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Review article

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DISTINCT GENERATORS FOR ASPIRATION AND EXPIRATION REFLEXES: LOCALIZATION, MECHANISMS AND EFFECTS

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Re-evaluation of our earlier c-Fos-like immuno-reactive studies and brainstem transection/lesion experiments in over 40 anaesthetized, non-paralyzed cats allowed comparison of two distinct airway defensive reflexes with the distinct generators for inspiration (I) and expiration (E), described recently in juvenile rats. The spiration reflex (AspR) is characterized by solitary rapid and strong inspiratory effort with a reciprocal inhibition, preventing a subsequent active expiration, while the expiration reflex (ExpR) manifests by rapid and strong expiratory effort, starting without a preceding, inspiration, or reciprocal inhibition of occasional spontaneous inspiration. The retro-trapezoid nucleus/parafacial respiratory group neurones described as the distinct generator for active E in rats, are activated also during the ExpR in adult cats. Brainstem transection 5 mm above the obex eliminates the E generator and the ExpR, but preserves the I generator located in the pre-Bötzinger Complex, and also the AspR. This suggests the existence of a distinct I generator in cats as well as rats, and its contribution to the generation of the AspR. Persistence of the AspR in adult cats during asphyxic gasping, their similar character and the strong activation of I neurones at many places in the medulla and pons, suggest a common brainstem neuronal circuit contributing to generation of both the gasping and the gasp-like AspR. That the AspR and ExpR have distinct multilevel brainstem control mechanisms supports the dual theory of control and provides unique models for testing respiratory rhythm and pattern generation. The AspR may be compared with the powerful "auto-resuscitation effects of asphyxic gasping"; the ExpR may underly the effectiveness of the laryngeal chemoreflexes in prevention of lung diseases.

Key words: *auto-resuscitation, brainstem, cat, eupnoea, gasping, respiratory rhythmogenesis, aspiration reflex, expiration reflex*

INTRODUCTION

Distinct rhythm generators for inspiration (I) and expiration (E) have been described recently for juvenile rats (1); they can induce different rhythms for inspiration and expiration, accompanied by reciprocal inhibition in several experimental and clinical conditions. The respiratory rhythms can be modified reflexly; in juvenile rats with intact vagus nerves, continuous positive airway pressure (CPAP +0.4 kPa) inhibited phasic abdominal muscle activity and +0.9 kPa changed the EMG discharge from phasic to tonic; -0.4 kPa negative airway pressure triggered a series of fast inspirations at about 66 breaths min^{-1}; spontaneous inspirations were being suppressed by Fentanyl (1). Therefore, it is not surprising that these distinct I and E generators could be separately provoked to strong reflex activities, particularly by stimulation of rapidly adapting receptors (RARs), capable of inducing 3-10 reflex respiratory muscle contractions in 1 s.

The existence of distinct generators for I and E is consistent with two distinct airway reflexes provoked by activation of RARs: the aspiration reflex (AspR), evoked by various methods of nasopharyngeal (Nph) stimulation (2-4), and the expiration reflex (ExpR), induced primarily by stimulation of the glottal area (Gl) in cats and some other mammals (5, 6). The gasp-like AspR is characterized by rapid and very strong solitary inspiratory effort without subsequent active expiration. In contrast, the ExpR consists of a prompt solitary expiratory effort without a preceding inspiration. Both reflexes, accompanied by strong reciprocal inhibition of inspiratory or expiratory muscles, are dual ventilatory processes, similar to the rhythms produced by the I and E generators. Therefore, the main components of the two reflexes, the localization of brainstem central structures and their mechanisms and effects, will be compared with the distinct I and E rhythm generators.

MAIN COMPONENTS OF THE ASPR AND EXPR COMPARED TO A COUGH AND QUIET BREATH IN CATS

Fig. 1 schematically illustrates the main components of the AspR and ExpR, compared with the cough reflex and quiet breath in anaesthetized spontaneously breathing cats.

The AspR includes the following ten main components:

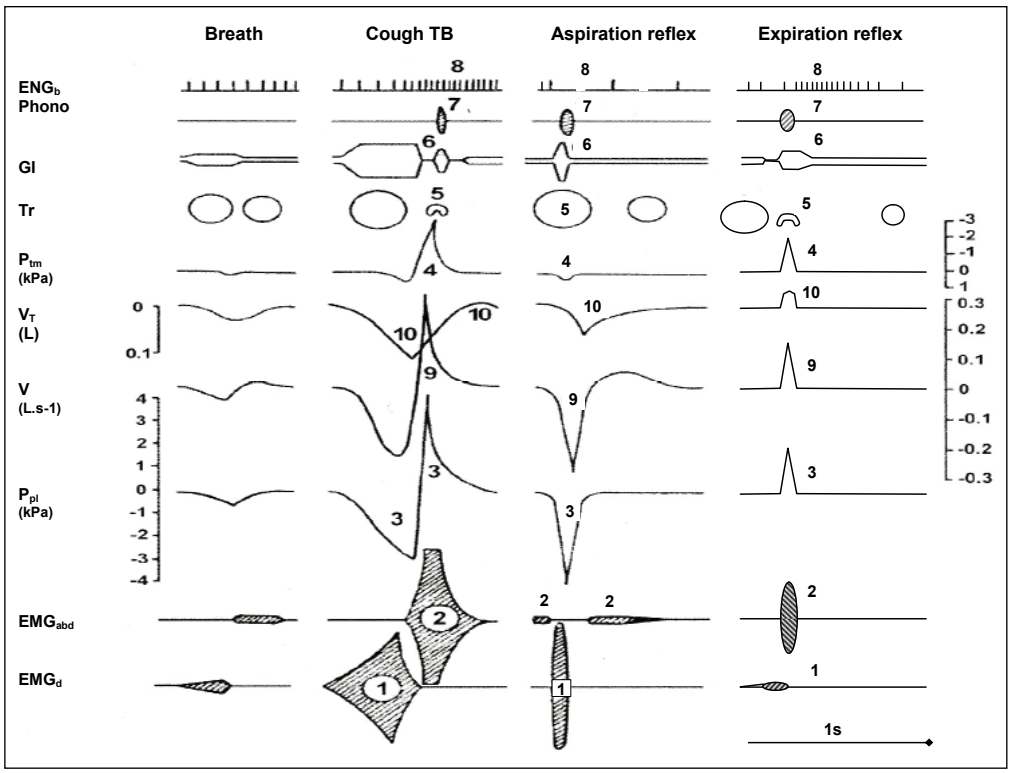

Fig. 1. Schematic illustration of ten main components (indicated by numbers) of the AspRs and ExpRs, compared with the cough reflex and quiet breath in anaesthetized cats. Abbreviations: ENGb- electroneurogram of a bronchoconstrictor fibre activity, Phono- acoustic signal, Gl- glottal lumen, Tr- tracheal lumen, Ptm- transmural pressure, V_T- tidal volume, $\dot{V}$ - airflow, Ppl- pleural pressure, EMGabd- abdominal electromyogram, EMGd- diaphragmal EMG (modified from Ref. No. 7 with permission).

1) a short-lasting high-frequency activity in the phrenic nerve or the inspiratory muscles, indicating a rapid, strong, spasmodic sniff- and gasp-like inspiration; 2) no subsequent active expiration, but even a reflex interruption of any spontaneous activity of the abdominal muscles, suggesting an inhibition of active expiration and an exhalation performed passively; 3) a marked inspiratory pleural pressure decrease (-4 kPa), followed by a passive return of intrathoracic pressure to values slightly above zero, promoting an increased venous return of blood to the heart and supporting blood supply to various organs and tissues; 4) a marked positive increase in transmural pressure, promoting; 5) a passive inspiratory dilation of the intrathoracic airways; 6) a rapid short-lasting inspiratory reflex dilation of the pharyngeal lumen and reflex opening of the glottis, allowing lung inflation, followed by a glottal narrowing during the post-inspiratory phase which inhibits subsequent lung deflation; 7) a sniff-like sound; 8) reflex inhibition of spontaneous or any increased bronchoconstrictor fibre activity, resulting in transient bronchodilation; 9) a rapid inspiratory airflow (280- 420 ml·s^{-1}); 10) a moderately increased inspiratory tidal volume (7).

The ten main components of ExpR are:

1) no preceding inspiration or even a reflex interruption of an occasional inspiration; 2) a solitary, short-lasting activity in the abdominal muscles, indicating a prompt expiratory effort (30-150 ms); 3) a sudden marked expiratory increase in the intrathoracic (pleural) pressure (+2.2 kPa), contributing to the systolic ejection of the blood from the heart; 4) a negative transmural pressure; causing 5) an expiratory compression of the intrathoracic airways; 6) a reflex glottal closure, promoting a pressure increase during the compressive phase, followed by reflex glottal opening allowing a rapid expulsion of airflow together with any irritants or fluids during the expulsive phase; 7) a brisk explosive sound; 8) a reflex bronchoconstriction indicated by ~2-fold increase of baseline bronchoconstrictor fibre activity; 9) a rapid and marked expiratory airflow (~130 ml·s^{-1}); 10) a moderately increased expiratory tidal volume.

