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Thrombin Effects on Astrocytes: Autonomic Failure in Trauma, Burns, and Infection

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Abstract

Historically, astrocytes had been thought to perform principally maintenance functions within the brain. However, studies have now revealed the active role astrocytes play in the regulation of neuronal excitability and synaptic communications within neural circuits. This function is especially important to the control of autonomic mechanisms that are regulated by the hindbrain. Astrocytes enmeshed within the important autonomic regulatory circuits are now considered critical to the proper function of hindbrain circuits controlling glycemia, gastrointestinal, and cardiorespiratory functions. Recently, hindbrain astrocytes have also been implicated in pathophysiological changes in autonomic function associated with severe trauma, burns and systemic infection. A common factor in these pathological insults is the generation of significant levels of circulating thrombin. Physiological studies show that thrombin powerfully activates hindbrain astrocytes in critical autonomic control circuits that trigger drastic and, possibly, lethal effects. Such an interaction may help explain why COVID-19 infections, which produce disseminated thrombosis, can predispose patients to severe hyperglycemia and respiratory arrest.

Keywords: Nucleus of the solitary tract; Trauma; Hyperglycemia; Respiratory arrest

Central Nervous System Autonomic Control

The dorsal hindbrain is a critical site in the control of digestive, metabolic, and cardiorespiratory functions. At the heart of this homeostatic control nexus is the Nucleus of the Solitary Tract (NST) which receives physiological data from cranial nerve afferents including the vagus nerve. These visceral afferent data includes information about blood pressure, respiration depth, CO_2 and O_2 concentrations, hepatic portal glucose concentrations, gastrointestinal motility, etc [1]. This region of the hindbrain is also outside the "blood-brain barrier" and, therefore, accessible to blood gases, metabolic fuels such as glucose and larger molecules in the circulation such as peptide hormones and proteins. The NST parses this vast array of neural and chemosensory information to higher-order autonomic control networks to regulate gastrointestinal, metabolic, cardiorespiratory, endocrine, and behavioural functions [1-4].

In the case of glucose regulation, sensors in the NST can detect the level of circulating glucose. If glucose concentrations fall significantly, NST neurons and their connections with endocrine and sympathetic control areas in the hindbrain are activated, triggering a Counter-Regulatory Reflex (CRR) activation of pancreatic glucagon and adrenal epinephrine release that drives hepatic glycogenolysis and a rapid increase in circulating glucose [5].

This same general hindbrain region is also a critical part of the neurocircuitry that generates respiration. In particular, the lateral portion of the NST receives data from vagal intercostal stretch receptors that monitor the depth and frequency of inspiration. This information is used to trigger hindbrain circuit elements that terminate inspiration and initiate expiration [1].

Astrocytes and Neuronal Control

Long thought to only have a passive role in maintaining neuronal networks, it is now clear that astrocytes directly regulate neuronal excitability and synaptic efficacy. A single astrocyte may contact thousands of presynaptic terminals and postsynaptic neurons in which astrocytes can regulate neurotransmission and neuron excitability. The NST has an especially dense concentration of astrocytes compared with the rest of the brain [6]. Astrocytes can be activated by neurotransmitters released

from neuronal presynaptic terminals, or gliotransmitters released by other astrocytes. Further, astrocytes are sensitive to local, homeostatically regulated parameters such as blood gas tension and glucose availability [7-9]. Astrocytes are also stimulated by markers of immune activation such as cytokines [10,11] and markers of traumatic injury and severe infection such as thrombin [12,13]. These agents can act to increase astrocytic calcium levels [14]. This increase in astrocytic calcium is, in turn, is coupled to a release of gliotransmitters [15] such as glutamate, ATP, adenosine and D-serine, among others. Astrocyte gliotransmission can potently affect the excitability of adjacent NST neuronal circuitry [8,13,16].

