The Pivotal Role of Beta-adrenoreceptors in Critical Illness Pathophysiology

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IV

Introduction

The coordinated, emergent regulation of nervous, endocrine, hemodynamic and metabolic processes in response to critical illness is characterized by marked release of catecholamines. Despite several-fold increases in circulating catecholamines, which correlate with clinical outcome, there is a limited understanding of the receptor and cellular consequences of this fundamental critical illness response. Beta-adrenoreceptors are pivotal in the response to this catecholamine surge, playing disparate roles in shaping physiological responses during different stages of critical illness. Here we review mechanisms and common disease processes through which acute and chronic alterations in β-adrenoreceptor physiology may affect important components of critical illness and discuss emerging therapeutic roles for beta-adrenoreceptor manipulation.

New Concepts in Adrenoreceptor Signaling Biology

The original concept for the consequences of activation of β_1- and β_2-adrenoreceptors by catecholamines involving a common linear signaling pathway has changed dramatically. The classic paradigm proposed that agonist binding induces conformational changes in both receptor subtypes. These conformational changes increase affinity for the stimulatory G protein (Gs, **Fig. 1**). Interaction with either the β_1 or β_2-adrenoreceptor causes Gs to disassemble into a βγ subunit and an α subunit. The α subunit activates adenylate cyclase, that uses adenosine triphosphate (ATP) to generate cyclic adenosine monophosphate (cAMP). cAMP disinhibits protein kinase A (PKA), which in turn phosphorylates a variety of targets within the cytosol, including L-type calcium channels on the cell membrane and phospholamban and ryanodine receptors on the sarcoplasmic reticulum [1]. However, only β_2- and β_3-adrenoreceptors couple to inhibitory G protein (Gi). Selective stimulation of β_1- and β_2-adrenoreceptor subtypes elicits different physiological responses. β_1-adrenoreceptor stimulation, but not β_2-adrenoreceptor stimulation, induces cardiomyocyte hypertrophy [2, 3]. Transgenic mice with cardiomyocyte-specific over expression of the β_1-adrenoreceptor develop progressive cardiac hypertrophy and heart failure, whereas β_2-adrenoreceptor transgenic mice do not show such abnormalities [4, 5]. Isolated cardiomyocytes undergo apoptosis on β_1-selective stimulation, and β_2 stimulation may protect against this [6]. These β_1- and β_2-adrenoreceptor responses cannot be adequately explained by the classic concept of differential coupling of β_1- and β_2-adrenoreceptor to Gs and Gi proteins.