The ten main components of the tracheo-bronchial cough reflex, are:

1) a strong activity of the phrenic nerve, the diaphragm and other inspiratory muscles, causing deep longer-lasting initial inspiration; 2) a very strong activation of the abdominal and other expiratory muscles, resulting in a powerful expiratory effort; 3) a considerable decrease followed by a large increase in intrathoracic (pleural) pressure (+4 kPa), promoting an increased venous return to the heart, followed by marked ejection of blood to various tissues; 4) a highly negative transmural pressure; promoting 5) a dynamic expiratory compression of the intrathoracic airways; 6) after inspiratory dilation a reflex glottal closure in the compressive phase, causing an intrathoracic pressure increase, followed by prompt glottal opening, allowing a powerful expulsion of air with any irritants; 7) an explosive cough sound; 8) reflex bronchoconstriction indicated by about a 3- fold increase in bronchoconstrictor fibre activity; 9) very rapid expiratory airflow (500 ml·s^{-1}); 10) a large (about 5-fold) increase in expired tidal volume.

DISTINCT LOCALIZATION OF BRAINSTEM STRUCTURES FOR THE ASPR AND EXPR

Our previous results, obtained by the c-fos immuno-reactive method, were intricately re-evaluated to allow quantitative assessment and comparison of early c-fos gene production, indicating the level of activation of neurones involved in the two distinct airway reflexes. In separate experiments, 450±30 AspRs or 296±9 ExpRs were elicited during ~30 min, with recording of electrophysiological and cardio-respiratory parameters in pentobarbitone- anaesthetized spontaneously-breathing cats. The results indicated that the AspR induced by

Nph stimulation provoked much stronger activation of inspiratory modulated neurones in 16 of 35 investigated brainstem nuclei than did quiet breathing (8). These regions included the nucleus tractus solitarius, representing the first central station of the AspR, the caudal to middle ventrolateral medulla containing the pre-Botzinger complex (preBotC), known to be the site of the inspiratory rhythm generator (1, 9), and also the lateral tegmental field (10, 11), as well as the caudal medullary raphe and the ventrolateral pons (8), participating in the generation of gasping during severe brain hypoxia in decerebrate cats.

In experiments on another cats, stimulation of the glottal area provoking the ExpR induced strong immuno-reactivity, indicating powerful activation of expiratory modulated neurones in the middle to rostral ventrolateral medulla, including the retrotrapezoid-parafacial region, postulated to serve as the expiratory rhythm generator (1, 12), and the rostral midline midbrain, compared with eupnoea (13, 14). Topical lesions of the nuclei important for the ExpR with cold blockade and kainic acid microinjections inhibited or eliminated the ExpR, but had only scant effect on the AspR (15). *Table 1* provides a complex comparison of significantly different immuno-reactive activities in the separate brainstem nuclei, being induced by repetitive provocation of the AspR or the ExpR in separate cats, compared with quiet breathing, documenting the distinct localization of the structures involved in the generation of either the AspR or ExpR, respectively (8, 13, 14). These results suggest that the neurones known to generate the inspiratory rhythm, contribute to the induction of the AspR and of the neurones participating in the generation of expiratory rhythm (1, 9, 12) are involved in the production of the ExpR in adult cats.

Re-evaluation of results from successive rostral-to-caudal brainstem transection experiments (*Fig. 2*) with electrophysiological recording in anaesthetized non-paralyzed decerebrate cats showed that there was a gradual reduction in the intensity of the ExpR more than that of the AspR. After brainstem transection 5 mm above the obex (just below the nucleus retro-trapezoides/parafacial region, proposed as the localization of the expiratory rhythm generator), the ExpR was abolished but the AspR persisted, albeit in lower intensity, together with quiet breathing. A few minutes later, severe asphyxic gasping developed gradually, replacing the spontaneous inspirations (16).

Table 1. The average number of C-Fos positive neurones in particular brainstem structures (hemi-section- AGN/H within the 0.04 mm thick slices), induced by aspiration reflexes (AspRs) and expiration reflexes (ExpRs) in anaesthetized spontaneously breathing cats. Three separate groups of cats: non-stimulated (Control), with provocation of AspRs and ExpRs. Data analysis: by ANOVA (A) or Kruskal-Wallis test (KW) with Dunn post tests. Statistical significance: compared to control (*) and to AspRs (+). Symbols: * or +: $p<0.05$, ** or ++: $p<0.01$, *** or +++: $p<0.001$. Abbreviations of brainstem structures localized from 18 mm above to -4 mm below the obex: c- caudal, m- medial, v- ventral, 5SP- parvocellular division of the alaminar spinal trigeminal ncl, AQ- aqueduct, BC- brachium conjunctivum, COE- coeruel ncl, CUC- caudal division of cuneate ncl, FTC- central tegmental field of mesencephalon, FTL- medullary lateral tegmental field, GRC- caudal division of gracile ncl, IFT- infratrigeminal ncl, KF- Kolliker-Fuse ncl, LRN- lateral reticular ncl, NA- ambigual ncl, NPA- paraambigual ncl, NPBL- lateral parabrachial ncl, NPBM- medial parabrachial ncl, NRA- retroambigual ncl, NTS- solitary tract ncl, PAG- periaqueductal grey, RFN- retrofacial ncl, RTN- retrotrapezoid ncl, VII- facial ncl, VN- vestibular ncl. (comparison of data from Ref. No. 8 and 14 with permission).

