

The Pathophysiology of Sleep Apnoea: What We have Learned from Animal Models of Chronic Intermittent Hypoxia

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Abstract: Sleep apnoea is a common condition associated with significant morbidity and mortality. The English bulldog is the only animal known to have sleep apnoea. In recent years, a number of animal models have been developed which have contributed greatly to our knowledge of the condition. These models develop a number of pathophysiological changes similar to human sleep apnoea such as systemic and pulmonary hypertension, increased haematocrit, and effects on blood coagulability, cardiac rhythmogenesis and central nervous system and upper airway muscle function. This review will describe what has been learned from these models concerning the pathophysiology of sleep apnoea with special emphasis on the role played by intermittent hypoxia.

Keywords: Sleep apnoea, intermittent hypoxia, animal models, systemic hypertension, pulmonary hypertension, upper airway muscle.

INTRODUCTION

Sleep apnoea is a common condition in which there are recurrent apnoeas during sleep due to either a reduction in central drive to the respiratory muscles or (more commonly) to obstruction of the upper airway. It is associated with several acute changes such as fluctuations in blood pressure and arterial blood oxygen levels but the long-term consequences are a source of considerable morbidity and even mortality. Consequently, it is an area of intensive investigation using sleep apnoea patients and animal models of sleep apnoea, especially models of the intermittent hypoxia associated with the condition. The purpose of this review is to survey the contribution that animal models have given to our understanding of its pathophysiology.

1. SYSTEMIC HYPERTENSION

An association between sleep apnoea and systemic hypertension has been explored extensively, especially in the last decade. Approximately 50% of sleep apnoea patients also have been reported to have systemic hypertension [1] whereas 30% of patients with systemic hypertension also have sleep apnoea [2]. The high prevalence of sleep apnoea suggests that it is a major contributor to cardiovascular morbidity and mortality [3, 4]. Establishing the cause of the link between hypertension and sleep apnoea has been difficult to determine using human studies because of the degree of invasiveness required to adequately investigate cardiovascular function. However, it has been shown that sleep apnoea is associated with elevated sympathetic nerve activity [5, 6]. In a series of seminal studies using rats, Fletcher and co-workers showed that chronic intermittent hypoxia and asphyxia (cycles of normoxia and hypoxia/asphyxia twice per

minute for 6-8 hours per day for several weeks) caused systemic hypertension [7-13]. They also examined the mechanism of this effect. It was not caused by arousal from sleep [12] but it was abolished by denervating the carotid bodies [7], by sympathectomy [8], by denervating the renal artery or removal of the adrenal medulla [11] and by blockade of the renin-angiotensin system [13].

Chronic intermittent hypoxia in rats not only caused a persistent elevation in sympathetic activity but also increased the sensitivity of the sympathetic response to peripheral arterial chemoreceptor stimulation although the mechanism was not through an alteration in baroreflex gain [14]. Systemic hypertension was shown also to occur in a sophisticated model of sleep apnoea in dogs in which the trachea was occluded intermittently during sleep for 1-3 months [15], demonstrating that the hypertension was caused by either intermittent hypoxia/asphyxia or by the changes in intrathoracic pressure caused by occlusion. In the same study, persistent arousal from sleep did not cause an elevation of blood pressure.

More recently, some of the central [16] and peripheral [17] cellular effects involved in the hypertensive response have been elucidated in rats treated with chronic intermittent hypoxia. Chronic intermittent asphyxia in rats was shown to increase endothelin-mediated vasoconstriction [18]. Chronic intermittent hypoxia caused systemic hypertension also in mice [19] and vasoconstrictor responses were enhanced by chronic intermittent hypoxia treatment in mice [20]. These studies are revealing the details of the pathogenesis of hypertension in sleep apnoea which will be essential for effective clinical management of the condition.

2. PULMONARY HYPERTENSION

There is much dispute concerning the association of pulmonary hypertension and sleep apnoea. The reported prevalence of pulmonary hypertension in sleep apnoea patients is highly variable with values from 17-42% [21-27] and it has

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been argued that pulmonary hypertension only develops in patients with diurnal continuous hypoxia as well as nocturnal intermittent hypoxia [26, 28, 29]. Nevertheless, there have been several reports of pulmonary hypertension in sleep apnoea patients who do not have significant diurnal hypoxaemia [27, 30-32].

