Inspire or expire: a matter of life or death

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PART III

Respiratory stimulants

CHAPTER 7

CHAPTER 7
Pharmacology of viable mechanism agnostic respiratory stimulants for the reversal of drug-induced respiratory depression in humans

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Abstract

Introduction

Drug-induced respiratory depression is potentially fatal and can be caused by various drugs such as synthetic opioids and tranquilizers. The only class of respiratory depressants that has a specific reversal agent are opioids, such as naloxone. These reversal agents have limited utility in situations of polysubstance ingestion with agents from multiple respiratory depressant classes. Hence, there is an unmet need for drugs that stimulate breathing irrespective of the underlying cause of respiratory depression, i.e. mechanism agnostic respiratory stimulants.

Areas Covered

In this review, we discuss agnostic respiratory stimulants, tested in humans with promising results, i.e. ampakines, drugs that act at the carotid bodies, N-methyl-D-aspartate receptor antagonist ketamine, and orexin receptor-2-agonist danavorexton, and others that demonstrated positive effects in animals but not yet in humans.

Expert Opinion

Rapid, effective rescuing of individuals who overdosed on respiratory depressants saves lives. While naloxone is the preferred drug for reversing opioid-induced respiratory depression, its effectiveness is limited in cases involving non-opioids. While several agnostic respiratory stimulants showed promise in humans, further research is needed to optimize dosing, evaluate safety and efficacy in deeper respiratory depression (apnea). Additionally, future studies should combine agnostic stimulants with naloxone, to improve rapid, effective rescue from drug overdoses.

1. Drug-induced respiratory depression

Respiratory depression is a serious adverse effect caused by a range of drugs used in anesthesia, critical care, procedural sedation, and pain management.[1] These drugs that may cause respiratory depression include opioids, sedatives (e.g. benzodiazepines), anesthetics (e.g. propofol, barbiturates), and α2-adrenergic agents. Many (illicit) drugs used for hedonistic pleasure also pose a significant risk for respiratory depression (e.g. synthetic opioids, tranquilizers, ketamine, alcohol). The degree of respiratory depression varies depending on the specific drug, dosage, individual response, and concurrent use of other medications or substances. An example of the latter is the street drug Tranq, which is the combination of the potent opioid fentanyl with the veterinary α2-adrenergic agonist xylazine.[2] Particularly important is that most of these drugs are highly addictive. The addictive nature, coupled with their potentially fatal side effects, underlies the current opioid crisis, which claims thousands of lives each month.

The mechanism of respiratory depression varies depending on the drug class that is (ab)used. Best studied are the opioids that act on μ-opioid receptors within pontine central respiratory neuronal networks, particularly the preBötzinger complex and the parabrachial/Kölliker-Fuse complex.[3, 4] Their activation disrupts the respiratory rhythm generator, potentially leading to apnea, particularly when high doses are (ab)used. While apnea is often transient, with respiratory rhythm activity restored by slowly developing hypercapnic stimulation, high-dose opioids can cause prolonged apnea, that may have devastating effects on the cardiovascular system. Hypoxia and hypercapnia, secondary to apnea, will trigger cardiac dysrhythmias, bradycardia, and eventually a cardiac arrest.[5]

Rescuing individuals who have overdosed, both in the clinical and community settings, should focus on restoring respiratory and cardiac activity.[5] In cases of opioid overdose, the preferred first-line drug to restore rhythmic respiratory activity is naloxone, a competitive μ-opioid receptor antagonist.[5] High doses of naloxone are often required, but they can cause withdrawal symptoms in individuals with an opioid use disorder or severe pain in the clinical setting. Currently, intranasal and intramuscular naloxone are available for use in the community setting, while intravenous naloxone is the first choice in the clinical setting. Recently (May 2023), the FDA approved nalmefene nasal spray. Nalmefene is a long-acting opioid receptor antagonist, more potent than naloxone and therefore an attractive alternative to naloxone.[6, 7] However, nalmefe uptake from the nasal cavity is relatively slow with a peak concentration of about 30 min following administration.[7]

Many patients may not be helped by even high-dose opioid-receptor antagonists, particularly if the overdose involves high-affinity opioids (e.g. carfentanil) or non-opioid medications (e.g. Tranq).[8] Consequently, efforts are underway to develop so-called agnostic respiratory stimulants that can chemically revive individuals experiencing severe respiratory depression. These drugs restore respiratory activity by interacting with excitatory neuromodulators within the brainstem respiratory network or the carotid bodies.[9, 10] Notably, these mechanism agnostic stimulants offer the advantage of respiratory stimulation regardless of the underlying cause of respiratory depression. Additionally, as the drugs responsible for respiratory depression remain at their molecular site of action, secondary consequences associated with rescue interventions, such as those seen after naloxone administration (i.e. withdrawal, agitated delirium, recurrence of severe pain), can be avoided.

