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Review article

Pharmacologically evoked apnoeas. Receptors and nervous pathways involved

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ABSTRACT

This review analyses the knowledge about the incidence of transient apnoeic spells, induced by substances which activate vagal chemically sensitive afferents. It considers the specificity and expression of appropriate receptors, and relevant research on pontomedullary circuits contributing to a cessation of respiration. Insight is gained into an excitatory drive of 5-HT_{1A} serotonin receptors in overcoming opioid-induced respiratory inhibition.

1. Introduction

Apnoea is defined as an absence of breathing, with a cessation of respiratory muscle movement and an unchanged lung volume. According to the American Academy of Sleep Medicine, apnoea is defined as a drop of ≥90% from baseline in respiratory flow lasting for ≥10 s [1]. Prolonged apnoea, leading to severe oxygen shortage and CO_2 accumulation in blood, can be life-threatening. Sleep apnoea, the most common in the human population, might be either central, due to a temporary failure of respiratory rhythmogenesis and a complete withdrawal of the respiratory drive to the inspiratory muscles; or it can be of the highly-prevalent obstructive type, where upper-airway flow is absent, despite the continued activity of thoracic inspiratory muscles and the diaphragm [2,3]. Frequent episodes of sleep apnoea evoke chronic intermittent hypoxia and sleep fragmentation leading to substantial cardiovascular morbidity [4,5].

Central and peripheral mechanisms contributing to the arrest of breathing have been largely described, nevertheless therapeutic options targeting apnoea are limited. Since apnoea can by induced pharmacologically, it raises the possibility of studying this phenomenon in experimental animals. In this article, the following sections summarise the evidence of apnoeogenic effects of different compounds described thus far in experimental studies, and reveal the contribution of peripheral ascending pathways and medullary centres, leading to temporary respiratory suppression. The review also discusses pharmacological opportunities, including recent advances to counteract breathing arrest produced by opioids.

2. Pulmonary chemoreflex

The archetypal triad of apnoea, bradycardia and systemic hypotension was described as pulmonary chemoreflex by Dawes and Comroe [6]. It can be elicited by a certain number of chemically unrelated substances and is characteristic of the stimulation of vagal sensory C-fibre afferents. The pulmonary chemoreflex is occasionally confused with the von Bezold-Jarisch reflex, which also refers to apnoea and a reduction in heart rate and blood pressure, but happens when substances are injected into the coronary circulation [7,8]. Systemic injection of various extraneous or intrinsic substances in spontaneously breathing animals produces a transient apnoea, starting within 1–3 s of the trial and defined as a pause in breathing exceeding 5 s [9]. This coincides with a prompt disappearance of the phrenic bursts, the neural correlate of apnoea. The temporary arrest in the classical pulmonary chemoreflex is followed by accelerated breathing. The chemicals traditionally used to evoke the reflex are: phenylbiguanide, an amidine derivative and agonist of 5-HT_3 receptors; 5-hydroxytryptamine, a naturally occurring biogenic amine and neurotransmitter; and capsaicin, a $TRPV_1$ agonist, the active principal of hot peppers and a prototypical stimulant of vagal afferent C-fibres [10,11].

3. Apnoeic response

An injection of phenylbiguanide into pulmonary circulation to induce apnoea, both in conscious and anaesthetised rats [12–16], rabbits [17] and cats [11,18,19] was described. Apnoeic responses evoked by 5-hydroxytryptamine were reported by Yoshioka et al. [20] in rats, and

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by several authors in cats [11,21,22]. Post-capsaicin apnoea was characteristic for rats [23–27], cats [28,29] and dogs [30–33]. Respiration that followed the apnoeic spells provoked by all mentioned substances was rapid, shallow breathing, concomitant with bradycardia and hypotension.

The same pattern of cardiovascular and respiratory response evoked by the systemic challenge of enkephalin analogues and morphine was observed in conscious or decerebrated rats, and described as "pulmonary opiate receptor reflex" [15,34,35]. In anaesthetised rats, the respiratory effect of opioids was not fully replicated: the apnoea was ensued by a slowed breathing rate [36–40].

4. Peripheral receptors of afferent pathway

The cardiorespiratory responses to these chemicals are due to the activation of pulmonary C-fibre afferents. Serotonin 5-HT_3 and capsaicin TRPV1 receptors are located on vagal unmyelinated C-fibres and within nodose ganglia [41–50]. They are present on primary afferent terminals, in and around the nucleus of the solitary tract (NTS), the first central synapse integrating inputs from airways and baro- and chemoreceptive structures [26,48,51–54]. It is well documented that vagal afferents, which terminate in the medial NTS, are also endowed with μ-opioid receptors [55–58].

