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REVIEW

Crosstalk between catecholamines and erythropoiesis

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BACKGROUND: Erythropoiesis is regulated by a range of intrinsic and extrinsic factors, including different cytokines. Recently, the role of catecholamines has been highlighted in the development of erythroid cell lineages.
OBJECTIVE: This study focuses on the biological links interconnecting erythroid development and the sympathetic nervous system. The emerging evidence that underscores the role of catecholamines in the regulation of erythropoietin and other erythropoiesis cytokines are thoroughly reviewed, in addition to elements such as iron and the leptin hormone that are involved in erythropoiesis.
METHODS: Relevant English-language studies were identified and retrieved from the PubMed search engine (1981–2017) using the following keywords: "Erythropoiesis", "Catecholamines", "Nervous system", and "Cytokines."
RESULTS: Chronic social stress alters and suppresses erythroid development. However, the physiological release of catecholamines is an additional stimulator of erythropoiesis in the setting of anemia. Therefore, the severity and timing of catecholamine secretion might distinctly regulate erythroid homeostasis.
CONCLUSION: Understanding the relationship of catecholamines with different elements of the erythroid islands will be essential to find the tightly regulated production of red blood cells (RBCs) in both chronic and physiological catecholamine activation.

Keywords erythropoiesis, cytokines, catecholamines, chronic social stress, nervous system

Innervation of the bone marrow

Adrenergic and cholinergic nerve fibers have been found in the bone marrow (BM) and they contribute to the regulation of skeletal turnover and hematopoiesis (Artico et al., 2002). Recently, it has been shown that sympathetic nerve terminals interact with stromal cells with enriched expression of stromal cell-derived factor 1 (SDF-1) and Beta3 (β3) adrenergic receptors (Arranz and Méndez-Ferrer). In fact, these nerve fibers are closely associated with cells expressing green fluorescent protein (GFP) under the control of the 1.8-kb fragment of the *Nestin* gene that contains the second intron (Méndez-Ferrer et al., 2010). Furthermore, catecholamines are involved in the mobilization of hematopoietic stem cells (HSCs) through suppression of osteoblasts and alteration of the expression of genes involved in egression of cells from the BM (Saba et al., 2013). Moreover, the HSC-mobilizing effect of granulocyte colony-stimulating factor (G-CSF) depends on multiple signals, some of which are derived from the sympathetic nervous system (Katayama et al., 2006). However, some require increased levels of proteolytic enzymes or regulated expression of genes involved in egress/migration such as SDF-1 and C-X-C chemokine receptor type 4 (CXCR4) (Saba et al., 2013).

HSCs express a variety of neural receptors, including adrenergic, tachykinins, opioids, and somatostatin, which play different roles in various stress conditions (Katayama et al., 2006; Kalinkovich et al., 2009; Isern and Méndez-Ferrer, 2011). Adrenergic receptors (ADRs) are important neural receptors, which are expressed on HSCs from cord blood, peripheral blood, and BM (Spiegel et al., 2007). The expression level and type of neural receptors differ at various development stages of HSCs; however, it is well established that ADRs are key players in transmitting neural signals to the BM (Méndez-Ferrer, Battista, 2010). Furthermore, ADR

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receptors are expressed on BM stromal cells, including mesenchymal stem cells (MSCs), osteoblasts, adipocytes, adventitial reticular, and vascular cells, which are capable of regulating erythropoiesis (Hajifathali et al., 2014). Interestingly, secretion of catecholamines is not an exclusive feature of neural cells, but several non-neural cells can also produce neurotransmitters (Kuçi et al., 2006). The mRNA of tyrosine hydroxylase (TH), the rate-limiting enzyme in catecholamine synthesis, has been demonstrated in B and T lymphocytes and catecholamines have been shown to exert autocrine and paracrine mechanisms on lymphocytes (Maestroni et al., 1998; Cosentino et al., 2000). Moreover, macrophages and some cell lines such as U937 (promonocytic) produce catecholamines as their major metabolites. These findings are relevant for a better understanding of the regulatory role of the nervous system in immune function and hematopoiesis (Cosentino et al., 2000; Brown et al., 2003). However, the interaction of neural cells with hematopoietic/BM stromal cells is thought to be more complicated than previously anticipated, and might have implications in the regulation of BM niches, including the erythroblastic islands.

Catecholamines and erythroblastic islands

Erythropoiesis is a multi-step process that occurs at different developmental stages, including primitive, embryonic, and definitive erythropoiesis, which occur within the yolk sac/aorta-gonads-mesonephros (AGM), fetal liver, and BM, respectively (Baron et al., 2013). The production and mobilization of erythroid cells and HSCs from one hematopoietic organ to another requires the specific expression of transcription factors as well as the release of various hormones (Baron et al., 2013). The early stages of hematopoiesis in AGM are thought to be under the regulation of the nervous system. It has been demonstrated that GATA binding protein 3 (GATA3)-regulated secretion of catecholamine from sympathoadrenal cells contributes to the emergence of HSCs in the AGM region. Moreover, disorders related to catecholamine release can abrogate HSC production (Fitch et al., 2012). GATA3 is a key transcription factor for neural and hematopoietic development, and its deficiency causes severe abnormalities in the nervous system as well as megakaryocytic and erythroid development (Pandolfi et al., 1995; Chen and Zhang, 2001). GATA3 interacts with other GATA factors for neural development (Nardelli et al., 1999; Tsarovina et al., 2004). Alpha 2-adrenergic receptor (α2-ADR) is mainly expressed on fetal erythropoietic organs, and contains elements on the promoter for binding of GATA1 and nuclear factor, erythroid 2 (NF-E2). However, the interaction of erythropoiesis transcription factors such as GATA-1, friend of GATA-1 (FOG-1), GATA2, v-myb avian myeloblastosis viral oncogene homolog (c-myb), erythroid krüppel-like factor (EKLF), and stem cell leukemia (SCL) with catecholamines has not yet been defined.