In this brief review, we will explore the various agnostic respiratory stimulants that have been tested in humans and that resulted in positive results in the last 10 years. We performed a PubMed database search with the keywords 'Respiratory stimulant' AND 'Opioid-induced respiratory depression.' This resulted in 43 unique papers that were searched for additional relevant references. We restricted the discussion to studies that describe the effect of respiratory stimulants in humans. We will exclude a discussion on naloxone but here provide references to some recent reviews on naloxone efficacy and limitations in reversing opioid-induced respiratory depression.[1, 8-10]

2. Agnostic respiratory stimulants

The use of respiratory stimulants is not a new concept and has been used for centuries to 'revive' individuals in situations such as drowning or accelerate emergence from anesthesia. Historical examples of such substances include tobacco smoke, strychnine, cocaine, amphetamine, picrotoxin, and carbon dioxide (for a comprehensive historical overview of respiratory stimulants, See Table 1 and refer to Ref [11]). However, these treatments had serious adverse effects eventually leading to their abandonment. For example, carbon dioxide, which seems a logical respiratory stimulant as it has direct effects at the peripheral and central chemoreceptors, may cause serious neurocognitive defects, acidosis, hyperkalemia, increased dead space ventilation, and may eventually cause a hypercapnic coma.[12] Here we will focus on the pharmacology of various drugs that have undergone human testing for the purpose of reversing respiratory depression. The following drug classes will be discussed: drugs that emulate a hypoxic environment at the carotid bodies, N-methyl-D-aspartate receptor (NMDAR) antagonists, orexin receptor agonists, and ampakines; see Table 2. Thereafter, we will briefly discuss drugs that have been tested for use in humans but did not give positive results.

Substance	Year	Mechanism of action
Tobacco (nicotine)	1774	Agonist at nicotinic acetylcholine receptors at neuromuscular junctions and at central sites
Strychnine	1818	Antagonizes glycine binding to its receptor (NDMA)
Ephedrine	1885	Sympathomimetic that binds to adrenoceptors and inhibits neuronal norepinephrine reuptake
Atropine	Early 1900s	Antagonist of muscarinic acetylcholine receptors, causing parasympathetic inhibition and dominance of sympathetic activity
Amphetamine	1930s	Blocks catecholamine reuptake and to a lesser extent serotonin and dopamine reuptake
Cocaine	19th century	Block neuronal catecholamine reuptake and to a lesser extent serotonin and dopamine reuptake
Carbon dioxide	1930s	Activation of peripheral and central chemoreceptors
Pictrotoxin	1940s	Noncompetitive antagonist at the GABA-A receptor complex
Tetrazole derivates	1924	Increases cAMP and increases the release of acetylcholine
Methylphenidate	1960s	Causes the release of catecholamines and inhibits their neuronal reuptake, particularly of dopamine
Almitrine	1982	Stimulation of TASK-1 and TASK-3 potassium channels in the carotid body.
Caffeine	Unknown	Bronchodilation and enhances brain blood flow
Doxapram	1962	Stimulates peripheral chemoreceptors in the aortic and carotid bodies.

Table 1. Historical respiratory stimulants.