Level to the obex	Nuclei and regions	AGN/H		
		Control n=7	AspR n=6	ExpR n=6
-4 to -2.5 mm	NRA and adjacent FTL	3 ± 1 KW	22 ± 3 **	10 ± 4
	v and c GRC and CUC c NTS	8 ± 1 KW	19 ± 1 *	12 ± 2
-2 to -1 mm	NRA and adjacent FTL	15 ± 3 A	31 ± 2 **	18 ± 2 ++
	c NTS	17 ± 2 A	40 ± 6 **	23 ± 3++
0.5 to 2.5 mm	NTS and adjacent 5SP	17 ± 3 A	93 ± 10 ***	47 ± 7 * +++
	FTL and m part of 5SP	11 ± 2 KW	41 ± 4 **	11 ± 2 ++
	Raphe	2 ± 1 KW	15 ± 3 **	3 ± 1
	LRN, NA, NPA	15 ± 4 A	49 ± 11 **	65 ± 5 ***
3 to 4 mm	NA, NPA, RFN, LRN	11 ± 3 KW	55 ± 9 **	41 ± 7 *
4 to 5 mm	VN, dorsal 5SP	21 ± 4 KW	32 ± 4	42 ± 4 *
	RFN, LRN, v FTL	15 ± 5 A	33 ± 10	70 ± 8 *** ++
	Raphe	3 ± 2 KW	23 ± 8 *	6 ± 4
5 to 6 mm	LRN, c VII and RTN, m IFT, v FTL	7 ± 3 KW	12 ± 3	41 ± 8 **
	Raphe	5 ± 2 KW	21 ± 5 *	13 ± 4
10 to 10,5 mm	BC, COE, NPBM	12 ± 3 KW	94 ± 6 **	13 ± 4 ++
10.5 to 11 mm	BC, COE, NPBM	25 ± 4 KW	72 ± 10 **	35 ± 3
	NPBL, KF	79 ± 8 KW	266 ± 50 **	105 ± 14
12.5 to 14 mm	PAG lateral to AQ	78 ± 15 A	105 ± 10	38 ± 6** +++
	PAG v and ventrolateral to AQ	51 ± 6 KW	79 ± 5 *	57 ± 6
	FTC	28 ± 3 KW	63 ± 6 *	51 ± 7
17 to 18 mm	midline area	77 ± 9 A	69 ± 8	131 ± 11 *+

