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Panic Disorder and Regulation of Carbon Dioxide: A Literature Review

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Abstract:

Panic disorder is the most popular mental disorder in the world, and it has already been studied by a lot of people in the research field. The feeling of panic has evolved when people are in danger, so the panic disorder can be related to respiration and learned fear. During the panic attacks, some patients may have a sense of shortness of breath and the one of the therapeutic methods of treating panic disorder is breathing training as well. Breathing training is related to the hyperventilation after the panic attacks occur, which is related to the false suffocation alarm theory proposed by Klein. Several studies have been published to describe the relationship between panic disorder and the false suffocation alarm system. However, the mechanism which is acid-sensitive ion channels (ASICs) behind the false suffocation alarm has not been sufficiently researched yet. This literature review found out that panic disorder is closely related to respiratory system in human body and acid-sensitive ion channels have a pivotal role in detecting carbon dioxide concentration and pH level in human. The fear conditioning related to panic disorder and breathing of carbon dioxide is also discussed in this literature review. The researcher can consider the treatment of acid-sensitive ion channels for patients with panic disorder.

Keywords: panic disorder, false suffocation alarm, acid-sensitive ion channels

1. Introduction

As a subtype of anxiety disorder, panic disorder is one of the most prevalent mental problems in the world. In a meta-analysis, the authors found out that the rate of patients suffer from panic disorder in a total of 2530 participants in 10 studies is a pooled rate of 3 percent (Walker et al, 2021).

According to Diagnostic and Statistical Manual of Mental Disorder 5th edition, the definition of panic disorder is the mental state when panic attacks occur irregularly, unpredictably and often. The panic attacks can happen in anywhere, any condition and any time. The panic attacks can be evoked by any stimulation. When patients are having panic attack, they may feel fast heart rate, suffocated and out of control (American Psychiatric Association & American Psychiatric Association, 2013). Sometimes, the

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panic attacks are expected as when patients are scared by something, for example, the patient encounter a tiger, and they are too fear of death to have panic attacks. The fear of suffocation may also be the reason of the occurrence of panic attacks as well, for example, when people are breathing in too much carbon dioxide, which causes them to out of breath.

More specifically, the Diagnostic and Statistical Manual of Mental Disorder 5th edition, when the panic attack happens, four or more the symptoms may occur. As listed below: Speed up heart rate, sweating, shaking, feeling of shortness of breath, sensations of choking, pain in chest or other physical discomfort, sensation of dizziness, chills, feeling of tingling, sensation of unreality, nausea, sensation of out of control, scared of death (American Psychiatric Association, 2013).

