Recent insights into hyperventilation from the study of Rett syndrome

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The medical literature presents two major groups of disorder in which hyperventilation is a presenting feature. Disorders of mood, notably panic disorder, and disorders of brain stem function—developmental, vascular, traumatic, toxic, metabolic, degenerative or neoplastic. References to the underlying brain morphology leading to these conditions are few and imprecise, perhaps reflecting the inaccessibility of the brain stem to clinical medicine and the complexity of the neural basis of respiratory control. Even in Joubert’s syndrome, where hyperventilation is a major feature, hypoplasia of the cerebellar vermis and cyst of the fourth ventricle have been described but the exact pathophysiology is unclear.

The clinical medical literature gives more space to discussing the effects of hyperventilation, including the well known respiratory alkalosis with reduction in plasma ionised calcium, tingling sensations, tetany, induction of epileptic seizures, and induction of interictal epileptogenic activities seen on the electroencephalogram (EEG). In healthy children, especially girls, voluntary hyperventilation produces slow EEG waves, usually generalised over the cerebral cortex. Hyperventilation reduces oxygen delivery to the brain, and cardiac repolarisation abnormalities including ST depression and T wave inversion have been described.

From its delineation in 1937 to the 1980s, the “hyperventilation syndrome” was held responsible for much of the symptomatology of panic disorder; however, with increased accuracy of measurements, this notion was replaced by the view that autonomic instability underlies both hyperventilation and panic disorder.

Although there is a clear association between panic and hyperventilation, the neurological basis for this is still unresolved.

**Physiology of hyperventilation**

Hyperventilation or overbreathing is variously defined, according to the measures available and familiar to each scientific discipline. There is agreement that the breathing exercise must ventilate the lungs in excess of metabolic requirements at that particular point in time and thus induce measurable changes, usually a reduction in arterial or alveolar carbon dioxide tension below 35 mm Hg or an induction of central apnoea. Reduction of arterial or alveolar carbon dioxide tension constitutes a biochemical end point of hyperventilation, while induction of central apnoea is a physiological end point.

Although different in character, these two end points indicate the same physiological state. In their benchmark work often cited in physiological literature, Douglas and Haldane demonstrated that the apnoea following hyperventilation was solely caused by lack of carbon dioxide, with the threshold concentration about 36 mm Hg in the alveolar or arterial blood. Their work thus defined two end points, central apnoea and arterial or alveolar carbon dioxide concentration, either of which can indicate hyperventilation.

Using central apnoea as an end point which can be defined as cessation of breathing in expiration, it is possible to identify hyperventilation by monitoring breathing movements alone. In this case hyperventilation is indicated by increased amplitude and rate of breathing movement, which leads directly to cessation of breathing in expiration, as shown in fig 1. When breathing movement is continuously monitored the average rate and amplitude of movement can be determined for an individual, making it possible to identify other disturbances of rhythm in addition to hyperventilation. Without such continuous and non-invasive monitoring of breathing movement, hyperventilation may be missed or diagnosed in error and more subtle associated rhythm

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**Figure 1** Record of breathing movements showing hyperventilation. There was increase in amplitude and rate of breathing from 20 seconds ending in expiration at 80 seconds to mark the beginning of a central apnoea. This was followed by gradual expansion of the chest during the cessation of breathing (80–120 seconds).
disturbances of clinical significance may be overlooked.

Generation of breathing rhythm
Generation of respiratory rhythm is the subject of long standing debate. The controversy concerns whether there are respiratory pacemaker neurones akin to the sinoatrial node of the heart, or whether breathing rhythm is the result of inhibitory interactions within a network of medullary neurones. The subject is well reviewed by Blessing. It has been shown that in premature and neonatal mammals, breathing rhythm is generated in the medulla oblongata at a cross sectional level of the retrofacial nucleus in the ventrolateral medulla, in a specific area called the pre Bötzinger complex. However, no evidence has been found of such rhythm generation in this area in mature mammals.

