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REVIEW-SYMPOSIUM

Mechanisms underpinning sympathoexcitation in hypoxia

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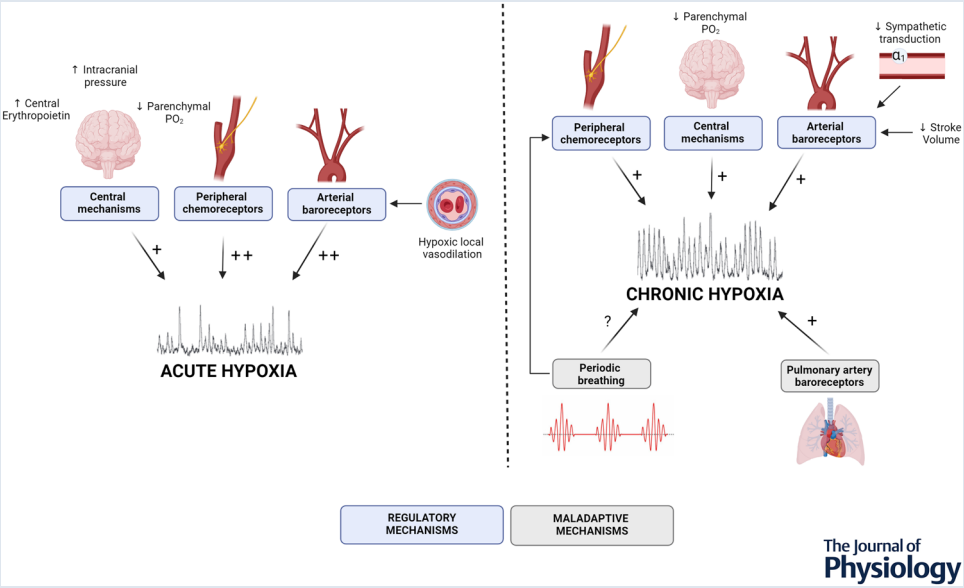

Abstract Sympathoexcitation is a hallmark of hypoxic exposure, occurring acutely, as well as persisting in acclimatised lowland populations and with generational exposure in highland native populations of the Andean and Tibetan plateaus. The mechanisms mediating altitude sympathoexcitation are multifactorial, involving alterations in both peripheral autonomic reflexes and central neural pathways, and are dependent on the duration of exposure. Initially, hypoxia-induced sympathoexcitation appears to be an adaptive response, primarily mediated by regulatory reflex mechanisms concerned with preserving systemic and cerebral tissue O_2 delivery

Lydia Simpson obtained her PhD in integrative cardiovascular physiology at Bangor University and is currently a postdoctoral researcher at the University of Innsbruck, under the supervision of Professor Justin Lawley. Her research focuses on cardiovascular regulation at rest and during physiological stress, with a specific interest in control of skeletal muscle blood flow and blood pressure via the autonomic nervous system.

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and maintaining arterial blood pressure. However, as exposure continues, sympathoexcitation is further augmented above that observed with acute exposure, despite acclimatisation processes that restore arterial oxygen content (C_{aO_2}). Under these conditions, sympathoexcitation may become maladaptive, giving rise to reduced vascular reactivity and mildly elevated blood pressure. Importantly, current evidence indicates the peripheral chemoreflex does not play a significant role in the augmentation of sympathoexcitation during altitude acclimatisation, although methodological limitations may underestimate its true contribution. Instead, processes that provide no obvious survival benefit in hypoxia appear to contribute, including elevated pulmonary arterial pressure. Nocturnal periodic breathing is also a potential mechanism contributing to altitude sympathoexcitation, although experimental studies are required. Despite recent advancements within the field, several areas remain unexplored, including the mechanisms responsible for the apparent normalisation of muscle sympathetic nerve activity during intermediate hypoxic exposures, the mechanisms accounting for persistent sympathoexcitation following descent from altitude and consideration of whether there are sex-based differences in sympathetic regulation at altitude.

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Abstract figure legend Mechanisms for sympathoexcitation with acute and chronic hypoxia.

Introduction

Over 80 million humans permanently inhabit altitudes above 2500 m, with 14.4 million living above 3500 m (Tremblay & Ainslie, 2021). Moreover, over 100 million people annually travel to high altitudes for leisure, economic or military purposes (Basnyat, 2014; Burtscher, 1999), and these numbers are expected to increase because of increasing accessibility and economic growth in mountainous regions. Ambient hypoxia at high altitudes elicits cardiovascular, ventilatory and haematological adjustments to preserve oxygen delivery in the face of reduced arterial oxygen tension (P_{O_2}). These adjustments include alterations in the sympathetic nervous system and its control of cardiovascular function. This review focuses on changes in sympathetic nervous system activity during acute and prolonged hypoxic exposure in lowland populations and discusses mediating mechanisms. Additionally, the available evidence from highland native populations is discussed to provide supportive insights into the potential mechanisms of sympathetic regulation following multigenerational exposure to altitude hypoxia.

Assessment of sympathetic nervous system activity

Several methods have been employed to assess the sympathetic nervous system (Grassi & Esler, 1999), including direct assessment of sympathetic nervous system activity (SNA) via microneurography (Shoemaker et al., 2018; Vallbo et al., 2004). Microneurography involves the percutaneous insertion of a tungsten microelectrode into a superficial nerve (peroneal, median or radial nerves) that allows for measurement of neural activity from postganglionic efferent sympathetic neurons innervating smooth muscle within skeletal muscle vasculature [muscle sympathetic nerve activity (MSNA)]. The MSNA signal consists of bursts of activity, each representing synchronised neural activity from multiple sympathetic neurons (i.e. multi-unit MSNA). MSNA can be quantified as burst incidence [i.e. number of bursts per hundred heartbeats (burst 100 HB^{-1})] and burst frequency [i.e. number of bursts per minute (burst min^{-1})], with each providing slightly different neurophysiological information. Burst incidence represents the central gating of sympathetic outflow/central sympathetic drive, reflecting the likelihood of a burst occurring within any cardiac cycle. Burst frequency is influenced by not only the incidence of MSNA bursts, but also heart rate (i.e. the number of opportunities for a burst to occur) and is reflective of the sympathetic activity that the vasculature is exposed to over time. Thus, MSNA burst frequency is commonly used as the primary index of MSNA. MSNA bursts can also be expressed relative to their size, providing information on the number and size of postganglionic efferent sympathetic neurons firing. However, this metric is highly dependent on the proximity of the microelectrode to the sympathetic neurons, which cannot be standardised between different tests (White et al., 2015). Although bursts can be normalised, burst size is

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a less reliable metric when comparing MSNA between individuals or within an individual on separate occasions, with few studies reporting MSNA burst size in response to hypoxia.

Circulating norepinephrine concentrations have long been used as a surrogate marker of global SNA, as a result of their proportional relationship to direct recordings of MSNA under various situations (Wallin et al., 1981), and have been widely employed at altitude. Importantly, plasma norepinephrine concentration depends on the rate of release by sympathetic nerve terminals, reuptake and breakdown, and is influenced by plasma volume (Esler et al., 1988). Hypoxia increases the rate of norepinephrine clearance (Leuenberger et al., 1991) and plasma volume contraction (Siebenmann et al., 2017) would concentrate norepinephrine independent of release and clearance, complicating the interpretation of these data. Indeed, despite elevations via direct assessment of MSNA, circulating norepinephrine has been reported to be increased (Leuenberger et al., 1991), unchanged (Rowell et al., 1989) or even decreased (Rostrup, 1998) during hypoxia, indicating that circulating norepinephrine is an unreliable marker of SNA under hypoxic conditions. Accordingly, this review focuses on direct recordings of MSNA via microneurography.