It is well known that chronic continuous hypoxia increases pulmonary arterial pressure and right ventricular mass so we set out using a rat model to determine if chronic intermittent hypoxia, similar to that in sleep apnoea, caused pulmonary hypertension [33, 34]. We treated rats with cycles of inspired hypoxia or asphyxia and normoxia twice per minute for 7-8 hours per day for several weeks and found that there was an increase in right ventricular mass [33, 34] and pulmonary arterial pressure [34]. Chronic continuous hypercapnia was found to prevent the pulmonary hypertension and right ventricular hypertrophy caused by chronic continuous hypoxia [35] but we found no such protective effect of chronic intermittent hypercapnia on the increase in right ventricular mass caused by chronic intermittent hypoxia [33, 34]. Chronic intermittent hypoxia has been reported also to cause pulmonary hypertension in mice [36, 37]. This finding that chronic intermittent hypoxia for 7-8 hours per day, followed by normoxia for the remainder of the time, caused a persistent elevation of pulmonary arterial pressure has implications not just for sleep apnoea but for a variety of other conditions in which there is nocturnal intermittent hypoxia and daytime normoxia since it implies that earlier intervention in terms of nocturnal oxygenation might be required to prevent the consolidation of permanent pulmonary hypertension.

3. HAEMATOCRIT

In sleep apnoea, the haematocrit has been reported to be either increased [26, 38, 39] or to be unaffected [40, 41]. The increase in haematocrit caused by chronic continuous hypoxia has been well described, prompting us to ask if chronic intermittent hypoxia, similar to that of sleep apnoea would raise haematocrit in our animal model. Fletcher and co-workers generally found no effect of chronic intermittent hypoxia on haematocrit [7, 9, 10] but did report an increase in one series of experiments [8]. We observed an unequivocal increase in haematocrit with chronic intermittent hypoxia [33] and an increase in haematocrit, red blood cell count and haemoglobin concentration with chronic intermittent asphyxia [34] and this has been subsequently confirmed in rats [18, 42] and mice [36]. Since it appears to be clear that intermittent hypoxia raises the haematocrit, perhaps the question that should be addressed is why it is that the findings have been inconsistent in patients with sleep apnoea. This may be partly related to the severity of apnoeas, the presence of other confounding conditions or the considerable individual variation in hypoxic responsiveness.

4. RESPIRATORY MUSCLE STRUCTURE AND FUNCTION

Respiratory muscle function is critical to the pathogenesis of obstructive sleep apnoea. The contraction of the diaphragm generates the subatmospheric pressure in the upper airway which predisposes this structurally-vulnerable region to collapse. Normally, contraction of the upper airway mus-

cles counteracts this by stabilizing the airway [43]. We have good evidence from both human studies and from animal models that there is abnormal motor output to these muscles (some aspects of this are discussed later in this review). However, there is also evidence from human and animal studies that the upper airway muscles themselves are affected. Abnormal upper airway muscle structure has been reported in humans with obstructive sleep apnoea [44-46] and in the English bulldog, a natural animal model of human sleep apnoea [47, 48].

In order to accurately examine the nature of these structural changes and to determine whether these changes have functional consequences, it is necessary to remove muscles from the body for histological and *in vitro* contractile analysis. This has created obvious practical limitations for human studies. Animal models do not pose these constraints and furthermore, allow for the use of a variety of interventions in order to determine the underlying mechanism of these effects. Nevertheless, upper airway muscle samples have been collected for analysis from severe snorers and from obstructive sleep apnoea patients during surgery aimed at alleviating the condition [44-46, 49]. The middle pharyngeal constrictor muscle had a lower percentage of slow type I and fast type IIb fibres and a greater percentage of fast type IIa fibres [49]. The genioglossus showed no change in type I fibres but had a decrease in type IIb and an increase in type IIa fibres [46]. A similar effect was seen for the musculus uvulae i.e. there was no change in slow fibres but there was a decrease in type IIb and an increase in type IIa fibres [44, 46]. The musculus uvulae also showed changes in enzyme activity geared towards greater anaerobic metabolism [44, 46] and greater force production [44]. The same group has also shown that these changes in fibre type, enzyme activity and force as well as fatigability in the musculus uvulae were correlated with upper airway collapsibility [45]. Taken together, these data suggest that obstructive sleep apnoea results in a transition in upper airway muscle from slow to fast, fatigable phenotype. This is generally corroborated by the findings in the English bulldog where there is a decrease in slow and an increase in fast fibres in the sternohyoid muscle [47].