Richter and colleagues have proposed an alternative hypothesis to explain the origin of breathing rhythm, proposing a model of an inhibitory network involving six distinct groups of respiratory neurones. Reciprocal inhibition between two groups of neurones, which they named early inspiratory and postinspiratory neurones, constitutes the primary mechanism of rhythm generation. Like two children on a seesaw, each subjected to the same gravitational pull, these two primary rhythm generators are both driven by the reticular activating system of the brain stem. The other four groups of respiratory neurones have mainly modulatory roles but are still essential in rhythmogenesis according to this model. The six groups of respiratory neurones in the Richter model are classified according to their electrical activity in relation to phrenic nerve activity during breathing. They are therefore named pre-inspiratory, early inspiratory, ramp or sometimes “throughout” inspiratory, late inspiratory, postinspiratory, and expiratory neurones in their firing order during one breathing cycle. Paton and Richter have also shown that receptors for inhibitory neurotransmitters such as glycine or γ-aminobutyric acid (GABA), which are essential for the model to work, are lacking in premature or neonatal mammals, but develop with maturity. This is a likely explanation for the observation that premature or neonatal mammals depend on pacemaker activity of their respiratory neurones while their inhibitory network is immature.

An inhibitory network of these six groups of neurones can explain normal breathing rhythm in mature mammals, hypoxic apnoea, apneusis, postinspiratory apnoea, and rapid shallow breathing. It cannot, however, explain some of the observed changes in breathing rhythms caused by stimulation of trigeminal, glossopharyngeal, or vagal afferent nerves. The Richter model suggests that rapid shallow breathing is caused by inhibition of expiratory neurones shortening the breathing cycle and increasing the rate of breathing. This means that expiration is entirely passive during rapid shallow breathing and, although the rate is fast, the depth is insufficient to reduce alveolar carbon dioxide concentration. The model thus cannot explain the neurological basis of hyperventilation.

Neuropathological correlate of disturbance in breathing rhythm
A disturbance of breathing rhythm, caused by surgical removal of an astrocytoma in the ventral aspect of the border between the lower pons and the medulla oblongata, provided a very rare opportunity to study respiratory rhythmogenesis in a 2 year old girl. The child developed a postoperative apneustic respiratory arrhythmia indicated by sustained inspiratory efforts lasting more than one minute and requiring repeated resuscitation and intensive care. It is known from animal studies that apneusis is caused by failure to activate serotoninergic nerves in the brain stem and can be corrected by serotonin 1A receptor agonists. Extrapolation of this knowledge to humans led to successful treatment of the postoperative apneustic respiratory arrhythmia with buspirone, a serotonin 1A receptor agonist. This confirms that inspiration is actively terminated by serotoninergic neurones in the brain stem of humans as in lower mammals. It has been established that the neurones responsible for terminating inspiration are situated at the ventrolateral aspect of the lower pons since lesion of this area causes apneusis in lower mammals.

Character of Rett syndrome
The classic Rett syndrome is the highly characteristic presentation of a profoundly disabling neurodevelopmental disorder, described almost exclusively in females, with a prevalence no less than 1 in 10 000 females. Brain weight deviates from the normal centiles soon after birth but may continue to increase up to a final size of 70–90% of the expected value. There is no evidence of abnormality in neuronal migration or myelination. Armstrong reported reduced dendritic territories in the frontal, parietal, and inferior temporal areas, a small midbrain, and a large increase in serotonin receptor density in the brain stem, with medullary nuclei known to have autonomic and cardiorespiratory functions specifically affected.

Breathing abnormality in Rett syndrome
Breathing dysrhythmia is a striking feature of Rett syndrome and is closely linked to the movement disorder and to agitation. These abnormalities usually appear towards the end of the regression period and are seen only in the awake state. Alternate hyperventilation and breath holding are striking in younger girls who may show associated hypoxia and low expired carbon dioxide, while in older women breath holding is most obvious and transcutaneous blood gases are often normal. Bursts of paroxysmal slow waves on the EEG increase in the drowsy or asleep states and diminish during intense hyperventilation in the alert state.

The Glasgow based peripheral nerve and autonomic unit has assessed over 50 Rett syndrome cases with controls of similar age. The
autonomic measures used were developed by Julu and colleagues\textsuperscript{19, 20} and combined with those previously employed by Southall, Kerr and colleagues\textsuperscript{19, 20} to permit one hour, videotaped, non-invasive, synchronised and computerised autonomic and respiratory recordings. The following observations from these studies are relevant to this discussion.

Hyperventilation was only one of 14 abnormalities of breathing rhythm found in subjects with classic Rett syndrome. Hyperventilation, deep breathing, rapid shallow breathing, and tachypnoea together constituted an “energetic breathing” component forming up to 25% of the total alert and conscious breathing time in the younger age group.\textsuperscript{23, 24}

The predominant rhythm in the youngest age group was protracted inspiration (including apneusis) while in older women prolonged breath holds were frequently terminated by Valsalva’s manoeuvres.\textsuperscript{21}

In every Rett case, cardiac vagal tone was very low, close to the neonatal level. This, associated with equally low baroreflex sensitivity, led to unrestrained sympathetic effects on blood pressure and heart rate which swung between extremes during the breathing dysrhythmia.\textsuperscript{22, 24}

Epileptogenic activity when present did not correlate with the hyperventilation.