Muscle sympathetic nerve activity responses to high altitude

Acute hypoxic exposure (5 min to 1) is associated with increases in MSNA, ranging from 20% to 100% (Halliwill & Minson, 2002; Rowell et al., 1989; Saito et al., 1988). A recent meta-analysis of 61 studies shows that elevations in MSNA primarily consist of increases in the frequency of MSNA bursts during acute exposures (Tymko et al., 2023), which occur in an intensity-dependent manner after arterial oxygen saturation (S_{aO_2}) falls below 85% (Duplain et al., 1999; Rowell et al., 1989; Saito et al., 1988; Somers et al., 1989a, b), with little change in MSNA burst incidence. Notably, there can be a delay in the onset of sympathoexcitation with hypoxic breathing, where measurable changes in MSNA occur after 5–10 min of exposure, probably as a result of the time required for arterial and tissue hypoxemia to develop (Rowell et al., 1989). Although exposures of up to 60 min consistently raise MSNA, MSNA appears to return to baseline values after 7–8 h of exposure (Hunt et al., 2008; Tamisier et al., 2007). However, with more prolonged exposure (24–36 h), MSNA is once again elevated (Duplain et al., 1999) and increases of up to 300% are observed following days to weeks at altitude (Fisher et al., 2018; Hansen & Sander, 2003; Lundby et al., 2018; Simpson et al., 2019; Tymko et al., 2023). These increases are far greater than those observed with acute exposure to a similar hypoxic stimulus (Fig. 1) (Duplain et al., 1999; Lundby et al., 2018; Simpson et al., 2019) and are driven by increases in MSNA burst incidence (Tymko et al., 2023). Moreover, elevations in MSNA remain throughout exposure (at least up to 50 days) (Lundby et al., 2018) and persist for up to 3 days following return to normoxia (Hansen & Sander, 2003; Mitchell et al., 2018).

No studies have examined whether longer-term acclimatisation (>50 days) or permanent residence at altitude is accompanied by normalisation of MSNA in lowland natives. Nevertheless, evidence from highland populations demonstrates sustained sympathoexcitation in natives from the Andean plateau and Himalayans, with MSNA 50% and 120% higher than in lowlanders at sea level (SL) (Fig. 1) (Lundby et al., 2018; Simpson et al., 2019). In Andeans, resting MSNA is similar to acclimatised lowlanders tested at the same altitude (Lundby et al., 2018). Yet, Sherpa exhibit 30% lower resting MSNA than acclimatised lowlanders at the same altitude (Simpson et al., 2019), suggesting that Sherpa have adapted with lower sympathetic activation. Nevertheless, altitude remains a sympathetic stress as MSNA decreases following deacclimatisation in Sherpa to lower altitude (1400 m) (Simpson et al., 2019). Importantly, because of the limited number of studies in highland populations, these findings should be interpreted with caution. Furthermore, studies investigating sympathetic control at altitude have primarily studied males; thus, there is a need to examine sympathetic responses in females at altitude.

In summary, acutely, hypoxia-induced increases in MSNA are modest and result primarily from elevations in heart rate (i.e. increasing the number of opportunities for bursts to occur), with little effect on burst incidence (i.e. the central gating of sympathetic outflow). However, with acclimatisation, profound elevations in MSNA occur, far greater than those observed with acute exposure. The augmentation of MSNA during acclimatisation results primarily from an increased burst incidence and resetting of the central gating of sympathetic outflow.

Potential reflex mechanisms for hypoxia-induced sympathoexcitation

Peripheral chemoreflex. Peripheral chemoreceptors, located in the carotid body and aortic arch, are the primary oxygen sensors in the body. Once arterial oxygen tension (P_{aO_2}) falls below ∼70 mmHg (equivalent to ∼3000 m), carotid sinus nerve afferent activity increases (Vidruk et al., 2001), eliciting a dose–response increase in minute ventilation (Powell et al., 1998), heart rate and MSNA (Blumberg et al., 1980; Gregor & Jänig, 1977). These responses attenuate the fall in P_{aO_2} and redistribute blood flow to the vital organs, thus serving as the first

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line of defence against systemic hypoxia. Sustained hypoxia sensitises carotid chemoreceptors resulting in a time-dependent increase in afferent discharge for a given fall in P_{aO_2} (Nielsen et al., 1988). This sensitisation reflects changes in ion channels, neurotransmitters and neuromodulators (i.e. ATP, endothelin and angiotensin II) within the carotid body (Powell, 2007) in addition to increases in the number of oxygen-sensing type 1 glomus cells (Wang et al., 2008). Enhanced central translation of carotid body input also occurs, where there is a greater efferent response for any given afferent input from the carotid chemoreceptors, at least in animal models (Dwinell & Powell, 1999). These chemoreflex modifications mediate a progressive increase in ventilation over the first ∼10 days at altitude (i.e. ventilatory acclimatisation; (Forster et al., 1971) that persists on return to SL, returning to pre-hypoxic values within 1–3 days (Dempsey et al., 1979).

Because of the temporal similarities between ventilatory and sympathetic responses to chronic hypoxia, it appears intuitive that carotid chemoreceptor sensitisation may also explain the time-dependent augmentation of MSNA. Although the carotid chemoreceptors accounts for ∼50% of the increase in MSNA during acute hypoxia in animal models (Gregor & Jänig, 1977), research examining its contribution during chronic hypoxia in does not exist. Moreover, supporting evidence of a major role during acclimatisation in humans is lacking. Sympathetic responsiveness to peripheral chemoreceptor activation does not mirror ventilatory responsiveness (Keir et al., 2019; Prasad et al., 2020) and there is a clear dissociation between the ventilatory and sympathetic responses during hypoxic exposure. Indeed, following 7–8 h of hypoxia, minute ventilation and ventilatory responsiveness to hypoxia are increased, but MSNA is reduced (Hunt et al., 2008; Tamisier et al., 2007). After longer exposure (15–17 days), Fisher et al. (2018) also found augmented ventilatory responsiveness to incremental hypoxia but no increase in MSNA responsiveness despite elevated resting MSNA. These findings suggest no sensitisation of the sympathetic response to hypoxia with acclimatisation, despite evidence of carotid body sensitisation. Moreover, inhibition of carotid chemoreceptors through low-dose dopamine infusion, to assess 'tonic' peripheral chemoreceptor drive, did not affect MSNA, suggesting a weak contribution of the carotid chemoreceptor to persistent sympathoexcitation at altitude. However, the vasodilatory effect of low-dose dopamine may have resulted in a baroreflex-mediated increase in MSNA to maintain arterial pressure in the study by Fisher et al. (2018), thus masking any decrease in MSNA as a result of peripheral chemoreceptor inhibition. Furthermore, low-dose dopamine infusion may not have inhibited the signal transduction pathway for the sympathetic chemoreflex. The carotid body contains both dopamine beta-hydroxylase cells, which initiate ventilatory responses to hypoxia, and tyrosine hydroxylase-containing TH cells, which appear to initiate sympathetic responses. Beta-hydroxylase cells are inhibited by low-dose dopamine, but TH cells are not (Pijacka et al., 2016; Zera et al., 2019), meaning that low-dose dopamine may be ineffective in examining peripheral chemoreceptor contribution to MSNA. These differences in signal transduction could explain the Fisher et al. (2018) findings, as well as the failure of low-dose dopamine to reduce the MSNA response to acute hypoxic exposure (Van De Borne et al., 1998).