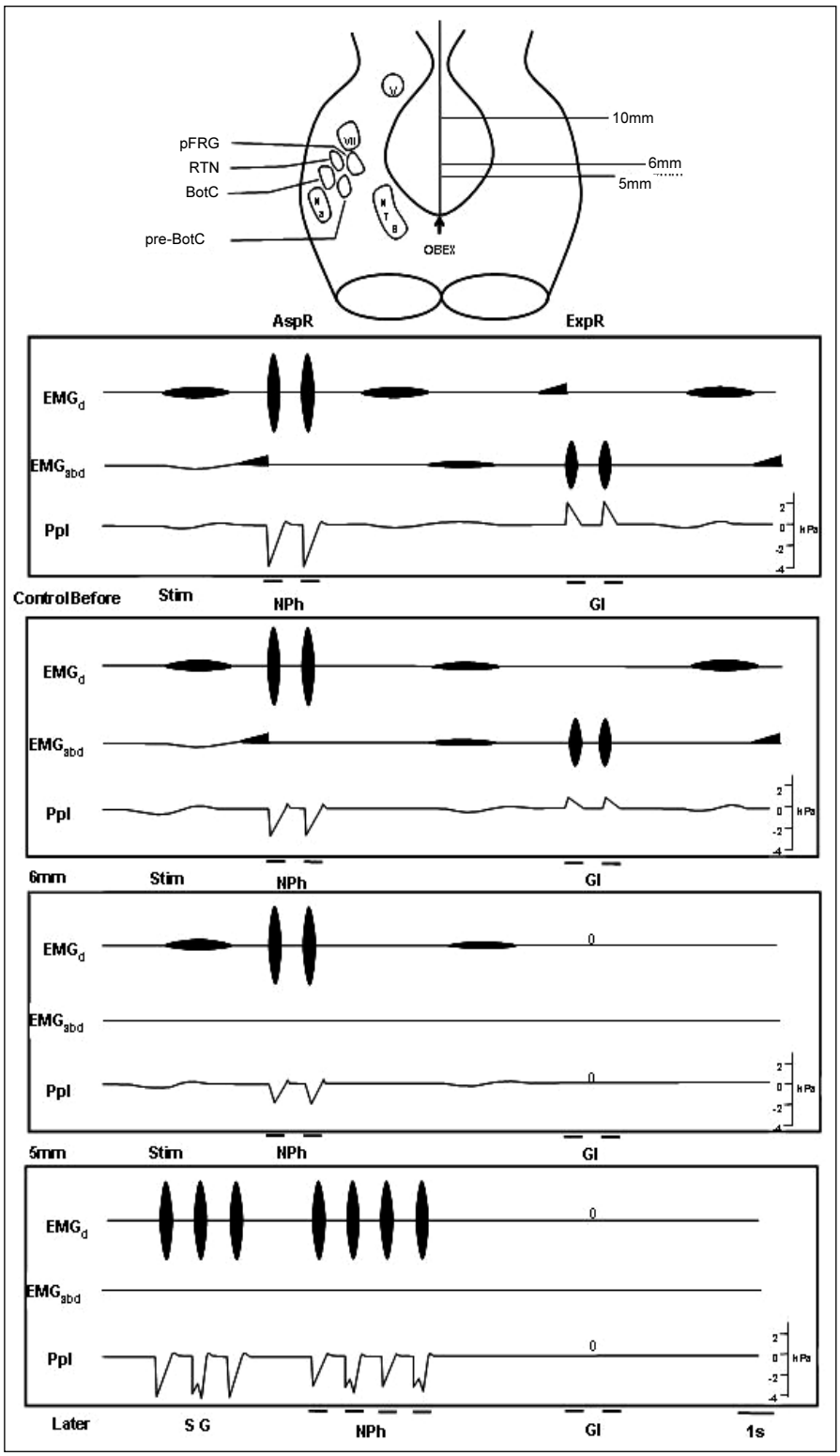

Fig. 2. Effects of consecutive brainstem transections on the AspR and the ExpR, evoked by contact stimulation (Stim) with a nylon fibre of the nasopharyngeal (Nph) and glottal (Gl) mucosa in anaesthetized spontaneously breathing cats. Parallel recording of diaphragmic and abdominal electromyograms (EMGd, EMGabd) and the pleural pressure (Ppl). The main results obtained by Jakus *et al*. (16) are schematically reconstructed with permission. Abbreviations of brainstem structures relative to consecutive transections at 10 mm, 6 mm and 5 mm above the obex.: V- nucleus n. trigeminalis VII- nucleus n. facialis., pFRG- paraFacial Respiratory Group, RTN- retrotrapezoid nucleus, BotC- Botzinger Complex, pre-BotC- pre-Botzinger Complex, NTS- nucleus tractus solitarius, NA- nucleus ambiguus.

RESPIRATORY RHYTHM AND PATTERN GENERATION AND ITS REFLEX MODIFICATIONS

The persistence of spontaneous breathing during severe brain hypoxia is strongly supported by stimulation of peripheral and central chemoreceptors, as indicated by rapid replacement of spontaneous breathing by gasping in mice with transected carotid sinus nerves during 90 s inhalation of 10% O_2 in N_2 (17). During the gasping stage (SG) in these transection experiments, practically every mechanical stimulus, applied to the nasopharynx in 1 s intervals, elicited nearly 2-times stronger gasp-like AspRs, than before. These results in adult cats confirm the elimination of expiratory activity after similar brainstem transection observed in juvenile rats (12), and the participation of the preBotC nucleus in generation of respiratory acts such as sighs and gasps (18), resembling the AspR. For activation of similar brainstem nuclei by AspR and gasps, and for the persistence of the AspR in the stage of asphyxic gasping,

(demonstrating their extraordinary refractory quality), a common generator for the AspR and gasping was presumed (16, 19).

In addition, the AspR in the gasping stage frequently consisted of 2 to 4- phasic inspirations without interposed active expirations or total lung deflation. During severe hypoxia and/or transitory brain ischemia in cats, spontaneous inspiratory oscillatory discharges of a frequency of 10.7±0.6 Hz were observed, demonstrating transient inspiratory rhythm generation. These spontaneous discharges occurred either at a transition from eupnoea to gasping, or from gasping to eupnoea even after 13-17 min of hypoxic coma at a BP of only 75±8 mm Hg, or from gasping to terminal apnoea after cardiac arrest by early renewal of the air supply (20). Therefore, the discharges may represent a transient form of inspiratory rhythm, provoked by activation of the neurones of the inspiratory rhythm generator, located in the preBotC (1, 9). A subset of inspiratory neurons of the preBotC, are directly inhibited by μ-opioid receptor agonists (21). Another group of rhythm generating neurones, insensitive to opioids, is located more rostro-ventrally to the preBotC. These neurones synaptically interact with preBotC neurones to form a circuit consisting of two coupled oscillators, each capable of independently generating rhythmic firing in the absence of the other (22).