Erythroblastic islands were first described based on careful analysis of sections of the BM in which erythroid progenitors proliferate, differentiate, and enucleate (Chasis and Mohandas, 2008). These islands are composed of erythroid blasts and progenitors (about 5–30 in human marrow) surrounding a central macrophage as a "nurse" cell that secretes various cytokines and enzymes, provides iron for maturation of erythroid cells, and phagocytoses the expelled nuclei of these cells (see 50th anniversary review by Chasis and Mohandas) (Chasis and Mohandas, 2008). These hematopoietic sub compartments are found in both adjacent and non-adjacent regions of BM sinusoids, and are localized in the entire marrow space (Fig. 1) (Yokoyama et al., 2003). Various positive and negative regulatory factors such as oxygen tension, cytokines, hormones, and even catecholamines can determine future erythropoiesis (An and Mohandas, 2011). Indeed, erythropoiesis is dependent upon conditions governing the BM or even those beyond the human marrow as well as the balance between feedback mechanisms within the island niche. The regulatory role of the nervous system is critical not only in the stromal BM but also in erythroid development, and can control erythropoiesis under various conditions.

Cells of the erythroid linage express adrenergic, dopamine, and serotonin receptors (Chuang et al., 1992). However, the neuroendocrine effect on differentiation of erythroid precursors is controversial, and remains poorly understood. Injury to autonomic nerves in the BM can lead to anemia and suppressed erythropoiesis. Studies have indicated that erythroid progenitors such as burst forming unit-erythroid (BFU-E) and colony forming unit-erythroid (CFU-E) are inhibited following sympathectomy using the neurotoxic agent, 6-hydroxydopamine (6-OHDA) (Penn et al., 2010). Moreover, 6-OHDA-treated rats have significantly decreased hemoglobin (Hb), hematocrit (HCT), and red blood cell (RBCs) seven days after treatment. Restoration of the nervous activity with injection of epinephrine contributes to normalized physiological erythropoiesis (Obayashi et al., 2000). Therefore, catecholamines have a negative effect on erythropoiesis, especially in patients with severe trauma (Silverboard et al., 2005). Persistent anemia in these patients has been observed for weeks, and sometimes blood transfusion is needed to treat them (Silverboard et al., 2005; Oddo et al., 2012). In these patients, catecholamine levels in the BM is remarkably enhanced, which could affect erythropoiesis by inducing the egression of HSCs from the BM to injured tissues, resulting in shortage of hematopoietic cells in the BM (Glass et al., 2012; Pasupuleti et al., 2014). Furthermore, hyperactivation of the sympathetic nervous system could induce inhibitory cytokines such as interleukin 6 (IL-6) and tumor necrosis factor (TNF) for erythropoiesis in BM stromal cells (Fonseca et al., 2005). In addition, norepinephrine (NE) injection at a dose of 1 ng/h for a week inhibits the growth of BFU-E and CFU-E. However, administration of propranolol to individuals with damaged tissue significantly reduces post-