Activation of Astrocytes and Gliotransmission

Astrocytes utilize a potent intracellular calcium signaling mechanism to transduce external stimuli arising from the chemical activation of receptors. As an example, receptors, such as the Proteinase-Activated Receptor (PAR) acted on by thrombin, are coupled to the phospholipase C (PLC)-inositol 3 phosphate (IP3). In turn, IP3, binds to receptors in the endoplasmic reticulum which causes the release of a substantial store of calcium ions. Increases in cytoplasmic calcium, in turn, can drive a number of cellular mechanisms including gliotransmission (e.g., adenosine release). (For more detailed discussion of cellular mechanisms of astrocyte activation, refer to [7,12,14,15,17].

Astrocytes in the Hindbrain Influence Homeostatic Regulation of Glucose Levels and Respiration

Hindbrain astrocytes are emerging as important sources of chemosensory control over autonomic and autonomous functions such as glucose homeostasis, gastrointestinal, cardiovascular and respiratory control [7-9, 16,17]. For example, astrocytes in the hindbrain have been implicated recently as important detectors of low glucose or glucose utilization and, when activated, these astrocytes trigger CRR [8,9] by releasing purinergic gliotransmitters onto NST neurons responsible for mediating CRR. Similarly, astrocytes in the hindbrain are known to detect plasma CO_2 levels and to release purinergic gliotransmitters onto respiratory rhythm-generating circuits, controlling the appropriate rate of respiration [7].

Trauma, Burns, Infection and Metabolic Regulatory Failure

Severe traumatic injuries, burns and serious infections can cause "metabolic self-destruction" [18]. This phenomenon is characterized by a catabolic profile including persistent hyperglycemia, functional insulin resistance and greatly elevated metabolic fuel use [19]. The association between these pathophysiological insults and hyperglycemia is practically axiomatic [18]. The severity of the pathological hyperglycemia is highly correlated with post-trauma or infection morbidity and mortality [20-22]. The outlook for such patients is grave indeed when the metabolic consequences of their trauma cannot be successfully addressed [23].

Under circumstances of "survivable" insults, this relationship between pathology and a stress-related increase in fuel availability assists in surmounting the traumatic event and subsequent healing [18]. However, the extreme and prolonged hyperglycemia associated with the global metabolic collapse of severe pathophysiology is not adaptive or helpful. Rather, it is better described as a pathophysiology in those individuals who may not survive the insult without timely and intensive clinical intervention. Until recently no detailed mechanism has been posited to connect severe trauma with metabolic control aside from a common citation of "CNS-stress-related sympathetic activation" [23,24].

Thrombin, Astrocytes, and Purinergic Control of Glycemia

There may be a convergence between the effects of thrombin and the hindbrain circuitry that initiates counter-regulatory responses in reaction to critical hypoglycemia. This hindbrain-mediated hyperglycemia response has recently been connected with the generation of circulating thrombin [14]. As mentioned above, thrombin (produced as a consequence of bleeding, burn injury or severe infection) is a protease and acts on a unique class of G-protein coupled receptor; the Protease-Activated Receptor (PAR). PARs possess their own tethered peptide ligand; a 5-amino acid peptide. Serine proteases (e.g., thrombin) cleave a blocking peptide from the tethered ligand allowing the short peptide to interact with the receptor within the extracellular loop to affect transmembrane signaling [14]. PAR1 activation of hindbrain astrocytes by thrombin produces downstream effects to control glycemia through the release of the purinergic gliotransmitter adenosine which, in turn, act on NST neurons that are part of the counter-regulatory response circuitry. This is supported by the facts that: pretreatment with a PAR1 antagonist blocked thrombin's effect to evoke hyperglycemia; suppression of astrocytic signaling also prevented thrombin-triggered changes in glycemia; and purinergic antagonists blocked thrombin-induced hyperglycemia. Thus, the involvement of purinergic gliotransmitter release in the thrombin induction of hyperglycemia is paralleled by our recent work showing that astrocytes activated by low glucose challenge trigger counter-regulatory responses through the release of purinergic agonists [8,9].