Substance	Examples	Mechanism of action	Benefits	Disadvantages
Drugs that emulate a hypoxic environment at the carotid bodies	Doxapram, ENA001	Closure of K^+- channels expressed on type 1 carotid body cells leads to the release of neurotransmitters, initiating a hyperventilatory response.	Reverses opioid- and nonopioid-induced respiratory depression	Analeptic effects (doxapram); infusion pain (ENA001)
N-methyl-D-aspartate receptor antagonists	Racemic ketamine, esketamine	Possible effects via inhibtion of the NMDA receptor or via activation of AMPARs (indirectly via hydroxy-norketamine)	Counteracts opioid-induced respiratory depression	Nausea/ vomiting, cardiovascular stimulation, psychedelic symptoms
Orexin receptor agonists	Danavorexton (TAK-925)	Tonic excitatory role of orexin in ventilatory control	Reverses opioid-induced respiratory depression.	Limited information available
Ampakines	CX717, XC1739	Positively allosterically modulators of AMPAR	Counteract opioid-induced respiratory depression	Limited research available, especially limited safety information

Table 2. Overview of effective respiratory stimulants currently available and those in development.

2.1. Drugs acting at the carotid bodies

Mechanism of action

The carotid bodies are two small, highly vascularized organs found in the bifurcation of the common carotid arteries.[13] They have the highest blood flow to metabolism ratio of any mammalian organ and contain the peripheral chemoreceptors that are important sensors of metabolic ventilatory control. The peripheral chemoreceptors sense the oxygen state of the arterial blood just prior to entering the brain compartment and in response to hypoxia cause the release of neuromodulators that activate the sinus nerve, a branch of the glossopharyngeal nerve. Its nerve axons end in the nucleus tractus solitarius, a brain region that interacts extensively with brainstem respiratory neurons.[13] The carotid body response to hypoxia is a brisk hyperventilatory response aimed at restoring the oxygen content of arterial blood.

Although the exact mechanism of hypoxic sensing at the carotid bodies remains incompletely understood, the process likely involves the closure of potassium channels expressed on type 1 carotid body cells.[13] Several drugs have been designed that stimulate breathing through the closure of these potassium channels. One such drug, doxapram, is available for use in humans, the other is the still-experimental drug ENA001.[14-16] Doxapram is an analeptic

drug that inhibits so-called background potassium channels that regulate neuronal excitability through the mediation of a background 'leak' K+ current: TASK1, TASK3, and TASK1/3 heterodimer potassium channels;[17] ENA001 inhibits calcium-activated potassium channels, BKCa-channels.[15, 16] Upon closure of these potassium channels, the carotid body type 1 cell releases neurotransmitters (e.g. acetylcholine, ATP), initiating a hyperventilatory response as long as any potential depression of respiratory activity in the central nervous system is surmounted.[13]

Products

Over the years, multiple drugs have been developed to target the carotid bodies and simulate a hypoxic response.[9, 10] Besides the still available doxapram, almitrine was effective in inducing a hyperventilatory response by interacting with the peripheral chemoreceptors.[14, 18] However, almitrine is no longer accessible due to the development of sensory distal neuropathy associated with its chronic use.[19] The most recent medication that acts on the carotid bodies is ENA001 (Enalare Therapeutics Inc., U.S.A.), previously referred to as GAL021.[15, 16]

Human data: doxapram

A human study on the effect of doxapram during total intravenous anesthesia showed that a single dose increased respiratory rate for no longer than 15 min, indicative of the rapid onset and offset of effect (blood effect-site equilibration half-life = 3 min).[18] In a more recent study, our research group investigated the effect of a continuous infusion of doxapram during alfentanil-induced respiratory depression. Due to its analeptic effects, doxapram caused a dose-dependent increase in cardiac output that led to an increase in the clearance of the opioid and consequently the reduction of analgesia.[20] Interestingly, despite the reduced opioid plasma concentrations, its respiratory stimulatory effect was limited. We relate this to the relatively low dose used in that study or possibly to a ceiling in efficacy (i.e., at severe respiratory depression originating within the brainstem, the efficacy of a peripherally acting pharmacologic ventilator may be insufficient). Despite its advantage in maintaining or even increasing cardiac output, doxapram is rarely used for the reversal of respiratory depression from potent opioids. This may be related to its analeptic side effect profile or low potency. Further studies are needed to determine the doxapram dose-response relationship.