Apnoea is assumed to arise from the stimulation of vagal sensory receptors in the lungs. It has been documented in the reports quoted above that the division of the vagi at the midcervical, or in the case of serotonin at the supranodosal level, excludes the apnoea and post-apnoeic pattern of breathing (reflex vagal mediation). There is one exception: post-capsaicin apnoea in vagotomised rats is abrogated by deafferentation of the larynx [24] (Table 1).

5. Local medullary effects of discussed chemicals

Research on the central impact of the afore-cited substances seems divergent. All of them have been applied at various levels of the neuraxis.

Microinjections of capsaicin to the commissural nucleus of NTS in rats induced a bradypnoeic response, with a tendency toward apnoea, not affecting tidal volume [59,60]. In medullary slices from neonate rats, capsaicin ceased the respiratory rhythm as suggested via depletion of glutamate and substance P in fibres within the preBötC [61]. The latest study showed that capsaicin applied in brainstem-spinal cord preparation from neonate rats induced a biphasic effect on respiratory rhythm: after an initial inhibition, stimulating it [62].

A selective ligand of 5-HT_{1A} serotonin receptors, 8-OH-DPAT, given on the ventral surface of cat's medulla either induced rapid, shallow breathing [63], or depressed expiratory neurones [64,65], whereas when delivered into the respiratory rhythm generating area, the pre-Bötzinger complex of decerebrate dogs, it did not detectably change the respiratory rate [66]. Serotonin applied microiontophoretically to NTS showed facilitating and depressive effects on respiratory neurones in cats [67], while phenylbiguanide (a serotonin agonist) appeared clearly excitatory in rats [68]. In decerebrate newborn kittens and rats, serotonin administered to the floor of the IV ventricle induced bradypnoea and dose-dependent apnoea [69,70] (Fig. 1).

Opioids showed unequivocal central depressive effects on respiration. Intraventricular microinjection of dermorphin, an exogenous peptide, evoked apnoea in rats, followed by bradypnoea [71]. Occasional apnoea was also observed after an endomorphin-1 injection into the Bötzinger complex of anaesthetised rats [72]. Endogenous enkephalins, present in brainstem respiratory regions [73], injected into NTS in rats resulted in the depression of respiratory rate and tidal volume [58,74,75], and given microiontophoretically to NTS in cats inhibited the activity of respiratory neurones [67]. Likewise, the systemically-injected, synthetic μ-receptor agonist fentanyl slowed respiratory rhythm by prolongation of inspiratory and expiratory discharges of bulbospinal neurones [76].

Table 1
Vagal pathway dependent apnoea induced by different agents; receptors involved.

Agent	Receptors	Source
Phenylbiguanide	5-HT_3	[12], [13], [10], [14], [35], [16]
5-HT	5-HT_3	[11], [21], [20]
Capsaicin	TRPV1	[23], [24], [11], [25], [26], [27]
Morphine	μ opioid	[37]
Dermorphin	μ opioid	[71], [38]
Fentanyl	μ opioid	[40]

6. Ascending projections and receptor distribution

As already mentioned, a peripheral source of generating apnoea evoked by the chemoreflex is attributed to vagal afferent C-fibres, projecting to NTS [77,78]. Experimental evidence shows that NTS is richly innervated by 5-HT-containing axons, originating centrally from caudal raphe nuclei (where 5-HT is synthetized), projecting to all regions of the brain and spinal cord, and peripherally from vagal afferents. Binding sites or mRNA for most of the 5-HT receptors have been localised within this nucleus [79–81], with an abundant expression of 5-HT_3 type [8]. Apnoea evoked by systemic injection of serotonin, with no access to CNS [82], is effected by the peripheral activation of 5-HT_3 receptors on vagal afferents [20,83]. Transduced to NTS, where 5-HT_3 receptors modulate central 5-HT release from caudal raphe neurons [52], it might either avert a facilitating drive on respiration from raphe pallidus, or foster an inhibitory effect of raphe magnus and obscurus [84–86], resulting in apnoea. A seemingly disparate shortening of apnoea of the laryngeal chemoreflex by activation of 5-HT_3 receptors within NTS in neonate rats [87] evidences their equivocal function.

C-type solitary tract afferent terminals in caudal NTS express vanilloid type 1 receptors, selectively activated by its agonist, capsaicin [88]. It has been recently shown that in vitro and in vivo rat and wild type mouse models, capsaicin-induced dose-dependent apnoea was mediated via TRPV1 activation at lung afferents, NTS and spinal cord ascending tracts [26]. This expands a hitherto determined pattern of capsaicin-induced apnoeic response, based primarily on vagal signalling [25,27–32,89,90].