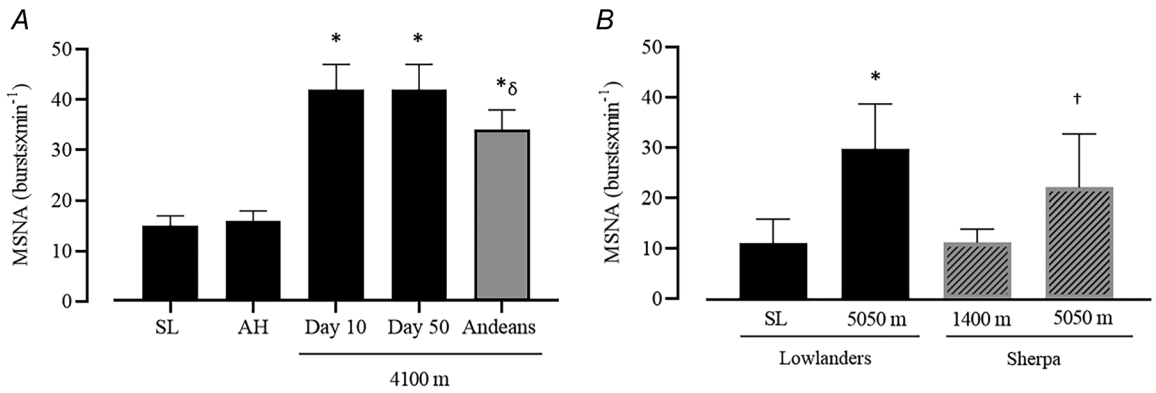

Figure 1. Resting MSNA during hypoxic exposure in lowlanders and highland populations
A, acute hypoxic exposure (corresponding to S_{aO_2} of 88%) for up to 1 h causes no discernible increase in MSNA; however, 10 days of exposure to 4100 m (corresponding to S_{aO_2} of 90%) caused a robust increase in MSNA, of almost 300%, in lowlanders. A further 40 days of acclimatisation to 4100 m was not accompanied by further changes in MSNA in lowlanders. Andean highlanders exhibited greater MSNA compared to lowlanders at sea level, although MSNA was slightly lower compared to Lowlanders tested at same altitude. *B*, Sherpa had lower level of MSNA compared to lowlanders at the same altitude, with Sherpa also exhibiting decreased MSNA following descent to 1400 m. Data adapted from Lundby et al. (2018) and Simpson et al. (2019).

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Another method to silence peripheral chemoreceptors, and assess 'tonic' peripheral chemoreceptor drive, is hyperoxic breathing (Astrand, 1954; Lahiri et al., 1987). By contrast to low-dose dopamine, this method silences both carotid and aortic chemoreceptor afferent firing, independent of the chemosensitive glomus cells involved. Hansen & Sander (2003) reported a reduction in MSNA burst frequency with 15 min of hyperoxic breathing following 4 weeks at 5260 m (Fig. 2). However, MSNA was reduced by only 25% and remained markedly elevated above SL values (∼170%). Furthermore, a shorter duration of hyperoxia (5 min) reduced MSNA after 10–20 days at 5050 m by only 10% (Simpson et al., 2019). Interestingly, the reduction in MSNA burst frequency was

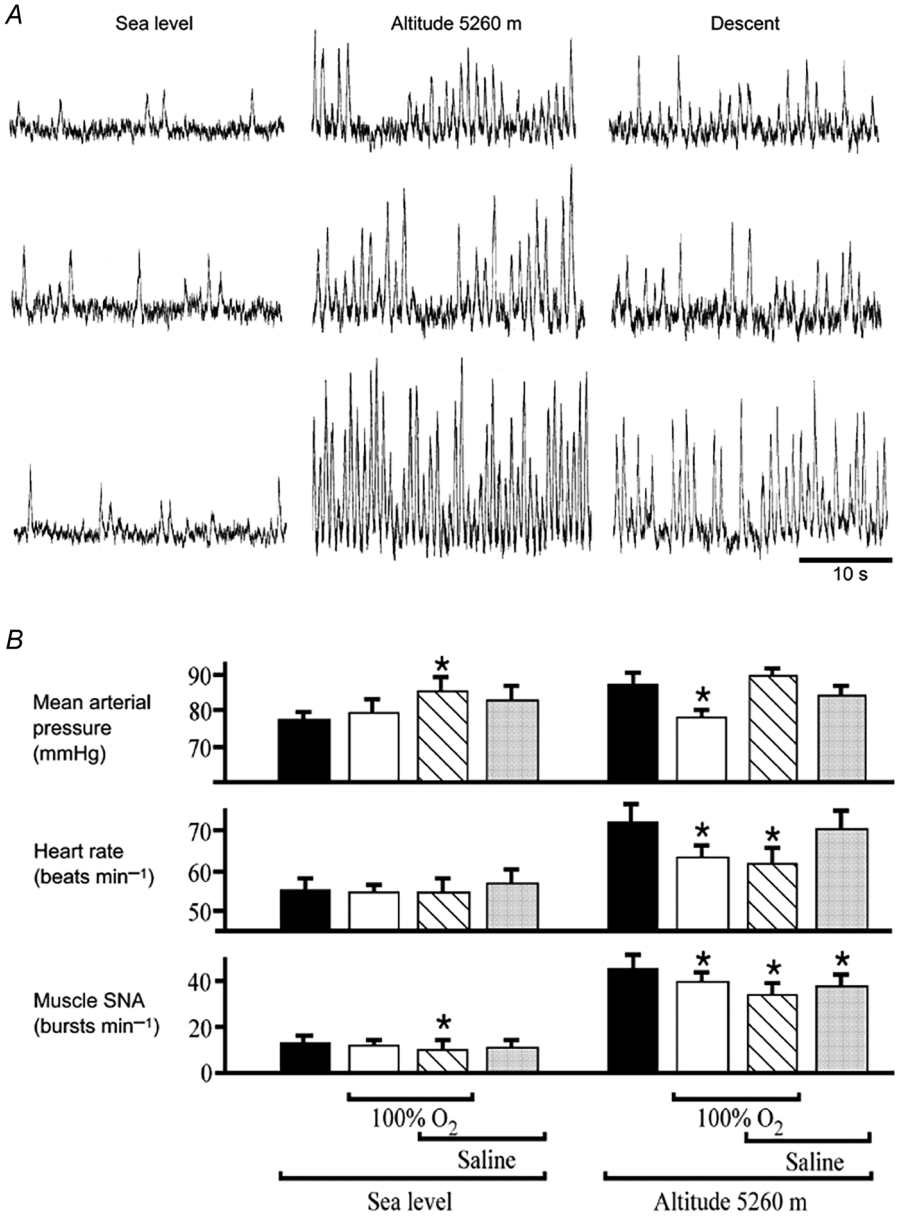

Figure 2. MSNA recordings during altitude acclimatisation and investigation of mechanisms mediating altitude sympathoexcitation
A, example MSNA recordings obtained in three Lowlanders at sea level, following 4 weeks at 5260 m and 3 days following descent. *B*, MSNA at rest, during 100% hyperoxic breathing and saline infusion, alone and in combination, at SL and 5260 m. Taken from Hansen & Sander (2003). Both hyperoxic breathing and saline infusion had no effect on MSNA burst frequency at SL, but significantly reduced MSNA at altitude, providing evidence of a role for the peripheral chemoreflex and arterial baroreflex in altitude sympathoexcitation. Nevertheless, MSNA remained elevated considerably above SL values, demonstrating a relatively minor effect for peripheral chemoreflex and arterial baroreflex on altitude sympathoexcitation.