Human data ENA001

The effect of ENA001 was tested in two human studies on drug-induced respiratory depression. In the first study, the effect of a continuous infusion of ENA001 on alfentanil-induced respiratory depression was studied.[21, 22] In a second study, the effect of ENA001 on propofol-induced

depression of the hypoxic ventilatory response was measured. The results of the later study are submitted.[23] In the first study, a 40–50% depression of minute ventilation, induced by alfentanil, was partly reversed by ENA001 (reversal of about 20–30%).[21] The effects were due to increases in both tidal volume and respiratory rate. Interestingly, the ENA001 blood effect-site equilibration half-life was not different from zero, indicative of an almost immediate effect following intravenous administration.[22] This is related to its side of action outside the blood-brain barrier and the very high blood flow of the carotid bodies. No effect on cardiac output was observed, an important difference compared to doxapram. Further studies are needed to determine the effect of ENA001 at deeper levels of opioid-induced respiratory depression (i.e., > 50%).

The difference in efficacy between doxapram and ENA-001 remains unknown but we relate the difference to receptor selectivity, with ENA-001 being the more selective and appropriate drug for stimulating the carotid bodies without causing analeptic side effects.

Limitations

Doxapram but not ENA001 causes considerable analeptic effects that include headache, dizziness, hypertension, flushing, sweating, nausea/vomiting, muscle spasms, and sometimes severe anxiety. Apart from pain on injection, no ENA001 side effects were noted in the human studies. While the initial results of studies on ENA001 are favorable, more research is needed to establish the efficacy of ENA001 in deep levels of respiratory depression. For example, it is important to determine whether apnea induced by high doses of synthetic opioids may be reversed by ENA001.[24] Additionally, other administration modes than the currently available intravenous formulation are needed to treat opioid overdoses in the community setting. Given its short blood-effect-site equilibration half-life, the drug needs to be administered as a continuous infusion for long-term effects. This currently restricts its use in the hospital setting, for example, for treatment or prevention of postoperative respiratory depression. This then has two advantages: it will sustain rhythmic breathing activity without affecting opioid analgesia, and may even allow higher doses of opioids to ensure adequate pain relief.

2.2. N-methyl-D-aspartate Receptor (NMDAR) antagonists

Mechanism of action

While the NMDAR antagonists, racemic ketamine and its S+-isomer esketamine, are considered to have their main site of action at the NMDA receptor, these are complex drugs that have multiple metabolites that are active and possibly involved in their respiratory effects;[25, 26] we will here use the generic name ketamine for either compounds. Ketamine is metabolized

into norketamine and subsequently into hydroxynorketamine (HNK). Particularly HNK may be involved in causing respiratory stimulation through mechanism agnostic activity at the glutamatergic modulate α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor (AMPAR).[25, 26] Animal data indicate that the AMPAR excites respiratory activity within several brainstem respiratory networks.[27] How such effects differ from the ampakines remains at present unknown as HNK is still poorly studied in models of opioid-induced respiratory depression. Other mechanisms of action that have been proposed in respiratory stimulation include:[28] blockade of glutamatergic NMDAR activity, although there is evidence that loss of glutamate drive may reduce respiratory rhythmic activity;[29] improved enhancement of monoaminergic neurotransmission causing enhanced sympathetic outflow with respiratory excitation.[30, 31]

Products

The NMDAR antagonist and neuroplastic drug ketamine were first designed in the early 1960s as an anesthetic agent.[32] Currently, racemic ketamine and its S(+) isomer esketamine are used as analgesics, sedatives, and antidepressants.[25] From the beginning, it was noticed that ketamine lacked the respiratory depressant effects typically associated with other intravenous and inhalational anesthetics. More recently, its respiratory stimulatory effects were systematically studied in humans and animals.[30, 31, 33]

Human data

In 1998, Mildh et al. studied the effect of a single subanesthetic bolus dose of racemic ketamine on moderate fentanyl-induced respiratory depression in exclusively male volunteers.[34] Ketamine attenuated fentanyl-induced respiratory depression without preventing a decrease in blood oxygenation. More recently, in a pharmacokinetic-pharmacodynamic modeling study, Jonkman et al. rigorously studied the effect of escalating doses of esketamine on remifentanil-induced respiratory depression in male and female volunteers.[31] They observed a dose-dependent respiratory stimulatory effect induced by esketamine although about 3 in 10 subjects remained unresponsive to the effects of esketamine, suggestive of a possible role of metabolic heterogeneity in the study outcome with the absence of sufficient HNK production in some subjects. At high doses, ketamine may produce naloxone-sensitive respiratory depression, indicating that at high doses ketamine may activate opioid receptors.[35]

Limitations

Ketamine has many adverse effects including nausea/vomiting and cardiovascular stimulation causing tachycardia and hypertension. Additionally, high-dose ketamine produces

psychedelic symptoms such as hallucinations, paranoia, and depersonalization and may cause panic attacks. While these effects may be inherent to the desired ketamine effect, they do compromise patient compliance. We see a place for ketamine in the perioperative period. Ketamine will have a tonic excitatory respiratory effect and cause profound analgesia. Consequently, perioperative ketamine may be opioid-sparing. This mechanism alone reduces respiratory events during post-anesthesia care.