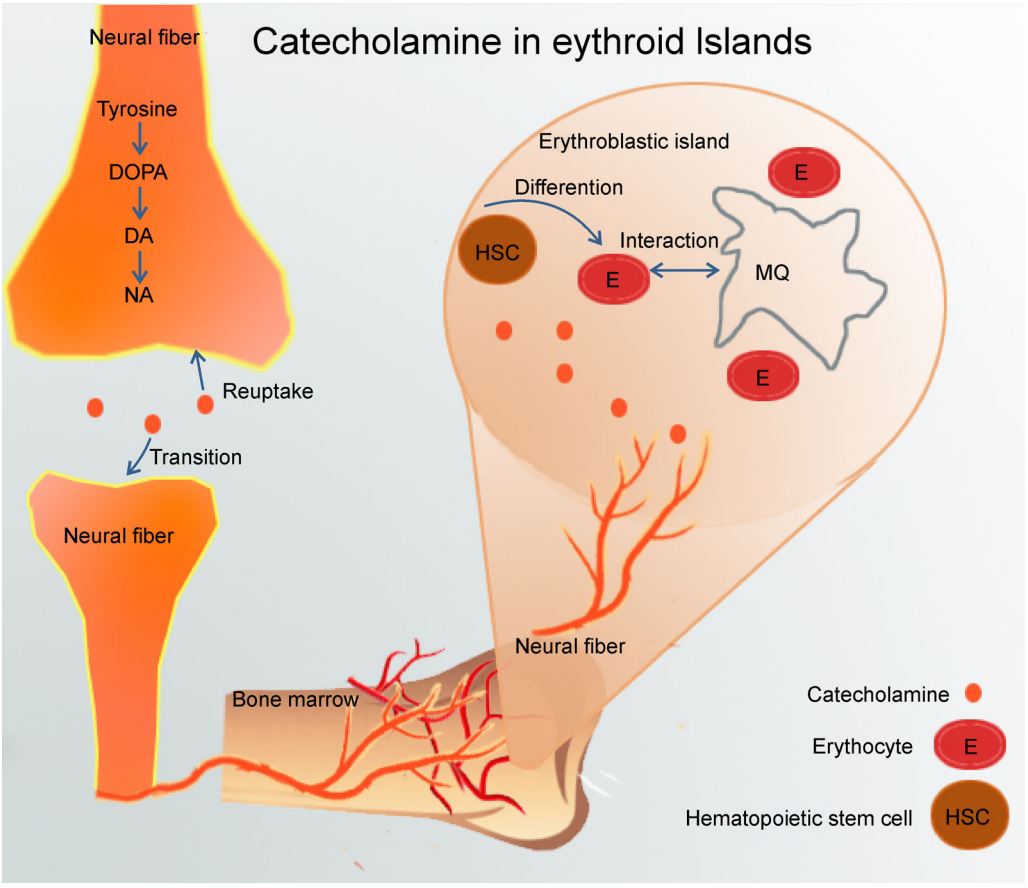

Figure 1 The position of catecholamines in erhythroblastic islands. Catecholamines released from neural fiber can affect erythroid islands, including differentiation of HSCs toward erythropoiesis and the interaction of erythrocytes with macrophages. Moreover, catecholamine production from nerve fibers is shown. Abbreviations: DOPA (D-3,4-dihydroxyphenylalanine), DA (Dopamine), NA (norepinephrine).

shock BM suppression (Elhassan et al., 2011). Voorthess et al. (2013) provided a different perspective on the role of chronic stress, indicating that chronic elevated catecholamine levels induce erythropoiesis in the BM with an increase in glucocorticoids. These findings suggest the controversial correlation between catecholamines and normal erythropoiesis. However, different *in-vitro* and *in-vivo* conditions could be effective depending on the interpretation of results.

The nature of nervous system activation is also important, in that the effect of the nervous system on erythropoiesis varies in conflict situation (CS) and paradoxical sleep deprivation (PSD) (Skurikhin et al., 2005). CS leads to increased erythrokaryocytes in the BM and reticulocytosis in the peripheral blood via dopamine, indicating a high contribution of catecholamines compared to erythropoiesis cytokines, which play a regulatory role (Provalova et al., 2003; Skurikhin et al., 2005). However, PSD leads to serotonin-suppressed erythropoiesis, and serotonin inhibitors can restore physiological hematopoiesis (Provalova et al., 2002; Skurikhin et al., 2005). Observational studies have determined that increased levels of C-reactive protein (CRP) and pro-inflammatory biomarkers in conditions of poor sleep duration suppress erythropoiesis (Knutson et al., 2007). Therefore, the type of secreted neurotransmitter affects the erythropoietic response.

Cross-talk between the nervous system and erythropoietin (EPO) – from secretion to signaling

The type of cytokine secreted, and the developmental stage of erythropoiesis are directly correlated. Although early stages of erythroid progenitors (BFU-E) are strongly influenced by c-kit, EPO is the major mediator of late erythroid progenitors and it is predominantly secreted in the kidneys (Nezuet al., 2014). EPO, a 34-kDa glycoprotein hormone, acts on the precursor of erythroid cells by inducing their proliferation and differentiation into mature erythrocytes. In addition, it is crucial for the survival of erythroid cells, especially CFU-E (Schneider et al., 1997; Moura et al., 2015). Embryos lacking EPO receptors die at 11–12.5 of gestation with markedly diminished erythropoiesis. These findings implicate EPO signaling is the fundamental growth factor in definitive erythropoiesis. Other cytokines/growth factors cannot likely

compensate for missing or aberrant EPO signaling (Schneider et al., 1997).

The expression of EPO mRNA is directly correlated with renal oxygen levels; therefore, hypoxia would induce an EPO secretory response (Schneider et al., 1997). However, other agents such as renal catecholamines and renin-angiotensin can interfere with the process of EPO release. For instance, a much weaker response to hypoxia-induced EPO has been observed in ischemia in kidneys, postulating the role of second messengers such as renal catecholamines in the oxygen-sensing mechanism that mediates EPO production (Scholzet al., 1991). The administration of beta (β)-ADR blockers, such as propranolol and butoxamine, to rabbits exposed to hypoxia inhibits EPO secretion (Finket al., 1975). 6-OHDA induces apoptosis in pheochromocytoma 12 (PC12) through decreased mitochondrial expression of B cell lymphoma 2 (Bcl-2), and significantly reduces EPO levels (Ge et al., 2012). Studies in humans showed a higher level of EPO with stimulating renin angiotensin system (RAS) following administration of β2ADR agonist (fenoterol) under normoxic conditions (Freudenthaler et al., 1999). Concomitant treatment with losartan (inhibitor of RAS) and fenoterol had no significant effect on EPO concentration (Freudenthaler et al., 1999), demonstrating positive feedback of adrenergic agonists on EPO secretion through RAS activation. However, Gebhard et al. demonstrated the role of renal nerves in regulating EPO via the neuropeptide Y (NPY) receptor but not β-ADRs (Gebhard et al., 2006). Other factors that induce EPO include prostaglandin E2 (PGE2). PGE2 can induce the liberation of EPO via catecholamines (Jewell et al., 2012). Moreover, PGE2 improves EPO-induced signaling by mediating the cyclic adenosine monophosphate/protein kinase A/CAMP Responsive Element Modulator (cAMP/PKA/CREM) pathway (Boer et al., 2002). EPO release under hypoxic conditions is mediated through decreased oxygen in the kidneys, but also through hypoxia in the brain as a result of elevated plasma levels of EPO (von Wussow et al., 2005). Furthermore, hypoxia also affects catecholamine release through unknown mechanisms (White and Lawson, 1997). In fact, hypoxia increases hematopoiesis through crosstalk between EPO and catecholamines. EPO receptors are expressed on non-erythroid clonal lines (e.g., PC12) and neural cells that have supportive roles in nervous system development through decreased apoptosis, increased survival of neural cells, and the release of catecholamines (Masuda et al., 1993). Taken together, a positive feedback loop is suggested between catecholamine stress hormones and EPO.

