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Progesterone is a promising therapeutic for the prevention of apnoea

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Sex steroid production and signalling, which starts *in utero*, is tightly controlled throughout life. Surges in sex hormones at critical junctures during pre- and post-natal development, as well as during the pubertal period, alter growth and behaviour and determine reproductive success. Sex hormones continue to shape physiological systems including cardiorespiratory function throughout adult life in both sexes. The menopause strikingly reveals the extensive protective effects of female sex steroid hormones, illustrating important roles beyond reproduction. The incidence of sleep-disordered breathing and cardiovascular disease rises dramatically in post-menopausal women.

Obstructive sleep apnoea, characterised by recurrent occlusions of the pharyngeal airway giving rise to repeated bouts of intermittent hypoxia, is described as an oxidative stress disorder wherein aberrant redox signalling can exacerbate disordered breathing and perpetuate co-morbidities such as hypertension. Antioxidants modulate the redox environment to prevent oxidative stress and have been explored as putative adjunctive therapies to ameliorate obstructive sleep apnoea.

Progesterone is a lipophilic sex steroid and neurosteroid that is recognised as a ventilatory stimulant, owing to early clinical reports of hyperventilation during pregnancy and the luteal phase of the oestrus cycle as well as the resultant loss of cyclic ventilatory variability associated with the menopause. Sleep apnoea during pregnancy has been associated with lower circulating levels of progesterone compared with pregnant women without the condition. Of interest, the progesterone receptor agonist chlormadinone acetate was shown to decrease the apnoea hypopnoea index and hypoxic episodes in a small mixed-sex study (Kimura *et al*., 1989).

Oestrogen and progesterone exert their actions by acting on their endogenous receptors, but they can also enhance antioxidant capacity either directly or indirectly. Antioxidants such as superoxide dismutase have been shown to decrease with age in rats, but progesterone therapy in aged rats increases the activity of superoxide dismutase. In addition, sex hormones can modulate a wide variety of signalling cascades, for example, enhancing insulin-like growth factor-1 and facilitating orexigenic signalling, both of which are inversely correlated with obstructive sleep apnoea. Receptors for progesterone and its metabolites are expressed at multiple sites of the integrated cardio-respiratory system. Moreover, progesterone and its metabolites stimulate pleiotropic

receptors in the brain such as $GABA_A$, nicotinic, 5-HT and glycine receptors that can modulate the control of breathing. Harnessing the benefits of hormones like progesterone is a potentially promising avenue of research in the search for effective pharmacotherapies for sleep-disordered breathing.

In this issue of *Experimental Physiology*, Joseph *et al*. (2020) examine the effects of supplemental progesterone on chronic intermittent hypoxia (CIH)-induced oxidative stress and the capacity to ameliorate the deleterious effects of exposure to CIH on cardiorespiratory function. Female rats underwent ovariohysterectomy and osmotic pump implantation for the delivery of vehicle or progesterone. Three experimental groups were established: vehicle treatment with subsequent exposure to normoxia or CIH, and progesterone treatment with subsequent exposure to CIH. The authors assessed breathing using whole body plethysmography. In addition, pro-oxidant NADPH oxidase activity and antioxidant enzyme activities of superoxide dismutase and glutathione peroxidase were determined in brainstem and cerebral cortex.

Joseph *et al*. (2020) reported CIH-induced oxidative stress in the cerebral cortex owing to upregulation of NADPH oxidase and decreases in antioxidant capacity. Progesterone supplementation reduced oxidative stress, preventing CIH-induced depletion of superoxide dismutase and glutathione peroxidase. Brainstem superoxide dismutase activity was unchanged following CIH, however NADPH oxidase activity was increased and this was prevented by progesterone supplementation. Progesterone protected against CIH-induced apnoeas, notwithstanding hyperventilation at rest evidenced by an elevated ventilatory equivalent (V_E/VCO_2). Interestingly, CIH-induced increases in hypoxic ventilatory responses were blocked by progesterone; however, CIH-induced hypertension was unaffected.

Chronic progesterone administration has been previously demonstrated to reduce the incidence of apnoea and increase the hypoxic ventilatory response in neonatal rat pups (Joseph *et al*., 2018, Lefter *et al*., 2007). It is generally considered that CIH-induced facilitation of afferent signalling from the carotid body to the brainstem is a major driver of CIH-induced cardiorespiratory morbidity. Progesterone could potentially reduce the oxidative environment within the CIH-exposed carotid body thereby preventing sensory facilitation, which would be consistent with the observed restoration of hypoxic ventilatory responsiveness and the decreased incidence of apnoea in CIH-exposed rats (Joseph et al. 2020), especially if one considers that enhanced carotid body chemoreflexes are the primary cause of destabilized breathing associated with exposure to CIH. If so, however, then one might also have expected attenuation of CIH-induced increases in blood

pressure, since increased carotid body chemoreflex control of sympathetic outflow is considered the major causal factor elaborating CIH-induced hypertension.

The findings suggest that ventilatory outcomes in the study by Joseph *et al*. (2020) may have arisen from progesterone signalling and/or antioxidant effects of the steroid hormone primarily within CNS structures modulating breathing. Of relevance, exposure to CIH has been shown to cause oxidative stress within rhythmogenic sites of the brainstem, causing dysrhythmic respiratory motor bursting, which proved amenable to antioxidant intervention. It is also conceivable that redox modulation at other sites within the neural circuitry regulating breathing may have contributed to the respiratory phenotype in CIH-exposed rats.

Recent studies have drawn focus to the potential role of the microbiota-gut-bran axis in the regulation of respiratory homeostasis (Lucking *et al*., 2018, O'Connor *et al*., 2019). Intriguingly, exposure to CIH and progesterone both independently alter gut microbiota composition. Thus, whereas redox disturbances at one or more sites within the integrative respiratory network most likely explains CIH-induced respiratory morbidity, there may also be contributions related to altered brainstem neurochemistry arising from changes to the gut microbiota (Lucking *et al*., 2018), which could be influenced by progesterone supplementation.

Whereas the lack of efficacy of progesterone supplementation in preventing CIH-induced hypertension is disappointing, the sex steroid or perhaps a downstream metabolite proves to be a potentially promising therapeutic in the treatment of CIH-induced apnoea. The important findings from the study by Joseph *et al*. (2020) suggest that sex steroids may be beneficial as an intervention for disordered breathing in various scenarios, and particularly for post-menopausal women.

Competing Interests

None.

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