2.3. Orexin receptor agonists

Mechanism of action

Neuropeptides orexin A and B are synthesized by neurons located in the lateral and dorsal hypothalamic area acting at type 1 (OX1R) or type 2 (OX2R) orexin receptors. These neuropeptides play a role in the regulatory role of appetite and the sleep-wake cycle.[36-41] Deficiency of orexin leads to narcolepsy, a disorder characterized by sleep attacks and cataplexy. Orexin A, in particular, is involved in the regulation of wakefulness and metabolic rate by acting at OX2R. Animal studies have demonstrated the significance of orexin in the control of breathing. For instance, mice with a knockout of the orexin gene exhibit a significant decrease in their sensitivity to carbon dioxide when awake but not asleep.[39, 40] This is related to the projection of orexin neurons into brainstem respiratory centers that express orexin receptors (including the preBötzinger complex) and is indicative of a tonic excitatory role of orexin in ventilatory control during wakefulness. Consequently, the administration of exogenous orexin stimulates breathing.

Product

Originally developed to treat narcolepsy, orexin receptor agonists were found to not only increase wakefulness but also stimulate breathing.[41] As a result, they have emerged as a new class of respiratory agonists. Among them, the orexin receptor agonist danavorexton (TAK-925) is the sole orexin receptor agonist that has been tested in a human trial for drug-induced respiratory depression to date.[41] Danavorexton is further studied in narcolepsy, idiopathic hypersomnia, and obstructive sleep apnea.

Human data

We recently studied the ability of the highly selective OX2R agonist danavorexton to reduce remifentanil-induced respiratory depression in 18 male volunteers.[41] Modest respiratory depression (30–40% reduction of isohypercapnic baseline ventilation) induced by remifentanil was effectively and dose-dependently reversed by danavorexton through increases in tidal volume and respiratory rate. The effect was sustained after danavorexton infusion

ended. Further pharmacokinetic and pharmacodynamic analyses are needed to determine the pharmacologic properties of danavorexton. Finally, pain relief from remifentanil remained unaffected by the OX2R agonist.

Limitations

While the initial findings of the study are promising, more research is needed to establish the safety, efficacy (e.g. effect on deep levels of respiratory depression and apnea), and broader applicability of danavorexton in the treatment of drug-induced respiratory depression, as well as to address the potential side effects, such as insomnia and hypertension, theoretically associated with its use. Although it seems that danavorexton is being developed for clinical use in the perioperative setting (it may be given at the end of anesthesia to arouse the patient with a secondary benefit of stimulation of respiration), for use in the community setting, danavorexton needs to be tested at deep levels of opioid-induced respiratory depression to determine whether it is able to fend respiratory depression from high-dose synthetic opioids.

2.4. Ampakines

Mechanism of action

Ampakines are benzamide compounds that positively allosterically modulate AMPAR-mediated synaptic response activity.[42] Glutamate-mediated transmission, facilitated by AMPARs, plays a crucial role in generating the respiratory rhythm in neuronal networks of the respiratory brainstem and in stimulating respiratory motoneurons.[1, 27]

Products

No ampakines have been registered for use as respiratory stimulants as yet. Various ampakines, however, have been tested in animal and human studies. Encouraging data emerged from two human studies, examining C×717 and CX1739, that completed phase 2 proof of concept trials (see https://drug-dev.com/respirerx-pharmaceuticals-announces-publication-of-preclinical-results-supporting-the-use-of-ampakines-in-the-treatment-of-human-spinal-cord-injury/).[43, 44] The results of a study on C×717 were published in 2010, while a study on C×1739 was completed in 2016 (clinicatrial.gov) Unfortunately, we were unable to locate a published paper on CX1739, apart from an abstract. However, ongoing research on both compounds continues to be conducted in animals.[45, 46]

