "Neuroplasticity in respiratory motor control - NIH". *Journal of Applied Physiology* 94.1 (1985): 358-374.
57. Robert C. Malenka, *et al.* "Postsynaptic factors control the duration of synaptic enhancement in area CA1 of the hippocampus". *Neuron* 6.1 (1991): 53-60.
58. Robert Malenka and Roger Nicoll. "Long-Term Potentiation--A Decade of Progress?" *Science* 17 (1999): 1870-1874.
59. G Kempermann, *et al.* "Activity-dependent regulation of neuronal plasticity". *Progress in Brain Research* (2000): 35-48.
60. Nicola Kemp, *et al.* "Long-term depression: a cascade of induction and expression mechanisms". *Science Direct* 65.4 (2001): 339-365.
61. H Daniel, *et al.* "Cellular mechanisms of cerebellar LTD". *Trends Neuroscience* 21.9 (1998): 401-407.
62. Rainald Mössner, *et al.* "BDNF but not nerve growth factor (NGF)". ScienceDirect.com. (2000).
63. William Cameron and Pedro Nunez-Abades. "Physiological changes accompanying anatomical remodeling of mammalian motoneurons during postnatal development". *Brain Research Bulletin* 53.5 (2000): 523-527.
64. C N LIU, *et al.* "Intraspinal sprouting of dorsal root axons; development of new collaterals and preterminals following partial denervation of the spinal cord in the cat". *Archives of Neurology and Psychiatry* 79.1 (1958): 46-61.
65. T L Baker, *et al.* "Respiratory plasticity: differential actions of continuous and episodic hypoxia and hypercapnia". *Respiratory Physiology* 129.1-2 (2001): 25-35.
66. R Kinkead, *et al.* "Plasticity in respiratory motor control: intermittent hypoxia and hypercapnia activate opposing serotonergic and noradrenergic modulatory systems". *Comparative Biochemistry and Physiology Part A: Molecular and Integrative Physiology* 130.2 (2001): 207-218.
67. M Elian, *et al.* "EEG and respiration in Rett syndrome". *Acta Neurologica Scandinavica* 83.2 (1991): 123-128.
68. A M Kerr, *et al.* "A review of the respiratory disorder in the Rett syndrome". *Brain and Development* (1992): 43-45.
69. T Matsuishi, *et al.* "Decreased cerebrospinal fluid levels of substance P in patients with Rett syndrome". *Annals of Neurology* 42.6 (1997): 978-981.
70. Sébastien Zanella, *et al.* "Necdin gene, respiratory disturbances and Prader-Willi Syndrome". *Advances in Experimental Medicine and Biology* (2008): 159-164.

Volume 9 Issue 10 October 2020

© All rights reserved by Prini Jain and Alok S Shah.