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secondary to decreases in heart rate, with no change in MSNA burst incidence. Thus, the peripheral chemoreflex contributes to hypoxia-induced elevations in MSNA, but its effect is mediated by increasing heart rate (i.e. increasing the number of opportunities for a burst to occur) rather than altering central sympathetic outflow. This further supports the idea that peripheral chemoreflex plays and important role in elevations in MSNA acutely, but not augmenting MSNA with acclimatisation.

Highland native Sherpa display a high ventilatory sensitivity to hypoxia, similar to that in lowlanders at altitude (Busch et al., 2017). By contrast, Andeans exhibit a blunted ventilatory responsiveness, around half that of Sherpa and acclimatised lowlanders (Beall et al., 1997). These findings indicate high peripheral chemoreflex sensitivity in Sherpa. Yet, their MSNA is markedly lower than acclimatised Lowlanders, again highlighting an apparent dissociation between the ventilatory and sympathetic arms of the chemoreflex. Furthermore, 5 min of hyperoxic breathing did not affect MSNA in Sherpa and resulted in only a minor 20% decrease in Andeans (Simpson et al., 2019; Simpson, Meah, Steele, Gasho et al., 2020), indicating that the peripheral chemoreflex also plays only a minor role in altitude sympathoexcitation following generational exposure.

Methodological considerations for investigation of the peripheral chemoreflex. Although the aforementioned evidence challenges the idea that peripheral chemoreflex sensitisation mediates the time-dependent increase in MSNA with altitude acclimatisation, it is important to acknowledge several methodological considerations that may underestimate its contribution. Longer hyperoxic exposures (i.e. above several minutes) may have a stimulatory effect on MSNA as a result of central chemoreceptor activation (secondary to increased arterial CO_2 tension), increased free radical production and the direct effects of hyperoxia on the brain (Daristotle et al., 1991; Fernandes et al., 2021), serving to mask any decrease from peripheral chemoreceptor inhibition. Multiple transient hyperoxic exposures (i.e. $<$1 min) that follow MSNA to a nadir have recently been proposed as the optimal approach to assess tonic peripheral chemoreceptor drive (Prasad et al., 2020), rather than steady-state assessments. Furthermore, it remains unclear whether there is an enhanced central processing of peripheral chemoreceptor afferent input in humans during chronic hypoxia (Accorsi-Mendonça et al., 2015) and whether this persists with hyperoxic breathing. Maintained enhanced central processing may sustain activation of the 'extended chemoreceptor pathway' and elevated MSNA, despite the removal of peripheral chemoreceptor afferent input. Lastly, a complexity of factors may explain a lack of correlation between ventilatory and MSNA responses to hypoxia (Fisher et al., 2018; Hunt et al., 2008; Keir et al., 2019; Prasad et al., 2020) and does not necessarily indicate that both are not mediated by similar mechanisms. Marked within-subject variability exists in the reproducibility of these responses (Prasad et al., 2020) and activation of secondary feedback mechanisms (e.g. pulmonary stretch receptors, arterial baroreflex, central chemoreflex activation) will differentially affect steady-state ventilation and MSNA, which all make it difficult to isolate the effects of the peripheral chemoreflex on these responses.

Overall, the available evidence does not support a major role for peripheral chemoreceptors in the elevation of MSNA during altitude acclimatisation and following generational exposure. However, this may reflect a lack of specific and appropriate methods used to isolate its contribution.

Altered respiratory–MSNA coupling. In addition to the direct effects of peripheral chemoreflex activation on sympathetic outflow, secondary effects of changes in ventilation may also play a role. MSNA is modulated by ventilation, where MSNA is inhibited during mid-inspiration and peaks in late expiration (Eckberg et al., 1985; Hagbarth & Vallbo, 1968; Seals et al., 1990). This respiratory coupling is mediated by not only afferent inputs from pulmonary stretch receptors, arterial baroreceptors, as a result of respiratory-related changes in intrathoracic pressure, venous return and arterial pressure, but also direct coupling between respiratory neurons and sympathetic neurons in the brainstem (Eckberg et al., 1985; Hagbarth & Vallbo, 1968; Malpas, 1998; Seals et al., 1990). In animal models, altered central respiratory–sympathetic coupling is observed following sustained (24 h) hypoxia (Moraes et al., 2014). Specifically, there is an increase in sympathetic discharge during the late phase of expiration, which is associated with the recruitment of respiratory neurons involved in active expiration. These alterations lead to increases in resting SNA. Nevertheless, because the pattern of within-breath SNA varies between species (Habler et al., 1994), hypoxic exposure in animal models may not be comparable in humans. Voluntary alterations in breathing patterns (frequency and tidal volume) do not affect steady-state levels of MSNA in normoxic humans (Fatouleh & Macefield, 2011; Limberg et al., 2013; Seals et al., 1993; St Croix et al., 1999; Van De Borne et al., 2000); although, the effect of ambient hypoxia on respiratory-MSNA coupling in humans has not been assessed.

Arterial baroreflex

Restraint of hypoxic vasodilatation. Acute hypoxia elicits the local release of vasodilators (Dinenno, 2016), leading to intensity-dependent vasodilatation in the coronary, splanchnic and skeletal muscle vasculature

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(González-Alonso et al., 2002; Heistad & Wheeler, 1970; Markwald et al., 2011; Rowell & Blackmon, 1986). This vasodilatation and marked reductions in total peripheral resistance increase tissue perfusion to maintain tissue O_2 consumption when arterial O_2 content (C_{aO_2}) is reduced. Elevated MSNA restrains hypoxic vasodilatory signalling, with a two-fold greater sympathetic restraint of resting vascular tone observed in acute hypoxia *vs*. normoxia (Weisbrod et al., 2001), preventing widespread vasodilatation from outstripping cardiovascular reserve. Arterial baroreceptors partly mediate this response because accentuated reductions in total peripheral resistance and a marked decrease in blood pressure (BP) during acute hypoxia have been observed in barodenervated rats compared to control animals (Walker & Brizzee, 1990).

During chronic hypoxic exposure, several acclimatisation processes restore C_{aO_2} to SL values or higher, removing one of the key stimuli for hypoxic vasodilatation (González-Alonso et al., 2001; Hanada et al., 2003; Roach et al., 1999). Studies in animals (Walsh & Marshall, 2006a, b) and humans (Calbet et al., 2014; Simpson et al., 2023) indicate that hypoxia-induced vasodilatation is largely abolished after 7–21 days of exposure, with vascular conductance and α-adrenergic restraint of vascular tone comparable to SL following 21 days at 4300 m (i.e. indicating no additional tonic vasodilatation compared to SL) (Simpson et al., 2023). Therefore, MSNA does not need to be elevated to restrain hypoxic vasodilatation beyond >7 days, meaning that MSNA remains elevated because of another sympathoexcitatory signal. Interestingly, attenuation of hypoxic vasodilatation may begin within the first 7–8 h of hypoxia (Gilmartin et al., 2006), which might explain the return of MSNA to normoxic levels after this exposure time and indicate that BP control is a primary mechanism mediating sympathoexcitation in acute hypoxia.