However, none of these studies examined the mechanism of the changes described. In the English bulldog, there were no changes in limb muscle structure, suggesting that it was the increased motor drive and contractile force experienced by the upper airway muscles that caused the changes [47]. In one study in rats, cycles of inspired 5% oxygen for 15 seconds followed by air every 5 minutes for 8 hours per day for 10 days were found to have no effect on fibre type or fatigue but there was an increase in force generation [50].

The effects of chronic continuous hypoxia on skeletal muscle structure in animals have been well investigated and, in general, have been found to cause transition from slow to fast [51-53]. This led us to hypothesize that the chronic intermittent hypoxia of sleep apnoea causes changes in upper airway muscle structure and function. We tested this hypothesis using our rat model. In general, we found that chronic intermittent hypoxia and asphyxia caused only slight changes in fibre type but caused an increase in muscle fatigability [54-56]. This was true for upper airway, diaphragm and limb muscles, suggesting a generalized effect of intermittent hypoxia per se rather than an effect secondary to in-

creased motor activity since the limb muscles would not be expected to experience increased motor activity. More recently, broadly similar findings have been reported in rats using a cycle of 10% oxygen and air every 4 minutes for several days [57]. We propose that this reduction in upper airway muscle endurance could precipitate a deleterious positive feedback in sleep apnoea whereby intermittent hypoxia enhances upper airway fatigue increasing vulnerability to airway collapse leading to further hypoxia. Since the effect is generalized, it might also be involved in the general fatigue experienced by patients with sleep apnoea [58].

We next examined the effects of chronic continuous hypoxia on muscle function since surprisingly little is known in this area, despite the data described earlier relating to structural changes in animals. The effects of chronic continuous hypoxia on muscle fatigue in humans is equivocal [59-62] because it is difficult to assess independent of confounding factors. We found that diaphragm fatigue was unchanged but sternohyoid fatigue was increased in rats exposed to hypobaric hypoxia for 6 weeks [63]. This is not in agreement with the findings of others [64, 65] but warrants further investigation since it is generally consistent with transition from slow to fast phenotype and with the effects of intermittent hypoxia. The importance of this relates to the chronic continuous hypoxia of altitude exposure and of respiratory disease. The possibility that chronic continuous hypoxia causes an increase in skeletal muscle fatigue is also consistent with the finding that exposure to altitude caused a large decrease in aerobic capacity in humans [66, 67], the opposite to what was previously believed. Also, it was reported that there was no fibre type transition [66]. Perhaps, the increase in fatigue without significant fibre type transition observed with intermittent hypoxia is also due to a reduction in aerobic capacity.

Recently, we have begun to explore the role of oxidative stress as a potential trigger of the maladaptive changes in skeletal muscle function that are seen in our animal model. Evidence is emerging that chronic intermittent hypoxia causes oxidative injury [68, 69] and there is increasing evidence that sleep apnoea is, at least in part, an oxidative stress disorder [70]. Although it appears that reactive oxygen species are required for optimum muscle function, excess free radical production is implicated in muscle dysfunction [71]. Though the expression of increased muscle fatigue (or injury) following chronic intermittent hypoxia is likely to result from a complex interplay of several processes we hypothesize that increased reactive oxygen species generated as a result of the recurrent hypoxia/reoxygenation cycles associated with intermittent hypoxic exposure are implicated in the impairment of skeletal muscle function that we see in our model. On-going studies in our laboratory have yielded results that are consistent with this hypothesis. Preliminary data indicate that a pro-oxidant challenge (glutathione depletion) exacerbates - whereas anti-oxidant treatment (N-acetyl cysteine) prevents - the deleterious effects of intermittent hypoxia on respiratory muscle function. The results suggest that endogenous glutathione stores may be especially important in limiting free-radical mediated muscle dysfunction.