Human data

Oertel and colleagues performed a human study with the ampakine CX717. In 16 healthy male volunteers, C×717 partly counteracted alfentanil-induced respiratory depression while

preserving analgesic effects with some increase in tiredness.[43] Participants received the ampakine before induction of alfentanil-induced respiratory depression, hence, we remain uninformed on the efficacy of C×717 in reversing established cases of opioid-induced respiratory depression. Compound C×1739 demonstrated favorable outcomes in a phase 2 human study.[44] In a preliminary report, C×1739 reduced remifentanil-induced respiratory depression at a steady-state plasma concentration of 2 ng/ml, but failed to be effective in reversing respiratory depression after a 1 μg/kg intravenous remifentanil bolus administration.

Limitations

The biggest limitation is the paucity of human studies that hampers a comprehensive understanding of their potential effects. Particularly there is little information on the safety of these drugs in humans. Future studies should address this issue.

3. Negative human studies

In addition to the above-mentioned drugs that showed positive results in experimental human studies as agnostic respiratory stimulants for reversing drug-induced respiratory depression, other agents were also tested for the same purpose but yielded negative outcomes. Here, we will provide a brief overview of these drugs for the sake of providing a comprehensive review.

3.1. Serotonin receptor agonists

The neuromodulator serotonin plays a crucial role in regulating inspiratory and expiratory respiratory activity, exhibiting actions that oppose those of μ-opioid receptor agonists.[1, 9, 10] The exact mechanism by which serotonin receptor agonists stimulate respiration is not fully understood, but it is believed that they enhance the excitability of respiratory neurons in the medullary respiratory centers. This may involve the stimulation of excitatory neurotransmitter release, such as glutamate, or the reduction of inhibitory neurotransmitter activity, like γ-amino-butyric acid. Furthermore, serotonin receptor agonists may heighten the sensitivity of peripheral chemoreceptors to variations in arterial oxygen and carbon dioxide levels, contributing to increased ventilation.

Previously, we discussed a series of serotonin agonists targeting receptor subtypes 1a, 4a, and 7a.[1] While most studies showed that these drugs effectively prevented or reversed respiratory depression induced by μ-opioid analgesics in animal models,[10] serotonin 4a receptor agonist BIMU8 failed to reverse sufentanil-induced respiratory depression in rats and caused muscle rigidity in goats.[40, 47, 48] Human studies evaluating the efficacy of selective serotonin agonists

specifically targeting the 1a and 4a receptor subtypes in reversing morphine-induced respiratory depression (buspirone and mosapride) consistently yielded negative results.[49, 50] This lack of effectiveness may be attributed to the inability of these serotonin agonists to penetrate the blood-brain barrier adequately, resulting in insufficient concentrations at the brainstem respiratory centers. Recently, Florian et al.[51] studied the antidepressant paroxetine, a selective serotonin reuptake inhibitor. They observed a significant decrease in the ventilatory response to hypercapnia. These findings suggest that further investigation into selective serotonin agonists that are able to cross the blood-brain barrier is necessary to enhance our understanding of their therapeutic potential in this context.

3.2. Thyrotropin-releasing hormone (TRH) and analogs

TRH is a tripeptide hormone (p-Glu-His-Pro-NH2) produced in the hypothalamus.[52] It plays a regulatory role in the secretion of thyroid-stimulating hormone from the anterior pituitary gland and prolactin from the pituitary gland. TRH exerts its effects by binding to the G-protein-coupled receptor TRH receptor, expressed widely in the brain and peripheral tissues, indicative of its broad functionality.[53]