Higher animals, including cats and pigs, are more suitable for clinically applicable research. In adult cats *in vivo*, chemical interruption of synaptic activity within the preBotC also abolished the respiratory rhythm, but not the gasping (23). Stimulation of both the laryngeal and pharyngeal mucous membranes by a nylon fibre through a tracheotomy in cats with intact vagal afferentation increased the intensity of the cough reaction by evoking interposed spasmodic inspiratory efforts, mediated by stimulation of pharyngeal RARs with subsequent stronger expiratory efforts (3, 7). The intensity of these interposed inspirations gradually decreased during the I-phase of the cough cycle relative to the increasing momentary lung volume, activating the slowly-adapting receptors that mediate the Hering-Breuer inspiration inhibitory reflex (HBIIR). During the compressive phase of cough, the lung deflation is hindered, which evokes an increase of expiratory effort, termed the Hering-Breuer expiration facilitating reflex, gradually decreasing during the lung deflation (24). Interaction of the inspiratory facilitation caused by rapid lung inflation with the HBIIR and expiration facilitatory reflexes may contribute to frequent repetition of cough efforts, manifesting in attacks of coughing, particularly in cases of airway inflammation, hyper-reactivity, *etc*.

Lesioning of >70% of preBotC in awake goats eliminated diaphragm activity and spontaneous breathing, preserving the activity of the expiratory rhythm generator (25). The propriobulbar I neurones of preBotC, co-expressing neurokinin 1 and μ-opioid receptors, important for generation of the inspiratory rhythm, can be inhibited to sub-threshold level by opioids, and the signal transmission from the pre-inspiratory neurones, arising from higher levels, is blocked. This results in so-called quantal breathing, transient apnoea or arrhythmic polypnoeic breathing (21, 26, 27). Similar apnoeic episodes are induced by endogenous endorphins during birth to prevent meconium aspiration into the gradually expanding lungs, usually for ~2 days. Retardation in the development of the central inspiratory control mechanisms, may cause a failure of "auto-resuscitation by gasping", which can contribute to SIDS (28). Therefore, in addition to phylogenetic differences in respiratory rhythmogenesis also ontogenetic and developmental aspects are still relevant topics (29).

MECHANISMS OF THE ASPR AND EXPR

Stimulation of polymodal RARs of the airways by irritants of various types elicits a prompt short-lasting solitary reaction in anaesthetized cats. Mechanical stimulation by a short contact, pressure pulse or airflow applied to the pharynx evokes a high-frequency response in the afferent single fibre of the glossopharyngeal nerve of 200- 350 Hz (30, 31). A typical AspR with an increased inspiratory effort can be provoked after complete elimination of vagal afferents by bilateral cervical vagotomy in cats, completed by successive resection of vagi above its pharyngeal branches (32). The increased inspiratory effort of the AspR can be ascribed to elimination of both the pulmonary HBIIR (24) and the marked inhibitory effect of adenosine produced in the nodose ganglion, manifesting as depression of various parameters of breathing in rats (33). However, some sniff-like inspirations could also be mediated from the upper airways also by trigeminal afferents (15, 32).

A very stabile AspR can be evoked by electrical stimulation of the Nph in the region of the tuba auditiva in cats by a 0.5 ms pulse of 4-9 V which, after a latency of 25±2 ms, provokes diaphragmal activity lasting 70±11 ms, causing peak inspiratory airflow of 280-420 $ml \cdot s^{-1}$ followed by a successive inhibition for 64±11 ms (3, 4, 34). In general, stimulation of the Nph in cats can regularly induce a powerful and very resistant, sniff- and gasp-like AspR under various conditions; *e.g.* in any moment of the normal or pathological respiratory cycle, in both wakefulness and very deep anaesthesia or hypothermia at 20°C, as well as its "fictive" form after muscle paralysis and mid-collicular decerebration. Similar deep spasmodic inspiration, which is the main component of the AspR, can be elicited by stimulation of the acupuncture point of the nasal phyltrum- GV 26 (3, 35) and from other sites of the head mediated mostly by the trigeminal nerve.

The AspR and ExpR can be induced by various methods of stimulation (mechanical contact, pressure pulses, air-flow, and electrical, chemical and thermal stimulations) and from several areas of the body, which allows their relatively easy testing. The AspR can be induced from the naso- and oro-pharynx and similar gasp-like spasmodic inspirations from various acupuncture points (3, 34, 35); the ExpR from the trachea and bronchi, in addition to the glottal area (36, 37). The mechanisms of both reflexes can be tested also after muscle paralysis, which allows separation of their mechanical and reflex effects. During the "fictive AspR" in paralyzed cats, rapid depolarization of neurones in the inspiratory generator was accompanied by strong activation of the phrenic nerve and a reciprocal inhibition of the intercostal nerve supplying the expiratory muscles (38). High-frequency activation of the inspiratory rhythm and pattern generator by AspR was synaptically transmitted to all tested phrenic motoneurons, including recruitment of 45% of cells quiescent during normal and hypercapnic inspiration up to a maximum instantaneous frequency 6-357 Hz (39). The highly active phrenic motoneurones together with the lateral branch of the hypoglossal nerve that dilates the upper airway, provide a very rapid inspiratory airflow with synchronous reciprocal inhibition of the abdominal muscles. Therefore, the distinct airway reflexes can be useful for model studies, at least in cats and pigs, where they have been analysed more completely (19, 40-46).