Thrombin and CNS-Mediated Respiratory Arrest

Our studies of the effects of thrombin to dysregulate glycemic control produced a completely unexpected result. That is, thrombin in the dorsal medulla not only caused increases in glycemia, but also produced a rapid, dramatic, and, potentially, lethal suppression of respiratory rhythm. Even fourth ventricular application of thrombin (4U) provoked a rapid suppression of respiration that required nearly 30 minutes to recover to near normal patterns. As a point of reference, a blood clot 50 um in diameter can produce up to several units of thrombin [25] **(Figure 1)**.

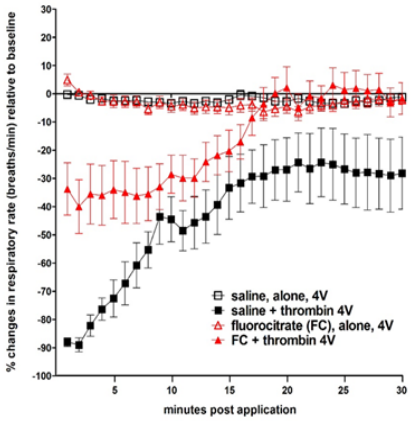

Figure 1: Plot of respiratory depression following fourth ventricular (4V) exposure to thrombin. 4V application of thrombin produced a dramatic and nearly immediate suppression of respiration that persisted for more than 30 mins after application (black boxes). Neither saline (open boxes) nor fluorocitrate (FC; astrocyte blocker; open triangles), alone, had any demonstrable effects on respiration. However, pretreatment of the hindbrain with FC markedly altered the dynamics of this respiratory response to thrombin in that the depression was not as large nor lasted as long. (Adapted from Rogers, Hasser, and Hermann; AJP 2020).

Unilateral nanoinjection of as little as 0.0003U of thrombin directly into the NST significantly depressed phrenic nerve frequency activity and increased apnea duration. As in the case with thrombin dysregulation of glycemic control, the effects of hindbrain thrombin to produce respiratory arrest were due to the activation of astrocytes and subsequent purinergic gliotransmission within the NST [14].

Perspective

Hindbrain astrocytes are emerging as important sources of chemosensory control over homeostatic functions such as glucose homeostasis, gastrointestinal, cardiovascular and respiratory control [7-9,16,17]. Often, these functions are regulated by astrocyte release of the purines, ATP and adenosine [8,9]. In particular, adenosine has been identified as a potent inhibitor of hindbrain respiratory rhythmogenesis [26]. Suppression of purinergic gliotransmission seems to block these pathological outcomes of thrombin exposure and this pharmacologic approach might prove useful in the immediate management of the effects of traumatic-produced thrombin effects on the brain.

Our observations of the effects of thrombin in the dorsal hindbrain to provoke pathological changes (first in gastrointestinal function [6], now in glycemic and respiratory control [14]), reveal the profound and damaging effects thrombin formation secondary to severe trauma, burns, or infection can have on critical autonomic control circuitry. In the case of glycemia control, modest thrombin effects, consistent with survivable injury, can increase circulating glucose, thereby enhancing fuel availability. However, the significant increase in circulating thrombin characteristic of truly severe injury or infection and the associated astrocyte-mediated collapse of autonomic controls is clearly pathophysiological [27-29].

Conclusion

The data suggesting that thrombin may have a powerful effect to cause respiratory arrest through action on hindbrain respiratory control circuits may be relevant to understanding the relationship between COVID-SARS infections and respiratory failure and arrest. Respiratory failure in COVID is complex and multifactorial. It is highly likely that respiratory failure is mainly caused by a dramatic and unbridled inflammation of alveoli and the resultant physical obstruction to air exchange. But this process is also associated with a massive and disseminated thrombosis and an increase in circulating thrombin. Direct thrombin effects in the hindbrain to suppress CNS-generated respiratory rhythm could add unsurvivable suppression of breathing to already seriously compromised air exchange mechanisms.

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