Opioids used as powerful analgesics depress the rate and depth of respiration and bring the risk of fatal apnoea. It has been evidenced that the number of both central and sleep apnoea and hypopnea episodes correlates with an increasing opioid dose [91,92]. Recent literature describes patients on chronic opioid therapy who experience an increased prevalence of central sleep apnoea, obstructive sleep apnoea or combination of both types [93–95].

As already mentioned, pioneering studies on the pulmonary opiate receptor reflex showed in decerebrate rats vagally mediated apnoea, after a systemic injection of enkephalin and morphine [34,35]. Opioid peptide-containing neurons and immunoreactivity for μ-, δ- and κ-receptors were found in medullary and pontine respiratory related regions [96]. The direct injection of DAMGO, a μ-receptor agonist to the pre-Bötzinger complex decreased respiratory discharges of rat brainstem slices [97]. Neurons of this complex are endowed with μ-receptors [98]. Also, an abundant distribution of μ-opioid receptors was found in the caudo-medial part of the rats' NTS [58].

A bolus injection of full opioid agonists (morphine, dermorphin or fentanyl) evoked apnoea conditioned on preserved vagal afferentation [37,38,40]. Exposure to fentanyl suppressed respiratory activity in both perfused rat and in vivo preparation [98] and was capable of turning rapid shallow breathing induced by phenylbiguanide into long-lasting apnoea [99,100]. Naloxone, a non-selective opioid receptor antagonist, administered into the cisterna magna or pre-Bötzinger complex prevented this effect [99,100].

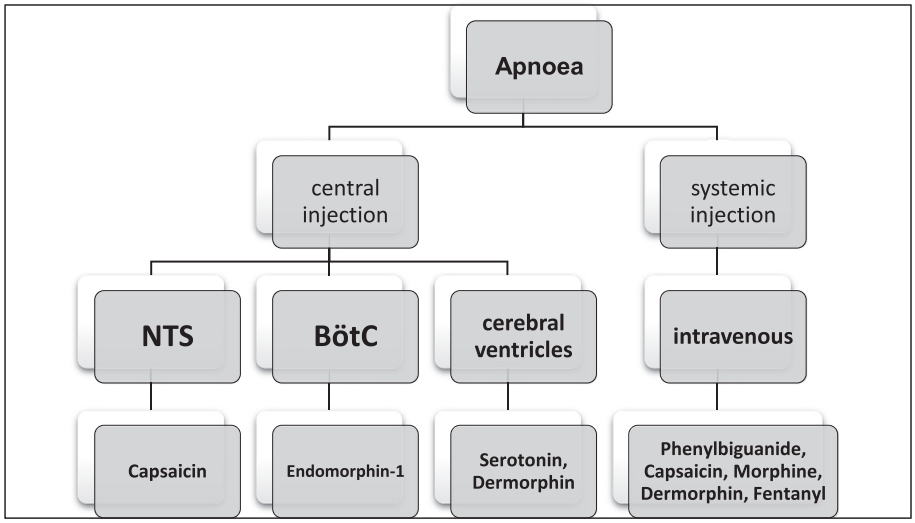

Fig. 1. A diagram presenting list of agents inducing apnoea after central and/or systemic application. BötC: Bötzinger complex; NTS: nucleus tractus solitarii.

7. Competitor of opioid depression

The reversal of morphine-induced apnoea in conscious and anaesthetised rats with 5-HT_{1A} receptor agonist (8-OH-DPAT) was first described by Sahibzada et al. [101], and appeared likewise effective in averting fentanyl respiratory depression of in situ preparation [102,103] and apnoea in intact anaesthetised rats [40]. This serotonergic ligand given intravenously suppressed medullary respiratory neuron discharges and phrenic nerve discharges [64,65]. Mention should be made here of an increased tidal volume induced by systemic injection of 8-OH-DPAT in vagotomised rats [104], particularly as it permeates the blood-brain barrier [105]. Most recent study by Iovino et al. [106] demonstrated that the stimulation of 5-HT_1 receptors in the pre-Bötzinger complex had excitatory effects on respiration, as well.