Sympathoexcitation during chronic hypoxic exposure has been associated with mild elevations in BP (∼5 mmHg) (Fisher et al., 2018; Hansen & Sander, 2003; Lundby et al., 2018; Tymko et al., 2023) and it was subsequently hypothesised (Hansen & Sander, 2003) that arterial baroreflex function may be impaired with altitude acclimatisation, allowing increased BP and sympathoexcitation. However, elevated BP is not a consistent finding (Keyes et al., 2017; Simpson et al., 2019) and subsequent studies have shown that arterial baroreflex function (i.e. gain) is well preserved after 10–20 days at 5050 m in lowlanders and is comparable in Sherpa and Andean highlanders. Furthermore, the reflex operates around a similar BP set point to that at SL (Simpson et al., 2019, 2020). Nevertheless, increased MSNA burst incidence with chronic altitude exposure indicates increased baroreflex gating of sympathetic outflow, which is necessary to maintain BP.

Reduced sympathetic transduction. The requirement for greater MSNA to maintain BP during acclimatisation appears to be a result of blunted vascular sympathetic transduction (i.e. translation of MSNA into vasoconstriction) (Berthelsen et al., 2020). There is desensitisation of α_1-adrenergic receptors, the primary mechanism for sympathetic-mediated vasoconstriction (Fairfax et al., 2013), with altitude acclimatisation (Simpson et al., 2023) that is not observed during acute exposures (Dinenno et al., 2003). Specifically, the vasoconstrictor response to local infusion of α1 agonist phenylephrine is almost abolished following 21 days at 4300 m (Simpson et al., 2023), and sympathetic transduction is inversely correlated with resting MSNA at altitude (Berthelsen et al., 2020). What remains unclear is whether MSNA is elevated to overcome the downregulation of α_1-adrenergic receptors, and thus represents a mechanism driving sympathoexcitation, or whether the downregulation of α_1-adrenergic receptors is a response to chronically elevated MSNA. Although α-adrenergic receptor responsiveness was not assessed, Lundby et al. (2018) reported reduced MAP in lowlanders on day 50 at 4300 m, compared to day 10, despite no change in MSNA. These findings indirectly suggest that elevations in MSNA may precede the blunting of sympathetic transduction, meaning reduced transduction is not mediating heightened MSNA. Indeed, chronic α-adrenergic receptor stimulation causes alterations in excitation–contraction coupling within vascular smooth muscle (Bartlett & Marshall, 2002; Ebeigbe, 1982; Franco-Obergon & Lopez-Barneo, 1996; Ueno et al., 1997), which may be an adaptive response to offset the detrimental effects of chronically heightened MSNA, including altered vascular reactivity (Tymko et al., 2020) and increases in BP. It is unclear whether, or for how long, desensitisation of α_1-adrenergic receptors persists following descent from altitude. If blunted sympathetic transduction persists, MSNA might remain elevated after return to SL as a way to regulate BP. Findings reported by Mitchell et al. (2018) support this possibility, although, elevated BP observed by Hansen & Sander (2003) following descent suggests against BP regulation being the primary mechanism for persistent elevations in MSNA.

Only a few studies have examined vascular control mechanisms in highland natives. Resting forearm vascular conductance in Andean highlanders is comparable to that of Lowlanders both at SL and after 3 weeks at the same altitude (4383 m), and α-adrenergic receptor blockade does not unmask any additional tonic vasodilatation (Hansen et al., 2021; Simpson et al., 2023). Andean highlanders also exhibit reduced sympathetic transduction (Berthelsen et al., 2020) and blunted α_1-adrenergic receptor responsiveness compared to Lowland populations at SL (Hansen et al., 2021; Simpson et al., 2023). Therefore, elevated MSNA does not oppose

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hypoxia-induced vasodilatation but may offset reduced α_1-adrenergic receptor responsiveness, at least in Andean highlanders. Whether sympathetic vascular control mechanisms differ in Sherpa is unclear, although indirect evidence suggests sympathetic transduction and α1-adrenergic receptor responsiveness are maintained in Sherpa at altitude and comparable to SL (Berthelsen et al., 2020; Simpson et al., 2019). Interestingly, significant hypoxic vasodilatation may persist in Sherpa because of their comparably lower C_{aO_2} (below that of SL values), a possibility supported by findings of greater exhaled NO (Beall et al., 1997) and peripheral blood flow in Sherpa (Erzurum et al., 2007). Thus, in contrast to Andeans and Lowlanders, greater tonic vasodilatation may be a stimulus contributing to sympathoexcitation in Sherpa at altitude.

Reduced stroke volume. Reductions in total blood volume begin within 24 h at altitude as a result of a decrease in plasma volume (Roche et al., 2022; Schlittler et al., 2021), which is an adaptive response to increase haemoglobin concentration early during exposure (Ryan et al., 2014; Schlittler et al., 2021). Models of acute and long-term hypovolemia show marked increases in MSNA (Fu et al., 2005; Levine et al., 2002; Ryan et al., 2011, 2012) that are linearly related to reductions in stroke volume (Levine et al., 2002; Ryan et al., 2011, 2012). Such reductions decrease baroreceptor distension, independent of arterial pressure (Angell-James, 1971), attenuating baroreflex sympathoinhibition and increasing MSNA. Indeed, the decrease in blood volume at altitude is associated with reduced left ventricular filling and stroke volume of 10–20% (Siebenmann et al., 2013; Stembridge et al., 2018). Thus, a decreased stroke volume probably contributes to altitude sympathoexcitation. Although arterial baroreflex deactivation would increase MSNA acutely, concurrent activation of the renin–angiotensin–aldosterone system would usually restore blood volume and reduce the need for chronically heightened MSNA. However, the renin–angiotensin–aldosterone system is down-regulated in hypoxia (Steele et al., 2020) and total blood volume remains depressed for the initial weeks at altitude (Siebenmann et al., 2017), such that MSNA would need to remain elevated in the absence of normal volume regulatory mechanisms.

Infusion of 1000 mL of saline after 4 weeks at 5260 m reduces MSNA by 20% (Hansen & Sander, 2003). Although rapid volume expansion would acutely decrease MSNA through arterial baroreceptor loading, regardless of the initial cause of sympathoexcitation, the reduction in MSNA with saline infusion was greater at altitude than SL (Fig. 2) (Hansen & Sander, 2003). These results support a role for reduced blood volume in altitude sympathoexcitation; however, several methodological issues complicate the interpretation of these findings. First, 1000 mL of saline infusion probably resulted in relative hypervolemia and acute hemodilution, which would decrease C_{aO_2} and may increase MSNA (Hanada et al., 2003). Second, saline is rapidly lost from the intravascular space. Thus, the lack of continuous saline infusion and lack of confirmation of blood volume restoration make these findings almost uninterpretable. Prevention of plasma volume reductions would provide greater mechanistic insight into the role of blood volume changes in altitude sympathoexcitation.

Although total blood volume is restored with longer-term exposure (Pugh, 1964), persistent elevations in pulmonary artery pressure and increased right ventricular afterload mean stroke volume remains depressed throughout acclimatisation (Stembridge et al., 2018). Moreover, despite significantly elevated total blood volume in high-altitude natives (Stembridge et al., 2019), absolute and relative stroke volume is lower than in acclimatising Lowlanders (Stembridge et al., 2014). Therefore, a smaller stroke volume with acclimatisation and generational hypoxic exposure may represent a stimulus for altitude-induced sympathoexcitation across populations.

