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Do monoamine-synthesizing cells constitute a complex network of oxygen sensors?

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SUMMARY

Oxygen represents an essential molecule for organisms. Because of this, sophisticated systems of sensors have evolved to monitor oxygenation of tissues. We propose that monoamine-synthesizing cells represent an important part of this system. It is well known that the carotid body, which contains chromaffin cells, serves as a chemical sensor of blood oxygenation. Similarly, the activity of adrenal medullary chromaffin cells is increased during hypoxia. Moreover, neurons located in the central nervous system containing catecholamines, serotonin, and histamine are also sensitive to hypoxia. On the basis of this common sensitivity of monoamine-synthesizing cells to changes in oxygenation we propose the hypothesis that these cells constitute a widely distributed network of sensors that monitor oxygen levels. The role of monoamine-synthesizing cells in monitoring tissue oxygen supply during both physiological and pathological conditions is also discussed.

Introduction

Oxygen represents an essential molecule for organisms, a concept which is particularly true for the central and peripheral nervous system [1]. Therefore, organisms have evolved a sophisticated system of sensors to monitor the oxygenation level of tissues [2]. We propose that monamine-synthesizing cells represent a major part of this system. Various populations of monoamine-synthesizing cells are distributed throughout organisms. In the periphery, monoamine-synthesizing cells are found mainly in the adrenal medulla and to a lesser extent in the carotid body, sympathetic ganglia, paraganglia, and the heart. Monoamine-synthesizing neurons in the central nervous system are divided into catecholamine-, serotonin-, and histamine-synthesizing neurons.

Monoamine-synthesizing neurons of brain are sensitive to hypoxia within the physiological range (for detailed review see [3]) and can therefore serve as central sensors for changes of CO_2 levels and pH [4]. For example, cells within the carotid body are well known as chemical sensors for detecting changes in blood levels of O_2, CO_2, and pH. However, the utility of the adrenal medulla as a chemical sensor is less understood (for review see [5]).

Hypothesis

This article proposes the idea that organisms possess a network of monoamine-synthesizing cells for monitoring the oxygenation of tissues at multiple levels. The common feature of these cells is a hypoxia-induced release of synthesized monoamines. Furthermore, both centrally and peripherally released monoamines modulate cardiovascular and respiratory functions in a manner designed to overcome hypoxia. The redundancy of these chemical sensors accents the importance of proper tissue oxygenation. The role of monoamine-synthesizing cells in the pathogenesis of diseases characterized by an altered ability to monitor tissue oxygenation is also discussed.

Peripherally localized monoamine-synthesizing cells

Monoamine-synthesizing cells in the periphery are predominately chromaffin cells, which are widely distributed throughout the organism. Chromaffin cells are derived from neural crest precursors, and synthesize catecholamines as well as other substances such as ATP and chromogranins [6,7]. These cells are located mainly in tissues associated with the autonomic nervous system such as the adrenal medulla, carotid body, and sympathetic ganglia. Another important source of chromaffin cells is the Zuckerkandl's organ and paraganglia of the autonomic nervous system. The primary secreted products of chromaffin cells are catecholamines. However, while adrenal medullary chromaffin cells synthesize both norepinephrine and epinephrine, chromaffin cells in other locations synthesize mainly norepinephrine [6].

Carotid body

The carotid (and also aortic) body is an arterial chemoreceptor with well-known functions as a sensor of blood O_2 saturation [8–11]. The carotid body monitors blood O_2 levels using O_2-sensitive

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channels, which are preferentially found in excitable neurosecretory cells [12]. The primary peripheral sensors of blood oxygenation in the carotid body consist of chief (type I) cells that are immunoreactive towards tyrosine hydroxylase, dopamine β-hydroxylase, phenylethanolamine N-methyltransferase, serotonin, glutamate decarboxylase, and gamma-aminobutyric acid. Microscopic studies have shown that almost all chief cells of the carotid body are catecholamine-fluorescence positive and current data suggests that the catecholamines of chief cells play at least a partial role in their chemoreceptive functions [13–15].

Adrenal medulla

Most potent stimuli that activate the adrenal medulla in rats are stressors such as hypoxia. For example, asphyxia results in intensive adrenal stimulation followed by a striking increase in catecholamine secretion by the adrenal medulla [16]. Also, either hypoxia or hypercapnia alone can elicit a huge increase in catecholamine secretion, showing a synergistic effect on epinephrine secretion from the adrenal medulla in dogs [17]. This elevated secretion of catecholamines, observed during asphyxia or hypercapnia, is not affected by denervation of the adrenal glands [18–20] suggesting that activation of the adrenal medulla during acute asphyxia occurs independently of the central nervous system. However, it has also been observed in the ovine fetus and adult rats that adrenal medullary catecholamine responses to hypoxia are mediated by both direct O_2 sensing as well as neural mechanisms [21–23]. Furthermore, blockade of neural input to the adrenals by hexamethonium reduced, but did not eliminate hypoxia-induced increases in plasma norepinephrine and epinephrine concentrations in ovine fetuses at 109–119 days of gestation [24].