Rett disorder clearly leads to difficulty in terminating inspiration.\textsuperscript{21, 24} This suggests dysfunction of the modulatory serotoninergic neurones in the brain stem as discussed above. It is consistent with the increased density of serotonin receptors in the brain stem,\textsuperscript{17} possibly an attempt to compensate for a subnormal function. Successful treatment with buspirone in a girl with severe apneustic dysrhythmia caused by Rett disorder has strengthened this hypothesis.\textsuperscript{21}

Neurological basis of hyperventilation
Both the pathological hyperventilation in Rett syndrome and the voluntary hyperventilation in control girls were associated with agitation and autonomic stimulation. In both Rett syndrome and control cases, during the initiation of hyperventilation, cold extremities and increase in blood pressure and heart rate indicated activation of the sympathetic vasoconstrictors and cardioaccelerators which are situated in the rostral part of ventrolateral medulla.\textsuperscript{22} At the same time there was parasympathetic activation in the caudal part of the ventrolateral medulla, shown by an increase in cardiac vagal tone, which rose to check and control the increase in both heart rate and blood pressure.\textsuperscript{21} In controls the rise in cardiac vagal tone was adequate, achieving smooth regulation of heart rate and blood pressure, whereas such parasympathetic damping effect was lacking in Rett syndrome leading to excessive swings of blood pressure and heart rate during hyperventilation.\textsuperscript{22} The autonomic responses to hyperventilation suggest that both rostral and caudal ventrolateral medulla are simultaneously activated during the initiation process; this is true for controls as well as for Rett syndrome cases.

It is not certain whether this medullary activation is achieved by excitation of neurones or by disinhibition (withdrawal of a tonic inhibition). Second and third order respiratory neurones, including those suspected to be rhythm generators, are arranged in a rostrocaudal chain in the ventrolateral medulla intermixed with the autonomic neurones.\textsuperscript{22} Simultaneous and continuous monitoring of breathing movement and autonomic tone has enabled us to observe an increase of autonomic activity synchronous with the increase in breathing rate and amplitude during both voluntary (control) and pathological (Rett) hyperventilation.\textsuperscript{22} Therefore, we can now state that there is a generalised activation of the ventrolateral medulla during hyperventilation, although the origin of this activation is beyond the scope of our studies.

Insight into hyperventilation gained from Rett syndrome studies
The unstable respiratory rhythm in Rett syndrome associated with a very low cardiac vagal tone at neonatal level is suggestive of an immature brain stem, capable of generating some normal rhythm but unable to sustain it for long. The hyperventilation seen in Rett syndrome may be caused by lack of inhibitory control of respiration, in which serotoninergic function is evidently subnormal. Viewed from the aspect of autonomic control, the immaturity is a probable cause of sympatho-parasympathetic disproportion, as well as of the dysfunction of the respiratory neurones, particularly rhytmogenesis. In the course of mammalian development, it appears that the excitatory system, represented by the sympathetic, is more robust than the more sophisticated, later developing, inhibitory system represented by some parasympathetic functions like that of cardiac vagal tone. This has been demonstrated recently in rodents through observations of respiratory control.\textsuperscript{27} There is reason to suspect that both the agitation and the hyperventilation are caused by subnormal integrative inhibition which is the manifestation of immaturity in the Rett brain stem. The lack of inhibition might also be responsible for the lowered seizure threshold in Rett syndrome. Brain stem neurotransmitters including serotonin play a major part in the early growth of the neocortex.\textsuperscript{28} A brain stem defect might be expected to lead to faulty interconnectivity of the higher centres in addition to later autonomic incompetence. It is probable that brain stem immaturity with subnormal serotoninergic function plays a role in other early developmental disorders, especially those associated with hyperventilation and other breathing dysrhythmias. This aspect of developmental disorder deserves closer consideration than it has yet received.

The improved physiological methods used in this investigation are now available for non-invasive and objective assessment of brain stem function. They will contribute to improving measures of breathing dysrhythmia and have the advantage of being well tolerated by profoundly disabled subjects. This methodology can be of
value for investigating both developmental and acquired disorders of the brain stem. A combination of physiological measures, imaging, and morphological methods should now bring a more objective approach to the disorders of mood and the mind.

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