Exposure to physiological doses of a β-adrenergic agonist (isoproterenol) induces differentiation of K562 cells to erythroid by stimulating p38 mitogen-activated protein kinases (MAPK)/cAMP signaling (Mei et al., 2013). β-agonist also leads to increased production of fetal hemoglobin (HbF) from these cells (Mei et al., 2013). Comparison of different neural receptors (β, α) indicates that the growth of the erythroid colony is mediated through stimulation of β-ADRs but not α-ADR. β-ADRs are the main receptors for most BM-cells such as MSCs and HSCs (Mladenovic and Adamson, 1984). Selective inhibition of β2-ADR results in the suppression of catechol-dependent increase in CFU-E growth (Mladenovic and Adamson, 1984). However, under these conditions, the presence of EPO is required for adrenergic-increased erythroid colony growth. In addition, blocking the adrenergic pathway has no substantial inhibitory effect on EPO-induced erythroid formation, which suggests that EPO and catecholamines have synergic biological activities compared to other signaling pathways (Mladenovic and Adamson, 1984).

Binding of EPO to its specific receptor (EPO-R) on erythroid progenitors leads to activation of different signaling pathways, including janus kinase/signal transducer and activator of transcription JAK/STAT5, MAPK, and peptidase inhibitor 3/V-Akt murine thymoma viral oncogene homolog 1 (PI3/AKt). Phosphorylation-stimulated homodimerization of STAT5 activates the genes involved in apoptosis, such as B cell lymphoma-extra large (BCl-X) (Boer et al., 2003). Moreover, the inhibitory effect of EPO on apoptosis is observed in PI3K/AKt with inactivation of proapoptotic molecules (Boer et al., 2003). Furthermore, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation by JAK2 and PI3K allows the expression of anti-apoptosis molecules after translocation into the nucleus (Cheung and Miller, 2001). In general, the EPO signaling pathway has a marked role in increased survival of erythroid progenitor cells. Nervous signaling in the regulation of different stages of hematopoiesis differentiation is often mediated by β-ADR (Katayama et al., 2006).

β-ADR belongs to a large family of G-protein coupled receptors (GPCRs) (Cole and Sood, 2012). Gas activation increases intracellular levels of cAMP by adenylyl cyclase. This leads to the stimulation of protein kinase A (PKA), which in turn phosphorylates various target proteins, including β-ADR kinase (BARK) (Rosenbaum et al., 2009). STAT3 and focal adhesion kinase (FAK) are activated through beta-adrenergic receptor kinase (BARK)-stimulated sarcoma (Src) kinases, leading to the modulation of cell trafficking and cellular resistance to apoptosis (Rosenbaum et al., 2009). Moreover, BCL2 family members can be activated by PKA, leading to increased cell survival (Rosenbaum et al., 2009). MAPK and PI3K signaling pathways for β-ADR stimulate inflammation and tissue invasion by activator protein 1/E26 transformation-specific (AP-1/Ets) and Akt-dependent activation of anti-apoptosis, respectively (Rosenbaum et al., 2009; Cole and Sood, 2012). Synergistic activation of mitogen-activated protein (MAP) kinase in EPO and β-ADR has been demonstrated in the expansion of erythroid cells. Moreover, the PKA/CAMP responsive element binding protein (CREB) pathway has a favorable effect on erythropoiesis, suggesting the synergic effect of β-ADR and EPO signals (Skurikhin et al., 2008). The severity and timing of β-