Oxygen-sensitive channels, which are preferentially found in the excitable neurosecretory cells of carotid bodies, are also found in neonatal adrenal chromaffin cells [12]. It has been reported that pheochromocytoma (PC12) cells respond to a reduction of pH with catecholamine secretion mediated by Ca^{2+} influx through voltage-gated N- and P/Q-type Ca^{2+} channels [25]. These findings indicate that the chromaffin cells can monitor changes in O_2/CO_2 concentration in blood and respond to hypoxia/hypercapnia or acidification of plasma by secretion of catecholamines.

According to the traditional view, the endocrine activity of the adrenal medulla is predominantly under the influence of central nervous system structures [26–28]. On the other hand, there are also clear data suggesting that adrenal medullary cells can respond directly to some types of perturbations of the internal environment [29,30] and it is suggested that the adrenal medulla might potentially inform the central nervous system about such changes [5]. This hypothesis is supported by anatomical data showing that adrenal medullary chromaffin cells are innervated by sensory fibers (e.g. vagal and splanchnic nerves) that could transmit information about O_2 levels to the central nervous system [31–35].

Other monoamine-synthesizing cells in periphery

The heart contains intrinsic cardiac, catecholamine synthesizing, adrenergic cells [36]. It is suggested that these locally produced catecholamines might participate in the regulation of cardiac activity [36,37]. Current thinking suggests that during hypoxia these catecholamines might enable cardiac tissue to overcome an adverse situation.

In the periphery, the source of histamine are mast cells predominantly localized adjacent to capillaries and venules [38]. Systemic hypoxia results in rapid mast cell degranulation. This reaction might play a key role in hypoxia-induced inflammation and the consequent adaptation of endothelial function [39]. The data suggests that histamine released during ischemic/reperfusion periods might also contribute to intestinal dysfunction [40]. Histamine-synthesizing cells are also found in intrinsic cardiac and intrathoracic extracardiac ganglia involved in cardiac regulation [41]. However, the effect of histamine released during ischemia on cardiac tissue remains controversial [42,43] with some data suggesting that histamine might play an important role in protecting cardiac tissue against hypoxia/reperfusion injury [44].

In the periphery, serotonin is localized predominantly in platelets, which show sensitivity to hypoxia [45]. It is possible that abnormalities in platelet function may conceivably lead to increases in plasma serotonin levels during hypoxic conditions [46].

Monoamine-synthesizing cells within the central nervous system

Monoamine-synthesizing neurons, an important part of the central chemosensory system, are localized mainly in the brain stem [4]. Furthermore, oxygen-chemosensitive neurons are distributed throughout the brain from the thalamus to the medulla and may form an oxygen-chemosensitive network [47]. The activity of catecholamine, serotonin, and histamine-synthesizing neurons is closely associated with oxygenation of surrounding tissue [3,48,49]. However, monoamine-synthesizing neurons are also activated by signals from peripheral chemoreceptors [50]. Therefore, monoamine-synthesizing neurons might be activated both directly and indirectly during hypoxic conditions.

Catecholaminergic, serotonergic, and histaminergic neurons are part of the ascending arousal system which widely innervates the cortex. However, during sleep their activity declines [51]. It is believed that during sleep the chemosensory properties of monoaminergic neurons enable them to modulate reactions of the organism to hypoxia. The chemosensitive properties of monoamine-synthesizing neurons are described in detail in the review of Haxhiu et al. [3]. Therefore, the next section primarily points out recent data.

Catecholaminergic neurons

Catecholaminergic neurons within the brain stem are activated during hypoxia [52,53]. However, activation of brain stem catecholaminergic neurons during hypoxia is independent of signals from the carotid body [54]. Therefore, catecholaminergic brain stem cell groups may represent part of the autonomic CO_2 sensing network [55]. Catecholaminergic cell groups localized in the brain stem are also involved in the regulation of cardiovascular system activity [56,57]. Therefore, chemosensory properties of catecholaminergic areas might participate in any rapid response of the cardiovascular system to hypoxia.

Serotonergic neurons

The data shows that serotonergic raphe neurons within the brain stem participate in the monitoring of CO_2 and pH within the physiological range [58–60]. The processes of these neurons are closely apposed to arterial blood vessels and are therefore in a prime location to monitor blood oxygenation [61]. Centrally released serotonin also participates in sympathoexcitation and the subsequent rise in blood pressure [62]. It is also suggested that chemosensory serotonergic neurons contribute to the interaction between the sleep/wake cycle and respiratory control [63].

Histaminergic neurons

Researchers using a c-fos study have shown activation of histaminergic neurons during hypoxia and hypercapnia in rats [64]. It is