EFFECTS OF THE ASPR AND EXPR IN CATS AND THEIR APPLICABILITY

There are three main conclusions of this study, demonstrating the great importance of these two distinct airway reflexes for various applications in experimental and clinico-physiological practice:

1) Re-evaluation of the brainstem localization and mechanisms of the AspR and the ExpR in adult cats indicated that these reflexes separately activate the neurones of distinct rhythm generators for I and E, respectively, and provide a

support for the dual theory of respiratory rhythmogenesis. Therefore, they may be useful models for study of respiratory rhythm and pattern generation, including testing of various drugs, nervous sensors and membrane channels, even in genetically modified animals.

2) Reassessment of the similarity of the brainstem structures (8, 16) and mechanisms of the gasp-like AspR in cats with hypoxic gasps (19, 43, 44) demonstrated, that the AspR may provide powerful effects. The very high glossopharyngeal afferent impulses (~300 Hz), induced by Nph stimulation in cats can reflexively activate and even reset the brainstem inspiratory centre to a frequency higher than its "resting" state, during eupnoea and anaesthesia, when it can evoke an AspR, manifesting as a sigh or a gasp. Such high-frequency activation, mostly representing "overdrive stimulation", may be widely transferred from the inspiratory centre through the dense synaptic connections and modulated by various mediators and neuromodulators. It can markedly modify the irritability of many ascending and descending neurones, or even reset the control mechanisms of practically all vital functions, operating mostly at lower frequencies. This may result in normalization of various functional disorders in cats, both by inhibition of some hyperactive states such as bronchoconstriction (2), apneusis and laryngospasm (44), or by facilitation of hypo-functional disorders or even failing activities: such as hypoxic apnoea and coma (41, 44-46).

3) Such resetting of central control mechanisms of various vital functions provides a unique possibility to normalize various dysfunctions "on demand", when appropriate functional disorders occur, mostly based on reverberation of pathological excitation or inhibition, but without irreparable morphological changes: *e.g.* recent myocardial infarction or stroke. Such a mechanism might explain the unexpectedly successful treatment of longer-lasting attacks of hiccough in patients (47), as well as the repeated interruption of paroxysmal supraventricular tachycardia (48), by simple introduction of a nasogastric catheter. In premature infants, introduction of a nasogastric catheter for feeding occasionally induced short but marked inspiratory efforts, accompanied by a transient tachycardia and hypertension, resembling the AspR of cats (49). Similar unexpected reflex broncho-protective and broncho-spasmolytic effects have been observed after voluntary deep inspirations through the nose, but not through the mouth in healthy subjects and mild asthmatics (50).

The occurrence of sigh and gasp in practically all mammals allows the study of their powerful restorative and "auto-resuscitative" potential in animal models. Intensive studies have been performed in pigs and other animals with potentially fatal ventricular fibrillation, induced by intracardial stimulation and its reversal by autoresuscitation effect of spontaneously developing gasping during postponed defibrillation; these stimuli have been tested in animal experiments and clinico-physiological studies using also technical models (51). In humans, upper airway pressure more negative than -1.2 kPa induces a "pharyngeal dilatory reflex", reversing upper airway obstruction, which is less effective in patients with sleep disordered breathing (52). Negative pharyngeal pressure, induced by inspiratory resistive loading, provokes genioglossal muscle activation in awake humans. Both central outputs to the genioglossal muscle and pharyngeal reflex-mediated activation are important in maintaining upper airway patency (53).

REVITALISATION EFFECTS OF THE ASPHYXIC GASPING AND THE ASPR

In infants dying of SIDS, asphyxic gasping was regularly detected before death (28). The reaction of normal and SIDS infants to excessive stress is schematically illustrated in *Fig. 3.*

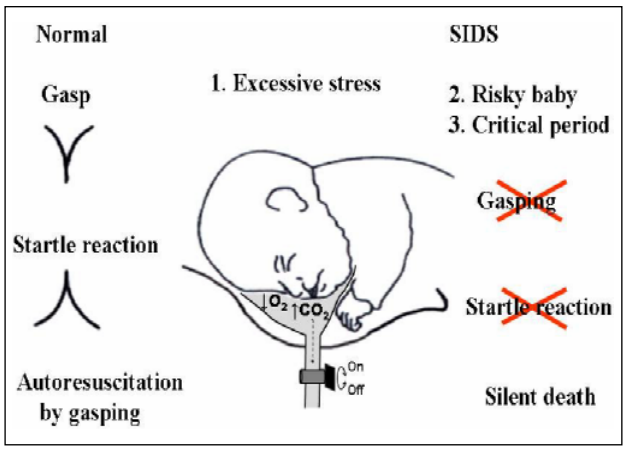

Fig. 3. Reaction of normal and SIDS infants to excessive stress.