Patients with panic disorder may have problems of breathing, which indicates that the panic disorder is related to the respiratory system in human. Respiration is crucial in human for many metabolic reactions and cells to function in human. The oxygen is inhaled in human body by the contraction and downwards movement of diaphragms and the volume of lungs will expand, the pressure in the lungs will decrease. So that, the inner pressure of lungs is smaller than the air pressure outside the lungs, the air will go into the lung. After that, carbon dioxide is breathed out of the body as a waste of metabolic reaction. (Petersson & Glenny, 2014)emphasising basic concepts and relating them to clinical scenarios. For each gas exchanging unit, the alveolar and effluent blood partial pressures of oxygen and carbon dioxide (PO2 and PCO2. The oxygen provide energy for human for aerobic respiration and carbon dioxide is responsible for maintain a caid-base balanced environment in human body (Grimm et al., 2015)definitions, history, concepts, classification, and considerations for anesthesia and analgesia -- Anesthetic risk and informed consent -- Anesthesia equipment -- Monitoring anesthetized patients -- Anesthetic emergencies and resuscitation -- Euthanasia and humane killing -- Section 2: Pharmacology -- General pharmacology of anesthetic and analgesic drugs -- Anticholinergics -- Adrenergic agents -- Sedatives and Tranquilizers -- Opioids -- Non-steroidal anti-inflammatory drugs -- Anesthetic and analgesic adjunctive drugs -- Muscle relaxants and neuromuscular blockade -- Injectable anesthetics -- Inhalation anesthetics -- Local anesthetics -- Section 3: Body fluids and thermoregulation -- Acid-base physiology -- Perioperative thermoregulation and heat balance -- Treatment of coagulation and platelet disorders -- Clinical pharmacology and administration of fluid, electrolyte, and blood component solutions -- Section 4: Cardiovascular system -- Cardiovascular physiology -- Cardiac output measurement -- Anesthesia for cardiopulmonary bypass -- Cardiac pacemakers and anesthesia -- Pathophysiology and anesthetic management of patients with cardiovascular disease -- Section 5: Respiratory system -- Physiology, pathophysiology, and anesthetic management of patients with respiratory disease -- Section 6: Nervous system -- Physiology, pathophysiology, and anesthetic management of patients with neurologic disease -- Nociception and pain -- Section 7: Hepatic system -- Physiology, pathophysiology, and anesthetic management of patients with hepatic disease -- Section 8: Gastrointestinal and endocrine systems -- Physiology, pathophysiology, and anesthetic management of patients with gastrointestinal and endocrine disease -- Section 9: Urogenital system -- Physiology, pathophysiology, and anesthetic management of patients with renal disease -- Anesthetic considerations for renal replacement therapy -- Anesthetic considerations during pregnancy and for the newborn -- Section 10: Comparative anesthesia and analgesia -- Comparative anesthesia and analgesia of dogs and cats -- Anesthesia and pain management of shelter populations -- Comparative anesthesia and analgesia of equine patients -- Comparative anesthesia and analgesia of ruminants and swine -- Comparative anesthesia and analgesia of laboratory animals -- Comparative anesthesia and analgesia of zoo animals and wildlife -- Comparative anesthesia and analgesia of aquatic",”edition”:”Fifth edition of Lumb and Jones”,”event-place”:”Ames, Iowa”,”ISBN”:”978-1-118-52623-1”,”language”:”en”,”number-of-pages”:”1061”,”publisher”:”Wiley Blackwell”,”publisher-place”:”Ames, Iowa”,”source”:”K10plus ISBN”,”title”:”Veterinary anesthesia and analgesia”,”editor”:[{“family”:”Grimm”,”given”:”Kurt A.”},{“family”:”Lamont”,”given”:”Leigh A.”},{“family”:”Tranquilli”,”given”:”William J.”},{“family”:”Greene”,”given”:”Stephen A.”},{“family”:”Robertson”,”given”:”Sheilah A.”}],”issued”:{“date-parts”:[[“2015”]]}}],”schema”:”https://github.com/citation-style-language/schema/raw/master/csl-citation.json”} . If there is not enough oxygen and too much carbon dioxide in human’s lungs, the patients may be suffocated. The sudden increased in the acidity of the blood in the body and decreased in pH value is called acidosis. Acidosis can cause various serious diseases such as tissue inflammation, ischemic stroke, traumatic brain injury, and epileptic seizures(Zhang et al., 2023). Therefore, it is a big problem if the respiratory system is dysfunctional in human’s body. Patients with panic disorder should learn carefully about how to manage their breath when they are in panic attacks, especially for those who are accompanied with carbon dioxide hypersensitivity.

Acid-sensitive ion channels have many types, and they have many subunits which are listed as following: ac-

id-sensing ion channel 1a, acid-sensing ion channel 1b, acid-sensing ion channel 2a, acid-sensing ion channel 2b, acid-sensing ion channel 3, and acid-sensing ion channel 4. (Zhang et al., 2023). These six subunits of acid-sensing ion channels share the similar structure with 500 amino acids as a sequence and are put in two transmembrane domains, a big extracellular loop which contain 350 amino acids and short intracellular Nand C-termini (Yingjun & Xun, 2013). Most of the acid-sensing ion channels are distributed mostly in peripheral nervous system and central nervous system, except the acid-sensing ion channel 4 is not in the peripheral nervous system (Vullo & Kellenberger, 2020). However, only the acid-sensing ion channel 1a is discussed in this literature review. This literature review reveals how the acid-sensitive ion channels are associated with suffocation alarm and respiration in human.

2. Panic Disorder

2.1 Evolution

The evolution of panic can be traced back to ancient times. Walter Cannon proposed phrase "fight or flight" to describe a condition when people are facing danger. People may choose fight or escape away when they are in a situation of danger (Walter Cannon, 1929)(Nesse et al, 1988). For example, when you are encountered a tiger, your heart rate will increase, sweat will excrete, the breathing gets faster, blood is shunted, and it involves metabolic changes as well. The series of reactions to danger and feeling of panic demonstrates that panic evolved through natural selection to fight or escape away from dangerous events (Nesse et al., 1998). In conclusion, the feeling of panic has evolved to protect people from immediate danger by run away or fight back and it is acted as a protection system.