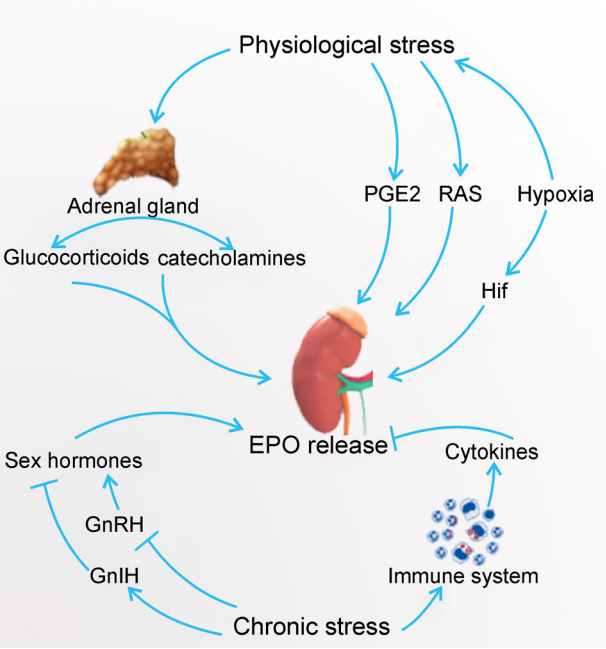

Figure 2 Function of physiological and chronic stress in EPO release. In physiological stress, the secretion of EPO increases through systems RAS, glucocorticoids, and HIF. Chronic stress-inhibits EPO release through inflammatory cytokines and inhibition of sex hormones. Abbreviations: PGE2 (Prostaglandin E2), RAS (Renin angiotensin system), HIF (Hypoxia inducible factor), EPO (Erythropoietin), GnRH (Gonadotropin releasing hormone), GnIH (Gonadotropin-inhibitory hormone).

ADR signaling activation could be both positive and negative regulators for EPO signaling. For instance, in acute stress conditions following significant secretion of catecholamine, the inhibitory effect of adrenergic signals on erythropoiesis was observed via p38/MAPK signaling (Schraml et al., 2009). Indeed, adrenergic agonists decrease HSC division and formation of erythroid colonies through p38/MAPK-upregulated reactive oxygen species (ROS) and p16. The role of ROS and p16 in DNA damage has been demonstrated, and these molecules induce cell aging and growth inhibition (Schraml et al., 2009). Moreover, chronic stress negatively affects erythropoiesis and results in anemic conditions. Most of the mechanisms related to chronic stress are discussed below.

Effect of stimulated nervous endings on cytokines involved in erythropoiesis

In addition to EPO, cytokines involved in the development of erythropoiesis are produced through the BM microenvironment such as central macrophages of erythroid islands, endothelial and reticular cells as well as MSCs (An and Mohandas, 2011). The nervous system can mediate the expression of stromal BM-producing cytokines (see details in Table 1). Catecholamines can upregulate inflammatory cytokines (Flierl et al., 2009). Elevated levels of inflammatory cytokines, mediators in diseases such as rheumatoid arthritis and Alzheimer's disease, as well as sleep deprivation lead to anemia (Rubio-Perez and Morillas-Ruiz, 2012). Moreover, the pathophysiology of major depression in relation to anemia could be an interesting clue to understanding the link between stress, inflammatory cytokines, and anemia (Miller et al., 2009). It has been shown that NF-κB, extracellular signal-regulated kinase 1/2 (ERK1/2), and p38 signaling pathways regulate many pro-inflammatory genes including IL-1, IL-6, and TNF (Kefaloyianni et al., 2006). Downstream mediators of β-ADR as well as pro-inflammatory cytokine receptors on macrophages and immune cells has been demonstrated through ERK1/2 and p38-dependent pathways and are independent of PKA and NF-κB signaling (Tan et al., 2007; Flierl et al., 2009). However, lipopolysaccharide (LPS), which increases inflammatory cytokines, suppresses β-agonists through inhibition of NF-κB activation in macrophages (Farmer and Pugin, 2000). Moreover, macrophage-derived catecholamines seem to act in a positive feedback and autocrine fashion for further increase in acute inflammatory response (Flierl et al., 2009). Catecholamines can stimulate or inhibit inflammatory cytokines such as TNF-α depending upon the activated receptor type. Therefore, α- and β- ADR appear to play stimulatory and inhibitory roles on TNF-α, receptively (Elenkov and Chrousos, 1999). Further studies are required to elucidate the direct effect of neural receptors on cells, including central macrophages of erythroid islands and immune cells of the human BM. Table 1 shows the effect of catecholamines on cytokines involved in erythropoiesis. Some inflammatory cytokines can increase the levels of catecholamines. For example, IL-1-stimulates catecholamine release from neuro-terminals and β-ADR-dependent glucocorticoid secretion (Rivier et al., 1989).

Under conditions of chronic stress, increased levels of catecholamines activate the hypothalamic–pituitary–adrenal (HPA) axis leading to increased secretion of corticotrophin-releasing hormone (CRH) (Tsigos and Chrousos, 2002). This hypophysiotropic hormone, in turn, acts on the pituitary gland to stimulate adrenocorticotropic hormone (ACTH) expression, and its release into the bloodstream, from which glucocorticoid production is induced in adrenal glands (Tsigos and Chrousos, 2002). The well-known evidence on direct involvement of glucocorticoids in erythropoiesis is called Cushing's syndrome, in which polycythemia is seen as an early clinical manifestation with significant levels of EPO (Magiakouet al., 2006). Glucocorticoid receptors (GRs) belong to the nuclear receptor super family, bind to their ligand, undergo homo-dimerization, and translocate into the nucleus. Cortisol binding to its receptor induces BFU-E, and the number of early erythroid progenitors is increased through stimulating the expression of receptor tyrosine kinase (Kit), myeloblastosis (Myb), and LIM domain only 2 (LMO2), as well as inhibiting GATA1 (von Lindern et al., 1999). Furthermore, cortisol decreases the inflammatory response via inhibition of NF-κB activation (Unlap and Jope, 1995).