One notable effect of TRH is its dose-dependent excitatory effect on respiratory activity, coinciding with increases in blood pressure and heart rate.[52] In various animal (including non-human primate) models of respiratory depression, TRH was able to reduce opioid-induced respiratory depression.[54, 55] However, when administered intravenously or intraperitoneally, TRH has a short half-life of less than 5 minutes and a poor ability to cross the blood-brain barrier due to its low lipophilicity. To overcome these limitations, several analogs of TRH have been developed with improved therapeutic selectivity and extended duration of action. An example of such an analog is taltirelin, which is registered in Japan for the treatment of spinocerebellar degeneration.[56] Taltirelin has been studied in animals but not in human models of opioid-induced respiratory depression. These analogs offer enhanced properties compared to TRH, enabling them to cross the blood-brain barrier more effectively and exhibit prolonged effects, making them more suitable for therapeutic applications. Recent animal studies demonstrated various shortcomings of the use of TRH or taltirelin with increased dead space ventilation, hypoxia, lactic acidosis, and enhanced opioid-induced muscle rigidity.[57] In humans, intravenous TRH doses up to 0.1 mg/kg failed to show any respiratory stimulation during remifentanil-induced respiratory depression.[58] This may indicate the need for higher TRH doses, but the cost of TRH and the emergence of adverse effects precluded increasing the TRH dose.

3.3. Tianeptine

Tianeptine is an atypical tricyclic atypical antidepressant and cognitive enhancer that produces neuroplastic changes and modulates noradrenergic, dopaminergic, and AMPAR glutamatergic pathways.[59, 60] As mentioned above, AMPARs play a crucial role in maintaining respiratory rhythmogenesis and inspiratory drive through their excitatory activity within the brainstem respiratory networks. These molecular actions prompted an animal study on the ability of tianeptine to reverse morphine-induced respiratory depression with positive results.[61] However, a series of experiments in humans failed to show any efficacy of tianeptine in reversal of alfentanil-induced respiratory depression (following oral tianeptine) or remifentanil-induced respiratory depression (in response to intravenous tianeptine).[62] In fact, it was observed that tianeptine enhanced remifentanil-induced respiratory depression, possibly related to the induction of sedation or to its (weak) μ-opioid receptor mechanism agnostic activity.[63] Interestingly, the animal data suggest that the sequence of tianeptine administration might affect its ability to reverse opioid-induced respiratory depression.[61] It seems that the presence of tianeptine in the brainstem preemptively prevents the development of opioid-induced respiratory depression, as observed in animal studies,[61] while administration after an established opioid-related respiratory depression is not effective as observed in humans.[62] Apparently, the sequence of events initiated by the opioid is not reversed by tianeptine.

In summary, we discussed three drug classes with absence of efficacy in reversing opioid-induced respiratory depression. While dissimilar in the mechanism of action, animal studies suggest that the common cause for the lack of sufficient drug availability within the brainstem respiratory networks might be responsible for the lack of efficacy. Additionally, lack of receptor selectivity may be involved in the many serotonin-receptor agonists that have been studied.

Conclusions

We provided a summary of agnostic respiratory stimulants that are either available for clinical use or under development for the treatment of drug-induced respiratory depression in humans. The majority of these drugs are designed to counteract respiratory depression caused by opioids, both in the clinical and community settings. Recent publications suggest that some of these respiratory stimulants have promising results in human studies, while others have demonstrated positive effects in animal studies but not yet in humans. Drugs with positive results in human studies are:

- drugs that act at potassium channels with the carotid bodies such as ENA001;
- the NMDAR antagonist ketamine that excites breathing possibly through mechanism agnostic activity of its metabolite HNK at the AMPAR;
- and the latest development is the type 2 orexin agonist, danavorexton, which excites breathing through interacting with the OX2R within the brainstem respiratory network;
- the ampakines, a group of drugs that excite respiratory activity by activation of the AMPAR system within brainstem respiratory network

While these drugs and their targets show promise, their efficacy and safety have not been sufficiently scrutinized to allow for their use as actual treatments for patients. It is particularly important to study their efficacy in case of high-dose synthetic opioid overdose. Respiratory stimulants studied in human models of drug-induced respiratory depression that did not yield positive results include tianeptine, thyrotropin-releasing hormone, and serotonin agonists. This may be due to the inability to get sufficient compound, at the given doses, to their site of action within the brainstem, possibly related to difficulty crossing the blood-brain barrier.

In summary, based on the available literature, it becomes apparent that the current body of evidence does not support the approval of these respiratory stimulants for widespread clinical use.

Expert opinion

There is an immediate need for the development of effective agents that can counter respiratory depression from any drug. Reasons for the need for such drugs are manifold. Firstly, we are currently facing a global crisis of drug overdoses, opioids, and non-opioids, which result in numerous fatalities, especially in the United States and Canada.[64] Respiratory depression complicated by a cardiac arrest, is the primary cause of death in these cases.[5] Therefore, it is crucial to have rapid and effective pharmacological interventions to rescue individuals experiencing an overdose and save their lives.