2.2 Hyperventilation

There are two opposite theories about how ways of respiration trigger panic disorder, which is Ley's hyperventilation theory and Klein's false suffocation alarm theory. First, Ley's hyperventilation theory is proposed in 1985 (Ley, 1985). It suggests that panic attacks have a close relationship with hyperventilation. According to Ley, hyperventilation, or rapid and deep breathing, causing a decrease in concentration of carbon dioxide in the blood, which can cause various physical symptoms such as dizziness, sensation of tingling and shortness of breath in the extremities. Ley argued that these physical symptoms can be misinterpreted as signs of a serious medical condition, which in turn can trigger intense fear and panic.

In contrast to Ley's theory, Klein's False Suffocation Alarm Theory (Klein, 1993) suggests that panic attacks are triggered by a misfiring of an evolved suffocation alarm system in the brain. This system is designed to detect signs of suffocation, such as elevated concentration of carbon dioxide (CO2) in the blood. Hypoventilation which is slow breathing can cause a rise in carbon dioxide in the vessels, which could lead to suffocation. The fear of death triggers the panic and people start to hyperventilate in order to breath in more oxygen. It is a viscous circle for patients with panic disorder: if the frequency of breathing is abnormal, it may evoke many physical discomfort such as headaches and chest pain. Then, the suffocation alarm within the patients with panic disorder may misinterpret these physical discomfort symptoms as dangerous and a threat to their life such as suffocation. After that, the patients may experience strong emotional reactions that may cause panic attacks (Kinkead et al., 2023)CO\n 2\n can also trigger innate behavioral and physiological responses associated with fear and escape but the changes in brain CO\n 2\n /pH required to induce ventilatory adjustments are generally lower than those evoking fear and escape. However, for patients suffering from panic disorder (PD.

The hyperventilation and hypoventilation can be both triggered by the feeling of danger and threat. The main difference between Ley's theory and Klein's theory is that Ley thought hyperventilation is the cause of panic while Klein thought hyperventilation is the response to the suffocation alarm during the panic. However, this literature review supports the Klein's theory and want to investigate further.

2.3 Carbon Dioxide Hypersensitivity

Carbon dioxide is a basic unit of living matter, which is proposed by a chemist named Antone Lavoisier. Carbon dioxide is important chemical signals that need closely monitoring to ensure good metabolic reaction and it is removed by the lungs during breathing. Carbon dioxide can evoke natural behavioural and physiological responses connected with fear-like feelings and run-away action (Kinkead et al., 2023)CO\n 2\n can also trigger innate behavioral and physiological responses associated with fear and escape but the changes in brain CO\n 2\n /pH required to induce ventilatory adjustments are generally lower than those evoking fear and escape. However, for patients suffering from panic disorder (PD. In this case, fear is learnable when it connected with carbon dioxide and patients with panic disorder, and the false suffocation alarm evolved to protect people from suffocation and fear evolved to prevent

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people from death as well. People with panic disorder can learn the fear from previous experience, their carbon dioxide monitor become more and more sensitive to the carbon dioxide in the vessels because the fear of death by suffocation. Eventually, the monitor is oversensitive, even a slightly increase in carbon dioxide will trigger panic (The carbon dioxide might be normal concentration in normal people). For example, there is a research (Gorman et al., 2001) shows that more patients with PD(panic disorder) and PMDD(premenstrual dysphoric disorder) had panic attacks than did controls or patients with major depression during carbon dioxide breathing of either 5% or 7% carbon dioxide. In Klein's theory (Klein, 1993), there is a concept of suffocation alarm threshold in human, and he believed that patients with lower suffocation alarm threshold is more susceptible to panic attack. There are two causes to lower the suffocation alarm threshold. First, hypoventilation, which cause an increase in concentration of carbon dioxide in the blood, occurs when people are threatened by or fear of something. It will make people feel out of breath and hence lower the threshold, making the suffocation monitor more sensitive to carbon dioxide and triggering panic attacks more easily. Second, an increase in acidity in blood can also cause the dropping in the suffocation alarm threshold. Carbon dioxide is acidic, if the level of carbon dioxide increases, the acidity will increase. Hence, as the suffocation alarm threshold decreases, the suffocation alarm is more likely to be triggered by the little fluctuation of carbon dioxide and panic attacks are more likely to occur as well.