Glucocorticoids are required for the rapid expansion of erythroid cells under immediate stress conditions (Bauer et al., 1999; Hattangadi et al., 2011). However, prolonged stress alters glucocorticoid-induced erythropoiesis. Excessive glucocorticoid production in circulation mediates feedback to the brain to regulate corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) secretion (Tsigos and Chrousos, 2002). Sustained stress regulates immune responses with resistant tissue macrophages in the BM, spleen, and lungs to glucocorticoids (Stark et al., 2001). Taken together, production of inflammatory cytokines that reduce EPO synthesis is increased from these glucocorticoid-insensitive cells (Lenget al., 1996; Wohleb et al., 2011). However, the mechanism of desensitization of the glucocorticoid receptor by chronic social threat on HSCs or erythroid progenitors remains unknown. Desensitization of the glucocorticoid receptors are seen in people facing long-term social hardships such as low economic status or post-traumatic stress disorders, who have anemia and increased expression of genes involved in inflammation, although they have elevated circulating glucocorticoid levels. Interestingly, the inhibitory function of glucocorticoids in the final differentiation of erythroid cells has been indicated (Tsiftsoglou et al., 1979; Leung and Gidari, 1981). Simultaneous exposure of erythroblasts with dexamethasone (DXM) and EPO results in inhibition of erythroid maturation without activation of apoptosis (Stellacci et al., 2009).

Glucocorticoid receptor (GRs) signaling and EPO both lead to STAT5 phosphorylation. Indeed, EPO and DXM individually stimulate STAT-5, inducing beta-globin expression for the maturation of erythroblasts (Stellacci et al., 2009). However, phosphorylated STAT-5 has not been observed in the co-stimulatory role of BFU-E with EPO and DXM due to signaling interference between EPOR and GR inside the cell, leading to inhibition of EPO signaling (Stellacci et al., 2009).

The interaction between the nervous system and body iron storage

Iron is a key element for developing new blood cells. Decreased iron storage could lead to reduced hemoglobin resulting in iron deficiency anemia (IDA) (Beguin and Jaspers, 2014). Studies have shown that chronic stress in rats results in decreased serum iron, serum ferritin, and BM iron (Wei et al., 2008). Moreover, the level of serum transferrin receptor and red cell distribution width (RDW) are increased, representing stress-inhibited erythropoiesis and formation of hemoglobin (Wei et al., 2008). The precise mechanism of catecholamines with iron is unknown; however, it has been observed that catecholamine elevates hepatic iron stores and hepcidin. Hepcidin is an acute phase protein, the expression of which in the liver is affected by inflammatory cytokines such as IL-6 (Nemeth et al., 2003). The link between chronic stress, hepcidin, and IL-6 has been demonstrated. The nervous system upregulates hepcidin expression through increased IL-6 and restricts the availability of iron storage for erythroid islands (Zhao et al., 2008). For instance, recent studies have demonstrated the interaction between iron levels and endurance exercise through the hepcidin/inflammatory cytokine system. Increased hepcidin and IL-6 has been suggested as a new mechanism for the incidence of iron deficiency among athletes (Peeling et al., 2008). However, an elevated level of catecholamines has been shown during training (Zouhal et al., 2013). Therefore, decreased catecholamine iron levels in endurance exercise via increased hepcidin and inflammatory cytokines have been considered. All three neurotransmitters (norepinephrine, epinephrine, and dopamine) are capable of binding to transferrin (Tf). The physiological function of Tf is iron transport, and it is released to Fe-dependent cells with a serum concentration of approximately 35 μM (Lambert et al., 2005). Complex formation of catecholamines with Fe (III) within Tf results in liberation of iron from Tf and decreased saturation of Tf (Sandrini et al., 2010). These data suggest iron-restricted suppression of erythropoiesis by catecholamines due to inaccessible iron for erythropoiesis.

Erythropoiesis-regulated hormones such as sex hormones (estrogen and testosterone) play a mediatory role on hepcidin and iron. Studies have demonstrated that 17-β-estradiol-suppressed hepcidin transcription leads to increased iron uptake (Yang et al., 2012). This mechanism can explain the increased iron stores following oral contraceptive use (Yang et al., 2012). Furthermore, estrogen receptors (ERs) are found on HSCs, and stimulation of ERs induces apoptosis and proliferation in short-term and long-term HSCs, respectively (Sanchez-Aguilera et al., 2014). However, estrogen-dependent production of EPO has been demonstrated (Yasuda et al., 1998). Testosterone injection also elevates serum iron levels and transferrin saturation by downregulating hepatic hepcidin mRNA expression and upregulating renal EPO levels (Guo et al., 2013). Testosterone inhibits the interaction of hepcidin with bone morphogenic protein (BMP), and interferes in BMP/mothers against DPP homolog (Smad) signaling for hepcidin function (Guo et al., 2013). Data concerning the cross-talk between sex hormones and catecholamines are contradictory. However, estradiol seems to negatively modulate catecholamine secretion from adrenal medulla and increases catecholamine release as well as tyrosine hydroxylase (TH) expression from the preoptic area of the hypothalamus (Hamill and Schroeder, 1990; Kim et al., 2000; Dart et al., 2002; Yanagihara et al., 2005). The feedback of catecholamines on sex hormones is likely to be negative. β-ADR agonists inhibit 17-beta-stradiol and increase testosterone (Walters and Sharma, 2003). However, individuals facing chronic stress have substantially lower testosterone levels, demonstrating the role of continuous secretion of catecholamines on the suppression of sex hormones (Francis, 1981).