5. CENTRAL CONTROL OF UPPER AIRWAY TONE

It is generally accepted that the dilator muscles of the upper airway play a pivotal role in the control and maintenance of upper airway patency. Reflex activation of the pharyngeal dilator muscles protects airway patency on a breath-by-breath basis and may be especially important in alleviating obstruction of the upper airway following collapse of the compliant pharyngeal segment [43]. Failure of the pharyngeal dilator muscles to oppose the collapsing pressure that is generated by the diaphragm and accessory muscles during inspiration predisposes to upper airway obstruction. Repeated occlusions of the pharyngeal airway during sleep is a characteristic feature of obstructive sleep apnoea - a severe form of sleep-disordered breathing. Although the causes of upper airway obstruction during sleep are likely to involve more than one mechanism there is evidence for abnormal upper airway muscle reflex control [72] and for abnormal central drive to the upper airway muscles [43]. We carried out a study [73] to examine the effects of chronic intermittent asphyxia on upper airway EMG responses to hypoxia and asphyxia. In animals exposed to 5 weeks of intermittent asphyxia, compared to control animals, we found that reflex activation of the sternohyoid (but not diaphragm) muscle to acute episodes of hypoxia and asphyxia was impaired [73]. Our result suggested a preferential impairment of cranial versus spinal respiratory motor recruitment in response to physiological stimuli. The significance of this is that if such an imbalance were to occur in humans it would likely increase the vulnerability of the upper airway to collapse, increasing the likelihood of further hypoxic or asphyxic insult thereby exacerbating the problem [73].

The mechanism responsible for the selective impairment of upper airway EMG responses in our study remains unclear. However, there is now compelling evidence that intermittent hypoxia results in oxidative neural injury [68, 69] and several neuronal populations show impaired function following intermittent hypoxic exposure [74-76]. This has recently been extended to hypoglossal motoneurons i.e. the principal motor supply to the pharyngeal dilator muscles [77]. As such, impaired reflex activation of the upper airway muscles following intermittent hypoxia/asphyxia may be related to intermittent hypoxia-induced alterations in the responsiveness of central respiratory structures or it may be secondary to injury within the neural control systems that modulate hypoglossal motor drive. In support of a free-radical mediated mechanism of dysfunction, reduced hypoglossal motoneuronal excitability observed following intermittent hypoxia was attenuated by chronic antioxidant administration [77].

The reflex upper airway muscle response to acute hypoxia is due to hypoxic stimulation of the peripheral arterial chemoreceptors. It is unlikely that the impaired upper airway muscle response to acute hypoxia in our study is due to impaired chemoreceptor function because chronic intermittent hypoxia (cycles of inspired 5% oxygen for 15 seconds followed by air for 5 minutes) has been shown to increase chemosensitivity in rats [78] and cats [79].

Taken together these studies suggest that intermittent hypoxia - a feature of sleep-disordered breathing due to recurrent apnoea - may in turn contribute to the pathophysiology of obstructive airway conditions through impairment of central respiratory control.

6. COAGUABILITY

Cardiovascular morbidity and mortality is greater in sleep apnoea patients [80, 81]. There is good evidence that sleep apnoea is associated with a hypercoaguable state and this could underlie the greater cardiovascular risk [see 82 for review]. Consistent with this hypercoaguability, sleep apnoea is also associated with higher plasma fibrinogen levels and lower fibrinolytic activity as well as greater platelet activation and aggregation [82]. Chronic continuous hypoxia is known to increase coaguability and platelet activation and aggregation. Hypercoaguability is seen in conditions where there is chronic continuous hypoxia such as exposure to altitude [83, 84] and chronic respiratory disease [85, 86]. A hypercoaguable state has also been demonstrated in animal models of chronic continuous hypoxia in dogs [87], rats [88] and mice [89]. In humans, platelet aggregation was found to be either increased, decreased or unchanged by exposure to altitude [90, 91] but was increased in chronic respiratory disease [92, 93]. Platelet aggregation was also increased in animal models of chronic continuous hypoxia in rats [88] and mice [89]. In view of the increase in platelet activation and aggregation seen in sleep apnoea patients and the strong evidence that chronic continuous hypoxia causes platelet activation and aggregation, we wondered if chronic intermittent hypoxia would cause a similar effect. We found that 3 weeks of intermittent asphyxia in our animal model did indeed cause an increase in platelet aggregation [94], suggesting that chronic intermittent hypoxia may contribute to the hypercoaguability of sleep apnoea.

7. CARDIAC ARRHYTHMIAS

Although there have been some notable exceptions [95-97], many studies suggest that there is a relationship between sleep apnoea and atrial and ventricular arrhythmias [98-105] and there is strong evidence for an association in patients with additional complications such as coronary heart disease [28-31] and heart failure [106-109]. There is also evidence for a link between sleep apnoea and clinically significant cardiac rhythm disturbances [110, 111] and there is a correlation between sleep apnoea severity and arrhythmia severity and treatment with nasal continuous positive airway pressure abolished the arrhythmias [111]. The clinical importance of this stems from evidence of a link between arrhythmias and an increased incidence of cardiovascular morbidity and mortality in sleep apnoea patients [96, 108, 110, for review see 112].