Nonspecific tactile stimulation of the foot of healthy infants elicits an arousal sequence commencing with a spinal withdrawal reflex, sometimes followed by respiratory and startle responses, occasionally ending in cortical arousal (54). Respiratory related stimulation, such as transient airway occlusion or a lack of O_2 and accumulation of CO_2 during sleep, evokes a sigh or gasp and a subsequent startle, associated with a neck extension and pharyngeal dilation. These reactions operate frequently as brainstem reflexes and may account for recovery of airway patency without evidence of cortical arousal. The magnitude of sigh, the intensity of startle with accompanying upper airway dilation and the subsequent increase in heart rate, correlated with the peak airway negative pressure, indicating graded intensity of the arousal reaction. For the shortness of upper airway closure, lung inflation and chemoreceptor stimulation are not prerequisites for the occurrence of these reflexes (55). Therefore, just as stimulation of upper airway receptors that elicit the AspR in cats (2, 3, 30, 31, 42), an upper airway negative pressure reflex in adults (52, 53) and in infants (49), may trigger these brainstem reflexes. Similar stress in a risky, premature baby, at a critical period of development (first 12 months of life), may result in a failure of autoresuscitation by gasping, manifesting as a silent death by SIDS.

Spontaneous gasps are regularly observed in various animals and in infants to prevent lung atelectasis (56). Continuous monitoring of infants with suspected SIDS in clinico-physiological trials indicated, that spontaneously developing agonal gasping, or a gasp reflex provoked after an alarm, resuscitated and saved some of the infants, as it does in animals (51, 55-60). Auto-resuscitation by gasping in infants usually starts with an increase in heart rate and BP, which may fail for various reasons (underdeveloped nervous control in premature infants, co-morbidities, exhaustion of functional reserves, *etc.*). Ineffective auto-resuscitation by gasping is assumed to contribute to the development of SIDS (28, 61) and sudden cardiac death. Asphyxic gasping may auto-resuscitate 10-15% of both animals and infants, depending on their onto- and phylo-genetic development and functional reserves of their vital systems. The brainstem-mediated cardiovascular reflexes are mainly responsible for survival in acutely hypoxic infants and adults, due to auto-resuscitation by gasping.

FUNCTIONS OF THE EXPR

The ExpR without a preceding inspiration serves as a component of the laryngeal chemoreflex, evoked by chemical or mechanical irritants from the laryngo-pharyngeal region, with its

aim to expel and prevent penetration of irritants deeper into the airways and lungs, together with the parallel protective reflex apnoea, laryngoconstriction and swallowing. Occasional inspiration with penetration of irritants into the lower airways evokes a cough reflex by stimulation of tracheo-broncho-pulmonary receptors, providing a more powerful expiratory effort, larger volume and stronger airflow for the expulsion of the irritants (2, 7, 15, 40). Penetration of irritants deeper into the lung may cause a development of a sino-bronchial syndrome and even fatal aspiration pneumonia. Such complications frequently result from exhaustion and failure of the pertinent components of the laryngeal chemoreflex, with a persistence of the more resistant gasp reflex (3, 15, 40). The EpxR is frequently evoked by gastro-oesophageal reflux mostly with dysfunction of the oesophageal sphincter or failure of separate components of the laryngeal chemoreflex, resulting in insufficiency of the apnoeic reflex, laryngoconstriction or the ExpR, and late onset of non-nutritional swallowing, *etc*. (6, 61).

CONCLUSIONS

Comparison of central neuronal structures, mechanisms and the effects of the two distinct airway reflexes with the generators for inspiration and expiration, indicated their similarity and supported the dual theory of respiratory neurogenesis. The AspR, characterized by solitary spasmodic inspiration without successive active expiration, and the ExpR manifesting as prompt expiration without preceding inspiration, may provide a unique model for study of various topics of respiratory rhythm and pattern generation. Both airway defensive reflexes have distinct characteristics, including reciprocal inhibition, and can contribute to prevention and reversal of severe life-threatening events. The AspR, like gasping, may prevent imminent death and even auto-resuscitate the moribund subject, while the ExpR as a component of laryngeal chemoreflex, can expel the irritants and inhibit their penetration into the lungs to prevent development of lung diseases.

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