3. Mechanism behind the false suffocation alarm

3.1 Acid-sensitive Ion Channels (ASICs)

The suffocation monitor has been mentioned a lot in the last paragraphs, however, the real detector of carbon dioxide concentration in humans is acid-sensitive ion channels. Among the all acid-sensitive ion channels, the acid-sensitive ion channel 1a has the function to detect the concentration of carbon dioxide by sensing the pH levels (Francios et al. 2015) in humans. There is a mouse experiment (Taugher, 2014) verify that the acid-sensitive ion channel 1a have the functionality to sense the concentration of carbon dioxide and are involved in expressing fear and panic. It is found out that, acid-sensing ion channel 1 is located and found in isolated mouse dendritic cells, T cells and B cells at mRNA and levels of protein (Yingjun & Xun, 2013). They tested 10% carbon dioxide -evoked freezing in bed nucleus of the stria terminalis (BNST) lesioned mice (acid sensitive ion channel 1a in bed nucleus of the stria terminalis is damaged in mouse brain) in comparison to sham controls. They found that 10% carbon dioxide caused freezing (Freezing means the disappearance of motion other than breathing because of fear and panic) behaviour that was absent in the compressed air in mouse. Moreover, bed nucleus of the stria terminal lesions mice have a significantly decreased carbon dioxide -evoked freezing behaviour, although they did not fully abandon it. Therefore, the mouse studies suggest that the bed nucleus of the stria terminals could be crucial for arousal of freezing behaviour in mouse when they encounter carbon dioxide. The results of their experiments increase the possibility of the hypothesis that acid-sensitive ion channel 1a is responsible for the carbon dioxide-induced responses in humans, which means that the more expression or function of acid-sensitive ion channel 1a, the carbon dioxide-triggered responses in humans are more likely to be more severe. Therefore, it also suggests the mechanism for more carbon dioxide sensitivity in patients with panic disorder in contrast to normal people and there might be more distribution of acid-sensitive ion channel 1a in panic disorder patients' body than normal people. Overall, the knockout of acid-sensitive ion channel 1a led to the dismiss of behaviours in several models of fear and anxiety, including fear conditioning and carbon dioxide -evoked freezing (Taugher, 2014). As the learning of fear is mentioned in the last paragraph, the concept of 'fear conditioning' is often associated with fear and panic disorder. The mouse experiment showed that the removal and inhibiting of acid-sensitive ion channel 1a had a disruptive effect on fear conditioning (Taugher, 2014). Furthermore, another group of researchers found out that the carbon dioxide by itself is not an unconditioned stimulus, but it increased memory of fear when combined with other fearful or dangerous things such as foot shocks. It was known that people without panic disorder may evoke panic during the inhalation of 10% carbon dioxide, so same as the human, the mouse are more likely to express freezing behaviours during the 10% inhalation of carbon dioxide. First of all, the researcher trained the experimental group of mice with a numbers of foot shocks and in the presence of 10% carbon dioxide (The two trainings do not happen at the same time). In the next day, when the researchers put the mouse back to the normal condition (no foot shocks and 10% carbon dioxide), they found out that the mice in experimental group showed more freezing behaviours than those mice in control group who did not have trainings with foot shocks and 10% carbon dioxide. In comparison, the mice with the removal of acid-sensitive ion channel 1a rarely show freezing behaviours compared to those mice still have the acid-sensitive ion channel 1a. In order to found

out that whether carbon dioxide itself acted as an unconditioned stimulus, the researchers exposed the air with normal concentration of carbon dioxide and no foot shocks to two groups of mice who with and without the trainings on the testing day. Surprisingly, neither the mice in both groups showed freezing behaviours. Therefore, the carbon dioxide itself is not served as an unconditioned stimulus, but it may evoke panic and fear-like responses when it is related to the feeling of suffocation and death.(Ziemann et al., 2009)whether it directly senses fear-evoking stimuli is unknown. Because the amygdala expresses acid sensing ion channel-1a (ASIC1a