Several lines of evidence indicate that caudal raphe nuclei, a cluster of active 5-HT neurons, projecting to the brainstem cardiorespiratory system, affect ventilatory responses. Electrical stimulation of obscurus and magnus nuclei depressed inspiratory movements leading to apnoea, whereas excitation of nucleus pallidus resulted in tachypnoeic as well as fictive tachypnoeic responses [84,85,107]. 5-HT released within these nuclei inhibits their activity via 5-HT_{1A} receptors [108], abundantly represented in this structure [80,109]. It follows that the activation of 5-HT_{1A} receptors with 8-OH-DPAT effectively limits the serotonergic system, thus counteracting an opioid apnoea.

It has to be considered that 5-HT_{1A} receptors are expressed in the majority of the rats' Bötzinger and pre-Bötzinger cells, and appeared similarly distributed within NTS and pontine parabrachial and Kölliker-Fuse nuclei (KF) [102,103,110,111]. The blockade of 5-HT_{1A} receptors in this latter site increased the occurrence of spontaneous apnoea [112]. Strikingly, the activation of 5-HT_{4a} receptors, distributed in the pre-Bötzinger region, prevented fentanyl-induced apnoea in rats as well [98], but turned to be less operative compared to the potency of the 5-HT_{1A} type, presumably due to their lower density [102].

The promising agents in countering opioid produced depression are ampakines, modulating amino-3-hydroxy-5-methyl-D-aspartate (AMPA) receptors - type of glutamate receptors. In rats intravenously administered ampakine-CX717 has been demonstrated to abolish fentanyl induced apnoea and respiratory depression without inhibiting analgesia [113]. As suggested by authors AMPA receptor-mediated glutamatergic excitation counteracts the μ-opioid receptor dependent depression of preBötC neuronal excitability.

A substance with strong inhibitory opioid interaction, neuropeptide FF (NPFF) is an endogenous opioid-modulation peptide involved in opiate-induced tolerance and dependence [114]. It was recently demonstrated [115] that in anaesthetised rats, intravenous pre-treatment with NPFF substantially reduced the occurrences of apnoea produced with systemic injection of endomorphin-1. The exact mechanism of this action remains unclear; nevertheless, the parallel coexistence of NPFF1 and μ-opioid receptors in rodent NTS [58,116] indicates the possibility of modulating opioid-induced respiratory depression.

8. Bulbopontine mediation

The pre-Bötzinger complex, whose neural circuitry is essential for rhythmic breathing [117], receives input from its contralateral side, but sends projections to the ventral respiratory group, pontine respiratory regions, bilateral hypoglossal and bilateral NTS nuclei [118]. Therefore, the activation of MOR receptors within the pre-Bötzinger complex might spread to the pontomedullary respiratory network, to generate post-opioid apnoea and depress the respiratory pattern.

NTS stands as a central link between the visceral sensory afferents transferred to the bulbopontine structures. NTS neurones, coupled with interneurons in the C-fibre pathway, project to the pontine respiratory group and are reciprocally interconnected with the Kölliker-Fuse nucleus of the parabrachial complex [119,120]. Most of the parabrachial output to NTS comes from the KF, identified as an apnoeic site, but some input from NTS also reaches the adjacent intertrigeminal region, associated with sensory apnoea [121–123] and linked with the midline apnoeic site of medullary raphe nuclei [124].

Therefore, NTS forms the principal relay station for reflex apnoea. It holds true regarding vagally dependent transient arrest of breathing after systemic administration of substances activating C-fibre afferents, discussed in the previous sections of this review.

As regards opioids, the situation is more complex. The essence lies in an abundant expression of opioid receptors and their depressive action on the brainstem respiratory network. It has to be considered that fentanyl (a full opioid agonist) reduced or blocked respiratory activity [98,103] and likewise depressed respiratory rate and prolonged inspiratory phase [102] both in intact rats and in the in situ working heart-brainstem preparation. It has to be mentioned that the in situ preparation lacks vagal feedback, as the lungs are removed [125]. The aforesaid opioid apnoea induced by systemic injection in the intact animals required a vagal connection.

9. Conclusion

Available knowledge on the brainstem network and neural mechanisms responsible for generation of apnoea and on the incidence of

transient apnoeic spells triggered by the substances described may contribute to our understanding of this arrest of breathing. Studies presented in this review suggest that the vagal afferent pathway plays a significant role in triggering apnoea; also of paramount importance are the medullary respiratory areas. Research on substances and receptors with the potency to eliminate opioid-induced respiratory inhibition are relevant when looking for treatment strategies in respiratory-control disorders. The results showing the potency of 5-HT_{1A} serotonin receptors in overcoming opioid-induced respiratory inhibition are encouraging. Nevertheless, further experiments are needed to confirm the latter and to prove the same activity for the promising neuropeptide FF.

Conflicts of interest

The authors declare that there are no conflicts of interests.

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