The conventional explanation for the increased incidence of arrhythmias is that it is due to the effects of hypoxia, hypercapnia, respiratory acidosis, increased sympathetic nerve activity and increased circulating catecholamines since all of these changes occur as a result of the apnoeas and all have been shown to be arrhythmogenic [113, 114]. However, the interaction of these factors is complex so that catecholamines, for example, may actually reduce arrhythmias induced by acidosis [113, 114].

Another major factor causing arrhythmias is hyper- and hypokalaemia. It is well known that plasma potassium (K^+) concentration is increased by systemic hypoxia [115, 116] and hypercapnia [117, 118] and it was also shown that there was a marked increase in K^+ in the duck during diving [119]. Patterson *et al.* [115] showed that K^+ values increased hyperbolically when PO_2 values were decreased from 140 to 60 and 40 mmHg and Fenn and Asano [117] observed that K^+ increased with inhalation of 10% CO_2 although they did not measure blood gas values. Quantitatively, the blood gas values occurring in sleep apnoea and in our rat models of sleep apnoea might be sufficient to induce hyperkalaemia. Furthermore, it is also well known that skeletal muscle contraction can raise arterial blood K^+ . In 1984, Linton *et al.* [120] showed that muscular exercise in man caused a large increase in arterial plasma K^+ concentration. In the following year, our laboratory showed that the tetanic contractions associated with passage of electrical current through muscle caused a substantial rise in arterial plasma K^+ in anaesthetized cats [121]. Is it possible that the intense contractions of the inspiratory muscles during airway occlusion, which occur during obstructive apnoeas, could release enough K^+ to raise arterial K^+ levels. We therefore believe that there are good grounds for hypothesizing that obstructive apnoeas cause a rise in arterial blood K^+ concentration. Surprisingly however, there appears to be no reports of arterial blood K^+ measurements in either sleep apnoea patients or in animal models of sleep apnoea.

We tested the hypothesis that intermittent apnoea causes hyperkalaemia which, in turn, contributes to the generation of arrhythmias. We conducted preliminary experiments in anaesthetized rats and showed that intermittent airway occlusion caused a progressive increase in serum K^+ and an increase in the incidence of arrhythmias [122]. We occluded the airway for 15 seconds every 30 seconds and found that there was a significant increase in K^+ from a control value of 3.9 ± 0.2 to 4.8 ± 0.2 mM after 6 hours with no change in the control group. While the control group had no arrhythmias, ventricular premature beats were observed in 5 out of 6 of the animals exposed to periodic airway occlusions. Quantitatively, the increase in K^+ would probably be insufficient to induce significant clinical manifestations. However, after 6 hours, we occluded for 30 seconds every minute for 30 minutes and found that the K^+ increased to 5.5 ± 0.4 mM. Therefore we anticipate that occlusions lasting 30 seconds and perhaps less would result in clinically significant elevations in K^+ (of perhaps 6.5 mM, see [123]) if applied for several hours.

The increase in arterial blood K^+ in these experiments is likely to be due to increased release from tissues such as muscle or liver or else it could result from decreased K^+ excretion. Although it will require investigation, we do not believe that decreased excretion is a major contributor because of the rapid rise in K^+ that we observed after 6 hours when we occluded for 30 seconds every minute for 30 minutes. Furthermore, hypoxia is known to increase rather than decrease K^+ excretion in animals [124] and humans [125]. As already pointed out, many of the changes associated with occlusion are known to increase arterial K^+ such as hypoxia, hypercapnia and tetanic muscular contractions. Another possibility might be a sympathico-adrenal-hepatic mechanism. Fenn and Asano [117] found that the rise in K^+ caused by

hypercapnia was reduced by adrenalectomy and abolished by β -antagonists, section of the spinal cord and clamping of the hepatic artery and portal vein. Therefore, the elevated sympathetic nerve activity associated with hypoxia/hypercapnia [126] and with sleep apnoea [127] may cause release of K^+ from the liver. Finally, hyperkalaemia is caused by both respiratory and metabolic acidosis (for review, see [128]) and both can occur as a result of apnoea due to hypercapnia [129] and possible tissue hypoxia respectively.

If there is a progressive increase in blood K^+ levels during the course of the night in sleep apnoea, then we would predict that arrhythmia incidence would also increase over time, would be correlated with K^+ levels and that both effects would be reversed by nasal continuous positive airway pressure. As described above, there is a considerable literature examining arrhythmia incidence in sleep apnoea but there appears to be just one paper reporting on arrhythmia incidence over the course of the night [130]. However, arrhythmia incidence was not related to time in this study.