Secondly, apart from non-pharmacological interventions such as artificial ventilation and cardiac resuscitation, the first choice of pharmacological rescue is currently naloxone. However, naloxone, an opioid receptor antagonist, has certain limitations that hinder its ability to effectively counteract drug-induced respiratory depression. These limitations include its short duration of action, difficulty in rapidly reversing high-affinity opioids, such as carfentanil, and

lastly, inability to reverse respiratory depression from non-opioids that produce serious respiratory effects, such as when combined with an opioid.[65] For example, the potent veterinary α2-receptor agonist xylazine was found in 90% of all illicit drug samples in Philadelphia in 2021 and cannot be antagonized with naloxone.[66] Its addition to fentanyl reduces the amount of fentanyl required to reach the fentanyl high. The lacing of fentanyl with xylazine reduces the production price but comes with deleterious effects, apart from severe respiratory depression, it could cause cutaneous ulcerations. Finally, in the community setting high naloxone doses (4 mg or greater) are often given to reverse an opioid overdose. This can lead to the emergence of withdrawal symptoms such as anxiety, agitation and aggressive behavior, or excited delirium. This may endanger healthcare providers and bystanders. Additionally, aggressive behavior may endanger the overdose victim, as well.

Thirdly, drug-induced respiratory depression may cause serious complications in the clinical setting as well, for example, during procedural sedation, following surgery, or in any patient treated with a sedative or sleep medication, particularly in combination with an opioid. It is important to be able to administer a respiratory stimulant that causes swift reversal of respiratory depression irrespective of its underlying cause, without causing agitation or pain.[10] To summarize, the development of non-opioid respiratory stimulants is critically needed to address the overwhelming number of overdose victims from both opioid and non-opioid drug overdoses. Additionally, these stimulants would be valuable in sustaining respiratory activity in the clinical setting

We above discussed the results of studies performed exclusively in humans. Many more drugs are being developed and several are tested in animal studies (see ref [11] for an overview of animal and experimental data). Such developments are aimed at various targets such as the cannabinoid 2 receptor, nicotinic acetylcholine receptor, oxytocin receptor, or the thiol redox state. Interestingly, some developments aim to treat overdose victims with monoclonal antibodies against specific opioids (e.g. oxycodone, fentanyl, or carfentanil) to neutralize the opioid or enhance its breakdown.[11] While such therapy does not act by causing respiratory stimulation (the ventilatory control system is not influenced by such therapy), it does reduce the opioid load at the μ-opioid receptor, thereby restoring breathing activity. Still, none of these experimental treatments have been studied in humans so far, but they will likely undergo human testing in the near future.

Finally, we strongly believe, that agnostic respiratory stimulants will become particularly essential tools for the treatment of a drug overdose in the community setting. These

treatments could serve as alternatives to naloxone, although combining agnostic respiratory stimulants with naloxone appears to be even more relevant. It seems well possible that the combination of low-dose naloxone with drugs targeting distinct molecular sites (e.g. the potassium channels of the carotid bodies) could result in rapid and effective reversal of deep respiratory depression (apnea), especially in cases of opioid or multiple drug overdoses. The two treatments may act synergistically without inducing withdrawal symptoms. However, research in this area remains limited even in experimental studies. For example, studies in rats demonstrated that combining naloxone with a nicotinic acetylcholine receptor agonist can effectively counter synthetic opioid-induced apnea.[67] Similarly, in rats, combining a vaccine against oxycodone with the opioid receptor antagonist naltrexone, offered greater efficacy in reducing oxycodone-induced respiratory depression than immunotherapy alone.[68] It is important to note that the later treatment is primarily focused on preventing respiratory events and should not be considered as an option for the acute treatment of an opioid-related respiratory event.

In summary, the development of agnostic respiratory stimulants is crucial for addressing drug overdoses in community settings. Combining these stimulants with naloxone may offer a more effective approach, and exploring synergistic combinations with targeted drugs is a promising avenue for rapid and effective reversal of respiratory depression. However, further research is needed to fully understand the potential of these treatments, especially in human studies.

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