Elevated intracranial pressure. Systemic hypoxia leads to an acute increase in intracranial pressure (ICP) as a result of profound vasodilatation of the cerebral arterioles and higher cerebral arterial and venous volumes (Lawley et al., 2016). Animal and human studies with invasive ICP monitoring show that upon hypoxia exposure, ICP increases by 7–10 mmHg and remains elevated for the first 6 h before gradually returning to normal levels within 24 h, at least in the absence of severe acute mountain sickness or high-altitude cerebral oedema. Human studies reveal that, even at physiological levels, ICP affects sympathetic vasomotor outflow (Schmidt et al., 2018). In awake individuals, increasing ICP by 7 mmHg, akin to hypoxia-induced elevations, results in a 17% increase in MSNA burst frequency. This effect is assumed to be mediated by a sympatho-excitatory central baroreflex, initially proposed by Cushing (1901). Heightened and dynamic fluctuations in ICP trigger sympathetic responses that increase arterial pressure to maintain adequate cerebral perfusion pressure and prevent cerebral ischemia. Overall, elevated ICP probably represents a mechanism for hypoxia-induced sympathoexcitation during the initial 24 h of exposure but is not involved in the persistent MSNA with longer-term exposure once ICP normalises.

Potential central mechanisms for hypoxia-induced sympathoexcitation

In addition to modified reflex control of the sympathetic nervous system, hypoxia may also heighten sympathetic

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outflow via central mechanisms (Fig. 3). Sympathetic outflow originates from the sympathetic preganglionic neurons in the intermediolateral cell column of the spinal cord. These neurons receive excitatory input primarily from sympathetic premotor neurons in the rostral ventrolateral medulla (RVLM) that, in turn, receive excitatory and inhibitory input from the nucleus tractus solitarius (NTS), caudal ventrolateral medulla, higher brain structures and circumventricular organs (Dampney, 2016; Dampney et al., 2003). RVLM neurons act as central oxygen sensors and are highly responsive to hypoxia because of their rich capillary network. In rats, lowered parenchymal P_{O_2} directly activates RVLM neurons, increasing vasomotor sympathetic activity and heart rate during hypoxia (Guyenet & Les Brown, 1986; Marina et al., 2015; Sun & Reis, 1994). However, activation of RVLM neurons may also occur indirectly via release of ATP and lactate from neighbouring astrocytes in response to tissue hypoxia (Angelova et al., 2015; Marina et al., 2015), with astrocytes detecting even mild decreases in brain oxygenation (i.e. reductions in brain parenchymal P_{O_2} of a few mmHg) (Angelova et al., 2015; Gourine & Funk, 2017). Hypoxia also stimulates erythropoietin (EPO) production from RVLM neurons, and EPO activates these neurons, increasing sympathetic nerve activity (Oshima et al., 2018). Additionally, EPO generated by the kidneys can pass through the blood–brain barrier and may activate RVLM neurons. In humans, EPO increases within 2 h of hypoxic exposure, reaching a maximum at 2 days before steadily declining and eventually stabilising just above SL values at around 2–3 weeks (Eckardt et al., 1989; Milledge & Cotes, 1985; Ryan et al., 2014). Thus, EPO may contribute to hypoxia-induced sympathoexcitation during initial exposure but probably becomes less significant with acclimatisation as haemoglobin rises. Altered concentrations of other peripherally circulating factors, including inflammatory mediators, and changes in osmolality, secondary to plasma volume contraction, may also increase MSNA via activation of circumventricular organs that lack a blood–brain barrier. Alterations in neurotransmission within the NTS, the integrating centre for many peripheral reflexes, have also been reported in sustained hypoxia. Electrophysiological studies demonstrate increased excitability of NTS neurons with sustained hypoxia (Accorsi-Mendonça et al., 2015; Zhang et al., 2009), increasing their neural discharge for any level of afferent stimulation. Such changes, which are partly mediated by microglial cell activation and neuroinflammation (Lima-Silveira et al., 2019), may amplify the sympathetic response to a given excitatory afferent input. Furthermore, RVLM neurons are also sensitive to changes in P_{CO_2} and pH (Seller et al., 1990). Although hyperventilation-induced reductions in P_{aCO_2} (and associated increases in pH) dampens the sympathetic response during acute hypoxia, as illustrated by greater increases in MSNA during isocapnic *vs*. poikliocapnic hypoxia (Tymko et al., 2023), renal compensation and partial restoration of blood and cerebral spinal fluid pH during acclimatisation (Forster et al., 1975) may reduce this sympathoinhibitory signal.

Importantly, the mechanisms discussed so far appear to elicit sympathoexcitation as a regulatory response to preserve systemic and cerebral tissue O_2 delivery and arterial BP during hypoxic exposure. However, several process that are arguably maladaptive to hypoxia may also contribute to hypoxia-induced sympathoexcitation.

Potential maladaptive mechanisms for hypoxia-induced sympathoexcitation

Elevated pulmonary arterial pressure. By contrast to systemic and cerebral vessels, hypoxia elicits vasoconstriction in the pulmonary vasculature [hypoxic pulmonary vasoconstriction (HPV)] (Naeije, 1992). Although HPV is beneficial when a small portion of the lung is hypoxia (i.e. poorly ventilated), HPV has little physiological benefit at altitude when hypoxia in the lung is global. Ambient hypoxia causes widespread HPV, increasing pulmonary vascular resistance and pulmonary artery pressure (PAP) (Groves et al., 1987). PAP increases within seconds of hypoxic exposure, followed by further increases over 2 h (Dorrington et al., 1997; Talbot et al., 2005). Despite progressive hypocapnia dampening HPV (Balanos et al., 2003), PAP increases further during prolonged hypoxia, secondary to increases in blood viscosity and nocturnal periodic breathing (see section below on 'Nocturnal periodic breathing'). Persistent elevations in PAP lead to pulmonary arteriolar remodelling (Groves et al., 1987; Hilty et al., 2016) that maintain the elevated PAP even on return to normoxia (Groves et al., 1987; Maufrais et al., 2016).

Duplain et al. (1999) found a strong positive correlation between PAP and resting MSNA during 15 min to 36 h of hypoxic exposure. Although causality was not established, HPV is primarily a local response intrinsic to pulmonary smooth muscle cells (Lloyd, 1966). Therefore, elevated PAP potentially drives altitude-induced sympathoexcitation in humans. Studies in experimental animals have demonstrated pressure-sensitive receptors in pulmonary arteries, located mainly in the bifurcation and extrapulmonary branches (Coleridge & Kidd, 1960), and have shown that isolated increases in PAP elicit systemic vasoconstriction and renal sympathoexcitation in normoxia (Ledsome, 1977; Moore et al., 2004a, b, 2011). The role of pulmonary baroreceptors in altitude-sympathoexcitation has recently been investigated in humans. Following 4–9 days at 4383 m, a 20% reduction in pulmonary systolic