Furthermore, chronic stress inhibits gonadotropin releasing hormone (GnRH) and stimulates gonadotropin-inhibitory hormone (GnIH), thereby suppressing sex hormones.

Thyroid hormones and their effect upon erythropoiesis are another example of the regulatory role of catecholamines. Studies have demonstrated that iron levels are associated with altered thyroid hormones. Hypothyroidism induced-IDA has been observed in diseases with dysfunction and reduced levels of thyroid hormones, implicating the important role of thyroid glands in mediating iron and erythrocyte metabolism (Antonijevic et al., 1999; Ikuyama, 2005). Moreover, this hormone has an intimate relevance with neural receptors (Popovic et al., 1977). Erythroid stimulation in the thyroid *in-vitro* has been blocked with β-ADR antagonists, particularly β2-ADR (Popovic et al., 1977). This study highlights β2-adrenergic receptor as the key player in thyroid hormone-enhanced erythroid growth (Popovic et al., 1977). Catecholamines in both systems (including the sympathetic nervous system (SNS) and adrenal medulla), in turn, activate thyroid hormones (see review by Silva and Bianco, 2008). In summary, the thyroid hormone-mediated increase in iron levels and erythropoiesis is exerted via an indirect mechanism called the stress hormone. However, in chronic stress conditions in animals, decreased serum levels of thyroid hormone, especially triiodotyronine (T3), have been observed in immune response mechanisms (Cremaschi et al., 2000).

The cooperation between leptin, stress, and erythropoiesis

Leptin is a non-glycosylated protein derived from adipocytes in both white and brown adipose tissue. Leptin mediates multiple responses to low energy levels and various metabolic changes (Kelesidis et al., 2010). Moreover, this lipid hormone has a substantial effect on the BM microenvironment. The *leptin* gene (obese gene) has been observed in adipocyte cells of stromal BM, which leads to signal transduction through receptors in primitive and more mature hematopoietic cells (Laharrague et al., 1998). The role of leptin in hematopoiesis has been demonstrated by several lines of evidence such as increased hematopoiesis through inducing lipolysis of marrow fat cells, thus expanding the number of lymphoid and myeloid progenitors (Kilroy et al., 2007; Claycombe et al., 2008). Fat cells are depleted in anemic states, and a correlation has been observed between the level of hemoglobin, red blood cells, and serum leptin (Togo et al., 2011). Furthermore, the association of leptin polymorphism with severity of anemia has been demonstrated (Vanasse et al., 2011). In major beta thalassemia patients, leptin levels were lower than in healthy subjects. The destruction of adipocytes following iron overload is a main reason for decreased leptin (Choobineh et al., 2009). However, leptin can have contradicting effects upon erythropoiesis. Studies have demonstrated increased leptin during infection and inflammation, thus inducing many acute phase factors such as IL-1, TNF, and IL-6 (Otero et al., 2005). Therefore, leptin appears to have a direct positive effect on erythroid development; however, in inflammatory conditions, it has a modulatory role in erythropoiesis.

Leptin and EPO act synergistically to enhance erythroid development (Mikhail et al., 1997). Indeed, stimulating EPO signaling is needed for leptin function in the induction of HSC differentiation to the erythroid lineage (Mikhail et al., 1997). In leptin signaling, STATs (STAT3 and STAT5) and the MAPK pathway are the main mediators (reviewed by Villanueva et al. (Villanueva and Myers, 2008). As mentioned above, EPO-activated STAT-5 has been identified as the key signaling for erythroid development. Therefore, phosphorylation and nuclear localization of STAT5 may contribute to EPO-leptin-induced HSC differentiation toward erythroid lineage.

Leptin released from adipocytes directly bind to their receptors on the ventromedial hypothalamus (VMH) in the brain, resulting in increased catecholamine secretion (Kahn and Minokoshi, 2013). Stimulating β-ADRs on adipocytes contributes to a rapid reduction in leptin release (Ricci et al., 2005). Furthermore, insulin acts as a favorable factor for erythropoiesis and contributes to increase leptin. Isoproterenol abrogates insulin-stimulated leptin with inhibition of the insulin ability to upregulate leptin biosynthesis. Indeed, catecholamines act as a negative feedback for leptin, and reduce the effects of leptin on the BM microenvironment and erythroid development (Ricci et al., 2005). In addition, in inflammatory conditions, both leptin and catecholamines suppress erythropoiesis by increased inflammatory cytokines.