4. Discussion

This literature review shows the importance of breathing and respiration of carbon dioxide in patients with panic disorder. The acid-sensitive ion channels are responsible for the carbon dioxide detection and evocation of panic disorder as well. In the mouse experiment, the results of that study show that the destruction of acid-sensitive ion channel1 A in mouse brain might weaken the response and sensitivity to carbon dioxide(Vullo & Kellenberger, 2020b). As the panic disorder is strongly associated with carbon dioxide breathing, the researcher can consider inventing some antagonist for the acid sensitive ion channels. In the same mouse experiment, the researchers have already found out that the acid-sensitive ion channel1 A antagonists is effective on reducing the response to carbon dioxide, especially for those with carbon dioxide hypersensitivity(Vullo & Kellenberger, 2020b). Researchers can invent more treatment or medicine about acid-sensitive ion channel 1 A to decrease the occurrence of panic attacks. There is an experiment found out that the breathing training is helpful in the cure of panic disorder, so the researcher can focus more on the respiratory regulation of patients to help them regulate their breath (Meuret et al., 2003).

4.1 Development from Childhood Separation Anxiety to Adulthood Panic Disorder

The children with separation anxiety disorder also have the symptom of carbon dioxide hypersensitivity. There is an experiment (Roberson-Nay et al., 2010)suggesting a link between the adult and child conditions. This study examines the influence of familial risk for PD on CO2 responses in children with SAD. We hypothesized that offspring with SAD of parents with PD would have distinct CO2 responses.\nMethods—Two hundred twelve nine-to-20 year-old offspring of parents with or without PD exposed to maintained 5% CO2 inhalation in the participants' homes. Anxiety symptoms, panic attacks, and respiratory physiology (respiratory frequency and tidal volume supported the hypothesis that the patients with childhood separation anxiety disorder might have the larger potential to have panic disorder when they grow up. The experiment shows that the API (Acute Panic Inventory) which rate 0-3 for 23 symptoms according to their severity. The results show that the children with separation anxiety disorder scores higher than the children without separation anxiety during the breathing in of 5% carbon dioxide. The children with separation anxiety display the symptoms of dyspnea and faster rate of breathing which are both signs of carbon dioxide hypersensitivity like the patients with panic disorder (Roberson-Nay et al., 2010) suggesting a link between the adult and child conditions. This study examines the influence of familial risk for PD on CO2 responses in children with SAD. We hypothesized that offspring with SAD of parents with PD would have distinct CO2 responses.\nMethods—Two hundred twelve nine-to-20 year-old offspring of parents with or without PD exposed to maintained 5% CO2 inhalation in the participants' homes. Anxiety symptoms, panic attacks, and respiratory physiology (respiratory frequency and tidal volume. Moreover, there is another research that found some evidence to back up this hypothesis as well. For example, there is a meta-analysis revealed that adults with separation anxiety disorder in the childhood have a bigger possibility to develop into panic disorders in their adulthood (Kossowsky et al., 2013).

4.2 The Relationship between Respiratory Diseases and Panic Disorder

People with respiratory diseases are prone to have panic disorder. For example, chronic obstructive pulmonary disease. In an analysis, the contrast experiments of three groups, which are patients with chronic obstructive pulmonary disease and panic disorder, patients with chronic obstructive pulmonary disease but without panic disorder and heathy control groups, show that the estimations of difficulty in breathing are varied significantly between three groups. The results show that the patients with chronic obstructive pulmonary disease always rated a higher level of breathing difficulty than patients with chronic obstructive pulmonary disease but without panic disorder and healthy control group. The healthy control group rated their level of difficulty in breathing as moderate, patients with obstructive pulmonary diseases but without panic disorder evaluated their difficulty of breathing as considerable, while patients with chronic obstructive pulmonary disease and panic disorder estimated their difficulty of breathing as severe. In this analysis, there is a positive linear increasing relationship between dyspnea

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and resistance of breathing for three groups. The rising anxiety caused increased, not reduced sensitivity to the breathing pressure. (Livermore et al, 2008).

The limitation of this study is that the references such as meta-analysis and literature review are not in recent 10 years, some are very old papers. The second limitation of this study is that this literature review only investigates one of the causes of panic attacks, which is the carbon dioxide sensor with suffocation alarm.

5. Conclusion

In conclusion, this study described the relationship between regulation of carbon dioxide and panic disorder. The theory of false suffocation alarm and mechanism which is acid-sensitive ion channel1 A behind the theory is elaborated in this literature review as well.

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