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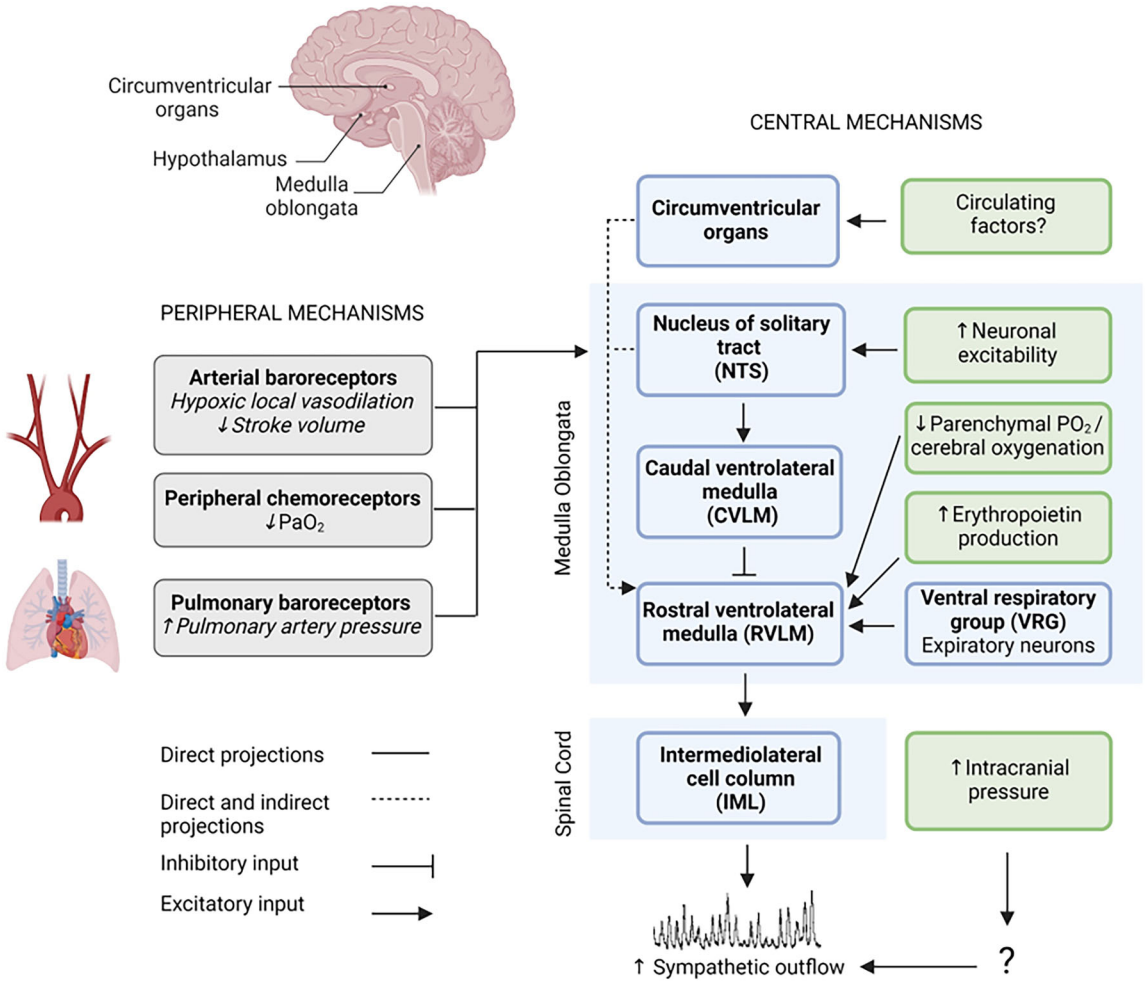

Figure 3. Schematic showing peripheral and central mechanisms contributing to sympathetic outflow in hypoxia
Sympathetic outflow is the product of the central integration of numerous inputs to the cardiovascular control centres in the medulla oblongata. These include afferent inputs from peripheral reflexes that project to the nucleus of solitary tract (NTS), whose neurons then project either directly or indirectly to sympathetic premotor neurons in the rostral ventrolateral medulla (RVLM). Evidence from humans demonstrates that altered afferent input from peripheral chemoreceptors (increased) and both pulmonary (increased) and arterial baroreceptors (decreased) contribute to hypoxia-induced sympathoexcitation. Notably, the reflex responses of pulmonary and arterial baroreceptors are directionally opposite, where activation of pulmonary baroreceptors appears to have an excitatory effect of sympathetic outflow and activation of arterial baroreceptors has an inhibitory effect on sympathetic outflow and project via the caudal ventrolateral medulla (CVLM). The RVLM is the primary nuclei determining the excitatory input to the sympathetic preganglionic neurons in the intermediolateral cell column (IML), where sympathetic outflow to originates, and is a site of convergence for other descending neural inputs from higher brain centres, including circumventricular organs. Circumventricular organs lack a blood-brain barrier, allowing alterations in peripherally circulating factors to influence central sympathetic outflow. Changes in osmolality, circulating erythropoietin, reactive oxygen species or inflammatory mediators during hypoxic exposure could contribute to increases in sympathetic outflow at altitude, although this remains to be explored in either animals or humans. There are also direct central connections between RVLM neurons and respiratory neurons that, alongside within-breath modulation of peripheral afferent inputs (i.e. baroreceptors, pulmonary stretch receptors), contribute to the well-known respiratory modulation of sympathetic outflow. In animal models, respiratory–sympathetic coupling is increased with hypoxia, associated with the recruitment of active expiratory neurons. RVLM neurons are also sensitive to O_2 and are activated in response to reductions in cerebral oxygenation and parenchymal P_{O_2}. These neurons also produce EPO in response to hypoxia, which has an excitatory effect on sympathetic outflow. Neuroinflammation has also been shown to increase the excitability of NTS neurons, leading to an increase in their neural discharge for any given excitatory input. Increases in intracranial pressure increase SNA in both animal models and humans, although, the exact neural pathways through which sympathetic outflow is elevated are unclear.

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pressure via inhaled nitric oxide was accompanied by a comparable decrease in MSNA in lowlanders (Simpson, Meah, Steele, Thapamagar et al., 2020), which resulted from a reduction in MSNA burst incidence with no effect on heart rate. Importantly, stroke volume was also unaffected, ruling out arterial baroreceptor unloading as an explanation for the sympathoinhibition. This was the first human evidence that elevated PAP contributes to altitude sympathoexcitation, possibly also explaining the heightened MSNA in those susceptible to high-altitude pulmonary oedema (Duplain et al., 1999). Nevertheless, in animals, there is a threshold PAP, below which systemic vasoconstriction does not occur (Moore et al., 2004a), indicating that the contribution of pulmonary baroreceptors to altitude sympathoexcitation is influenced by the severity of HPV and the prevailing PAP.

Differences in PAP may also contribute to differences in resting MSNA across highland populations. Andeans present with similar HPV and PAP to acclimatising lowlanders, whereas Tibetans may have a blunted HPV and only minimally increased PAP at altitude (Groves et al., 1993), although these findings are inconsistent (Foster et al., 2014). Thus, interventional studies are required to determine the role of pulmonary baroreceptors in sympathetic regulation in highland populations.