Conclusion and Future directions

Considering the paucity of evidence regarding the mechanisms of catecholamine in various body conditions on erythropoiesis, a broad range of research questions emerge without answers. The physiological and clinical realization of the nervous system on human marrow by such comprehensive studies would lead to further detailed planning of research toward factors influencing catecholamines. In this review, we investigated some considerable factors such as EPO, inflammatory cytokines, glucocorticoid, iron, sex hormones, thyroid hormones, and leptin (Fig. 3). In addition to catecholamines, the association of these agents with each other was also discussed. Factors involved in erythropoiesis appear to revolve around the nervous system, and catecholamines are the centerpiece. Therefore, the severity and duration of secretion of catecholamines and the neural receptor type stimulated could affect erythroid islands by direct and/or indirect mechanisms. In temporary physiological stress and according to the body's requirements, erythroblastic islands are induced to produce a higher number

Table 1 The effect of catecholamines on cytokines involved in erythropoiesis

Cytokine	Function of cytokine on erythropoiesis	Effect of catecholamines on cytokines	Reference
SCF	Enhancing erythroid proliferation	Unknown	Mutaet al., 1995
IL-1	Suppressing erythropoiesis	Increasing IL-1 expression	Furmanski and Johnson, 1990; Hetier et al., 1991
IL-2	Inhibition of erythroid progenitors	Increasing serum level of IL-2	Burdach and Levitt, 1987; Schulte et al., 1994
IL-3	Cooperating with EPO in erythropoiesis	Unknown	Böhmer, 2004
IL-6	Inhibiting erythropoiesis	Increasing the expression of IL-6	Fonseca et al., 2005; McCranor et al., 2014
IL-9	Supporting erythroid development	Unknown	Donahue et al., 1990
IL-10	Inhibiting burst-forming unit-erythroid growth	Inducing IL-10	Oehler et al., 1999; Woiciechowsky et al., 1999
IL-11	Stimulating multiple phases of erythropoiesis	Unknown	Quesniaux et al., 1992
TNF-α	Retarding proliferation and inducing apoptosis in erythroid cells	Decreasing/increasing the expression of TNF-α	Rusten and Jacobsen, 1995; Elenkov and Chrousos, 1999
IFN-γ	Inhibiting erythroid differentiation by inducing apoptosis	Decreasing/increasing the release IFN-γ	Elenkov and Chrousos, 2002; Peruzzo et al., 2008
TGF-β	Inhibiting proliferation by decreasing the number of erythroid progenitor cells	Stimulating the expression of TGF-β	Kaneko et al., 2009; Huntgeburth et al., 2011

Abbreviations: SCF, stem cell factor; IL, interleukin; TNF-α, tumor necrosis factor alpha ; IFN-γ, interferon gamma; TGF-β, transforming growth factor beta.

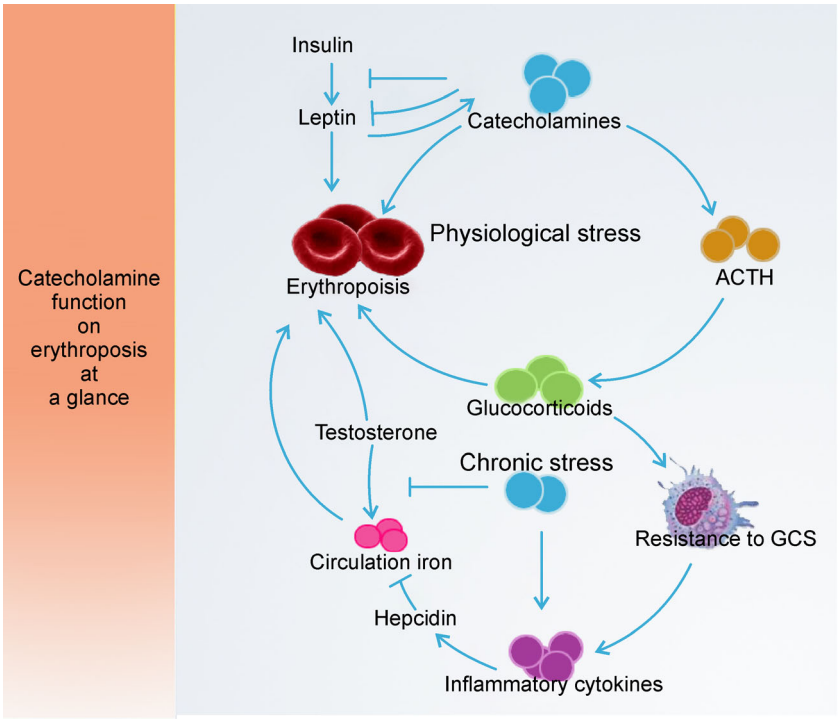

Figure 3 Effect of catecholamines in conditions of physiological and chronic stress on erythropoiesis. Factors involved in physiological stress-stimulated erythropoiesis include glucocorticoid and direct effect of catecholamines. Chronic decreased erythropoiesis due to stress is mediated by the resistance of immune cells to glucocorticoids and increased levels of inflammatory cytokines that inhibit hepcidin and block testosterone-stimulated circulating iron in elevated erythropoiesis. The increase of catecholamines by leptin has a negative feedback effect for leptin release and insulin-stimulated leptin. This inhibits leptin-stimulated erythroid development. Abbreviation: ACTH (Adrenocorticotropic hormone).

of circulating erythroid cells. Moreover, catecholamines secreted by neural and non-neural cells have a positive effect on erythroid development. However, chronic intermittent stress induces anemia due to elevated sympathetic tone leading to decreased EPO levels, decreased circulating iron through different factors such as increased inflammatory cytokine, as well as altered levels of various hormones and other agents. Therefore, the current challenge is directed at

unraveling the nervous system mechanisms in both physiological and chronic stress on cellular biology erythroblasts. Accurate examination of their effect on humans would provide useful insights to develop targeted surveillance on individuals under stress as well as novel therapeutic interventions for stress-induced anemia.

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Compliance with ethics guidelines

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