8. COGNITIVE FUNCTION

Significant cognitive functional impairment is associated with sleep apnoea (for review, see [131]). These include daytime hypersomnolence [132] and impaired memory [133], intellectual [134] and motor function [135]. This has been studied using non-invasive techniques such as neuropsychological testing [136], recording of evoked potentials [137], brain imaging [138] and EEG [139]. However, animal models allow much more extensive exploration of brain function using electrophysiological and histological techniques as well as sampling of brain tissue for cellular studies of necrosis and apoptosis. Results can also be correlated with behavioural studies.

A major question is - what causes such deficits? Studies with sleep apnoea patients have been inconclusive with some workers believing that the cause is sleep fragmentation and others believing that it is intermittent hypoxia (see [131]). Using rat models of sleep deprivation, it has been shown that there is no brain cell degeneration [140] or apoptosis [141] as a result of sustained waking. On the other hand, there have been extensive investigations of brain function using several different models of intermittent hypoxia showing electrophysiological changes, widespread necrosis and/or apoptosis and behavioural changes. Cycles of inspired air for 4 minutes followed by 10% oxygen for 4 minutes for 7.5 hours per day for several days caused cerebellar damage in rats [142]. Gozal *et al.* [74], using cycles of air and 10% oxygen inspired every 90 seconds or every 30 minutes for 12 hours per day for several days in rats, showed apoptosis in the CA1 region of the hippocampus and in the cortex but not in the CA3 region. The animals also had impairment of learning but they did not have sleep deprivation or fragmentation. Using the same model, Gozal *et al.* [143] found that these effects were greatest during development and suggested that this may be implicated in the severity of neurobehavioural deficits seen in children with sleep apnoea. Again using the same model, some of the cellular events underlying these changes have been elucidated [75, 76, 144-146] and correlated with behavioural changes [75, 76, 146]. The same group has recently developed a similar model in mice which is allowing new avenues of investigation of the

molecular mechanisms involved in the effects of intermittent hypoxia using a transgenic approach [69, 147, 148].

9. DIFFERENT PATTERNS OF INTERMITTENT HYPOXIA

One of the criticisms leveled at some models of intermittent hypoxia is that they do not mimic the pattern of intermittent hypoxia seen in sleep apnoea. Some models have used cycles of hypoxia and normoxia that do reasonably approximate what happens in sleep apnoea [7-13, 15, 33, 34, 54-56, 73] but others use durations of hypoxia that are much longer than the hypoxic episodes of sleep apnoea. This is probably because of technical difficulties in achieving rapid changes in inspired gas composition.

However, it would appear that, in general, similar effects are obtained over a wide range of cycle duration and pattern. Thus for example, the increase in haematocrit is seen using many different patterns of hypoxic exposure [18, 33, 36, 42] and the same is true for the increase in systemic arterial [7-13, 16-19] and pulmonary arterial pressure [34, 36, 37], for the effects on respiratory muscle structure and function [50, 54-57], for the central effects on upper airway muscle control [73, 77] and for the effects on cognitive function and brain cell apoptosis [74-76, 142, 144-146]. Indeed Gozal *et al.* [74] found that there was no statistical difference between the effect on brain cell apoptosis caused by hypoxic cycles as diverse as 1.5 minutes and 30 minutes.

SUMMARY

A body of evidence has accumulated from animal models implicating intermittent hypoxia/asphyxia in the pathophysiology of sleep apnoea. These animal models develop a number of pathophysiological changes similar to those seen in human sleep apnoea. We now have clear evidence that intermittent hypoxia causes systemic and pulmonary hypertension, increased haematocrit and blood coagulability. Furthermore, there is evidence that intermittent hypoxia/asphyxia impairs skeletal muscle function - including diaphragm and accessory muscles of respiration critical for effective pulmonary ventilation. Additionally, intermittent hypoxia impairs central neural structures including those involved in learning and memory as well as brainstem sites involved in the control of breathing. A picture is emerging implicating oxidative stress as a key trigger of intermittent hypoxia-induced impairment of function. The few studies employing antioxidant strategies that appear to ameliorate or prevent the deleterious effects of intermittent hypoxia are encouraging and further work is needed in this area as it may be of direct relevance to the treatment of sleep apnoea in humans. Might antioxidant treatments yet prove beneficial as adjunct therapies in the treatment of sleep-disordered breathing in humans?

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