Nocturnal periodic breathing. In addition to increased peripheral chemoreceptor sensitivity to O_2, prolonged hypoxia increases chemoreceptor sensitivity to CO_2. This increased sensitivity steepens the slope of the ventilatory response to CO_2 and moves the eupnoeic (i.e. resting) P_{aCO_2} closer to the apnoeic threshold. Such changes lead to ventilatory instability and predisposes individuals to periodic breathing during sleep (Berssenbrugge et al., 1983; Dempsey, 2005). Nocturnal periodic breathing, which persists with acclimatisation (Ainslie et al., 2013; Tellez et al., 2014), leads to cyclic oscillations in O_2 saturation, similar to those observed with intermittent hypoxia interventions. At SL, both short-term and long-term intermittent hypoxia cause MSNA elevations that remain following termination of the stimulus (Gilmartin et al., 2010; Tamisier et al., 2011). Indeed, Gilmartin et al. (2010) and Tamisier et al. (2011) reported that 9 h of nocturnal intermittent hypoxia in healthy humans for 2–4 weeks increases daytime BP and resting MSNA by between 30% and 50%, which was driven by increases in central gating of MSNA (i.e. burst incidence) with no change in heart rate. Thus, oscillations in O_2 saturation associated with nocturnal periodic breathing could contribute to the augmentation of MSNA with acclimatisation, above that observed with acute exposure. In animals, persistent elevations in SNA following intermittent hypoxia appear to be a consequence of carotid body sensitisation, with both angiotensin II and reactive oxygen species (ROS) partly mediating these adaptations (Marcus et al., 2010; Peng et al., 2003, 2006). However, hyperoxic breathing has little effect on the MSNA response following intermittent hypoxia in humans (Leuenberger et al., 2007; Ott et al., 2020), providing conflicting evidence for peripheral chemoreflex involvement compared to animal studies. In addition to their effects at the carotid body, angiotensin II and ROS may also act centrally to increase sympathetic outflow, with angiotensin II inhibitor losartan reducing lumbar SNA and MSNA following acute and chronic intermittent hypoxia in rats and humans, respectively (Jouett et al., 2017; Marcus et al., 2010). Angiotensin II generates ROS via stimulation of angiotensin II type receptors and NADPH oxidase within the brain that can activate central SNA pathways directly or indirectly by scavenging NO and reducing its tonic sympathoinhibition (Patel et al., 2001; Zhang et al., 2008). In animal models, chronic intermittent hypoxia has also been shown to alter respiratory–sympathetic coupling (Moraes et al., 2012; Zoccal et al., 2008), increasing sympathetic outflow, and elevating PAP, which may also promote sympathoexcitation via augmented activation of pulmonary baroceptors (see section above on 'Elevated pulmonary arterial pressure') (Simpson, Meah, Steele, Thapamagar et al., 2020). However, whether similar processes occur at altitude, when intermittent hypoxia is superimposed on a background of continuous hypoxia, is unclear. Continuous hypoxia may differentially alter the balance of pro-oxidant HIF1-α and antioxidant HIF2-α dependent enzymes, compared to intermittent hypoxia alone. Specifically, an upregulation of HIF2-α with sustained hypoxia may reduce ROS generation during subsequent periods of intermittent hypoxia, and attenuate its effects (Prabhakar & Semenza, 2012). Indeed, nocturnal periodic breathing may actually represent an adaptive response at altitude that increases rather than decreases mean nocturnal O_2 saturation and reduces the severity of hypoxia during sleep (Ainslie et al., 2013; Hackett et al., 1987; Normand et al., 1990).

Despite altitude adaptation, Andean natives, similar to Lowlanders, experience nocturnal periodic breathing at altitude, but Sherpa do not (Hackett et al., 1980). Thus, the Sherpa adaptation pattern of lower sympathetic activation may reflect the effect of chronic hypoxia alone, independent of nocturnal periodic breathing. However, the long-term consequences of nocturnal periodic breathing at altitude are yet to be investigated. Overall, it is plausible that nocturnal periodic breathing contributes to the sympathoexcitatory effect of altitude acclimatisation; however, this needs to be tested in studies preventing periodic breathing at altitude and examining the consequences on MSNA.

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Future directions

Despite recent advances, several questions remain regarding sympathetic regulation at altitude. First, the role of the peripheral chemoreflex in augmenting MSNA during acclimatisation remains highly debated. Although human studies (Fisher et al., 2018; Hansen & Sander, 2003; Simpson et al., 2019; Simpson, Meah, Steele, Gasho et al., 2020) provide evidence against a major role for the peripheral chemoreflex, a number of methodological issues may underestimate its contribution. Second, it is unclear whether nocturnal periodic breathing contributes to altitude-induced sympathoexcitation. Although it appears a plausible mechanism, based on intermittent hypoxia studies at SL, experimental studies are required to confirm this at altitude. Third, the mechanisms responsible for persistent elevations in MSNA following descent are also important to understand and may have additional clinical relevance in populations with hypoxemia and persistent sympathoexcitation. Lack of immediate reversal of the same mechanisms contributing to altitude sympathoexcitation, including peripheral chemoreceptor sensitisation and/or central facilitation and persistent elevations in pulmonary arterial pressure, probably explain persistent sympathoexcitation. However, persistent downregulation of α_1-adrenergic receptor sensitivity may also represent a contributing mechanism. Fourth, it remains to be determined whether the mechanisms mediating hypoxia-induced sympathoexcitation in lowland natives are similar in highland natives, as well as between different highland populations. Different adaptation strategies probably lead to differential activation of sympathoexcitatory mechanisms. Indeed, differences in peripheral chemoreflex sensitivity, EPO production, pulmonary arterial pressure and presence/absence of nocturnal periodic breathing are reported, and may impact sympathetic outflow. Last, it is yet to be determined whether sympathetic regulation with chronic and lifelong hypoxia is sex-specific. Although existing evidence from acute hypoxia suggests similar MSNA increases in men and women (Jones et al., 1999; Miller et al., 2019), time-dependent changes in the mechanisms mediating sympathoexcitation may lead to sex-based differences with chronic and life-long exposure. For example, the incidence of nocturnal periodic breathing and the magnitude of HPV appear to differ between males and females.

Summary

Sympathoexcitation is a hallmark of acute hypoxic exposure, which persists with acclimatisation in lowland populations and with generational exposure in highland natives. The mechanisms mediating this response are multifactorial and dependent on the duration of exposure. Although it appears to be intuitive that peripheral chemoreceptors are the primary mechanism elevating MSNA in hypoxia, current evidence suggests they play a more minor role, notwithstanding several methodological limitations. Instead, the arterial baroreflex appears integral to sympathoexcitation on initial exposure, restraining systemic vasodilatation, with increased ICP and EPO, as well as reduced cerebral oxygenation, also probably making minor contributions. After ∼7–8 h of exposure, hypoxic vasodilatory signalling is reduced, coinciding with reports of normalisation of MSNA. However, as hypoxic exposure is extended (over 24 h), reductions in stroke volume occur that augment MSNA once more via arterial baroreceptor unloading, a sympathoexcitatory stimulus that probably remains for the duration of exposure. Acutely, hypoxia-induced sympathoexcitation appears to be an adaptive response to maintain cardiovascular system stability during systemic hypoxia (i.e. preserve systemic and cerebral tissue O_2 delivery and BP). However, further increases in MSNA during prolonged hypoxia appear to be driven by sympathoexcitatory signals originating from mechanisms that do not have an obvious physiological benefit in hypoxia, including high pulmonary artery pressures and potentially nocturnal periodic breathing. Furthermore, heightened MSNA during acclimatisation appears to be maladaptive, impairing vascular function and often leading to elevated BP. Desensitisation of vascular α-adrenergic receptors appear to be a regulatory response to chronically elevated MSNA, which limits these detrimental consequences. However, persistent α-adrenergic receptor desensitisation and reduced sympathetic transduction may contribute to the persistent elevations in MSNA following descent from altitude, in addition to the lack of immediate reversal of high pulmonary artery pressures and peripheral chemoreceptor sensitisation. Although less research has examined mechanisms for sympathoexcitation in highland natives, these mechanisms overlap with those observed in Lowlanders. Lower sympathetic nervous system activation in Sherpa may be a result of the absence of these maladaptive responses to hypoxia (i.e. periodic breathing and high pulmonary pressures), which are still present in Andeans, who have maintained higher levels of sympathetic activation.

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Additional information

Competing interests

The authors declare they have no competing interests.

Author contributions

No experiments were performed for this review. All authors have contributed to the conception and design of the manuscript. All authors have contributed to the drafting of the manuscript and/or have revised it critically for important intellectual content. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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