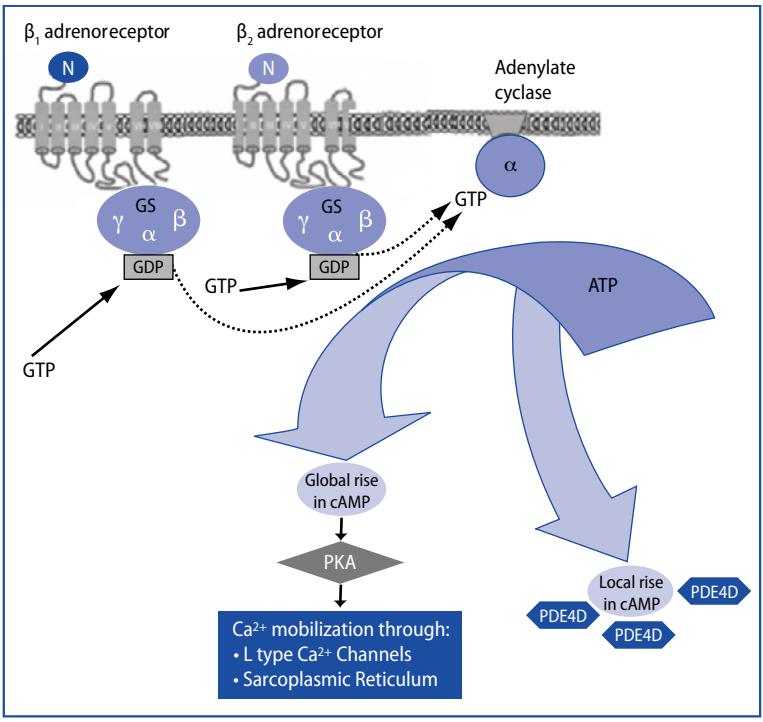

Fig. 1. During acute catecholaminergic stimulation, both beta-1 and beta-2 adrenoreceptor agonism results in the disassembly of stimulatory G-proteins (Gs) into βγ and α subunits. Subsequently, the α subunit activates adenylate cyclase, generating cyclic adenosine monophosphate (cAMP)-mediated disinhibition of protein kinase A (PKA) and consequent calcium mobilization. PDE: phosphodiesterase

Hence, a new multidimensional signaling paradigm has emerged from recent data (simplified in **Fig. 2**) where β-adrenoreceptors dynamically couple to multiple G proteins, signaling and scaffold proteins in a temporally and spatially regulated manner. Differences between β_1- and β_2-adrenoreceptor signaling occur mainly through compartmentalization of signaling events, such as the formation of signalosomes [7] and the localized control of cAMP degradation through phosphodiesterases [8]. For example, local β_1-adrenoreceptor-mediated cAMP signals propagate over a distance involving multiple sarcomeres in adult cardiomyocytes through the activation of cyclic nucleotide-gated ion channels and the guanosine-5'-triphosphate exchange factor exchange protein activated cAMP. By contrast, the β_2-adrenoreceptor-evoked cAMP signal remains strictly confined by phosphodiesterase- and Gi-independent mechanisms within specific cellular sub domains [8]. It is now recognized that the switch in coupling from Gs to Gi that occurs with β_2-adrenoreceptors is a time-dependent process. Temporal regulation is also recognized as being important in the change of β_1-adrenoreceptor signaling from PKA activation to activation of calcium/calmodulin-dependent protein kinase II [7].

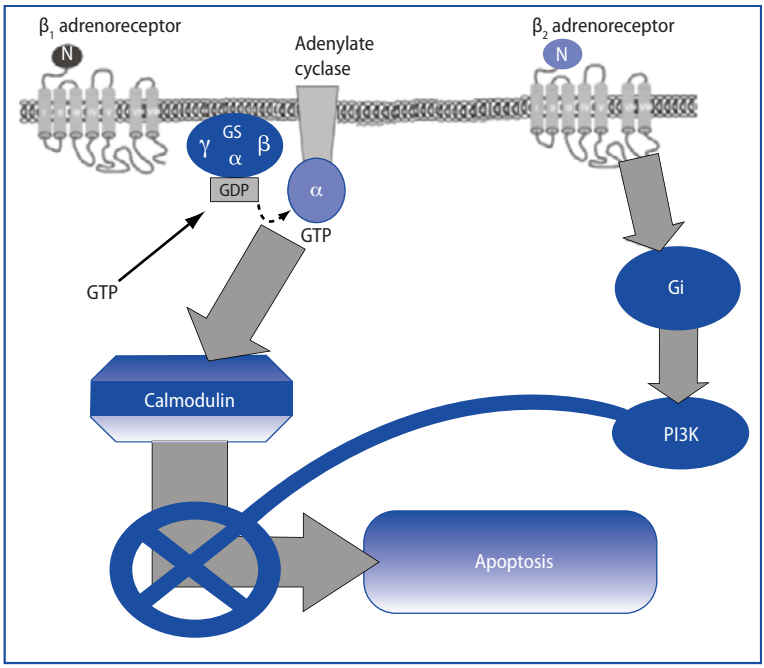

Fig. 2. Persistent activation of β-adrenoreceptors results in beta-subtype specific changes in cellular signaling. Continuous β_2 stimulation leads to inhibitory G protein (Gi) protective signaling pathways (e.g., phosphoinositide-3 kinase, PI3K) which reduces apoptosis. Temporal changes in β_1-adrenoreceptor stimulation lead to calmodulin mediated pathways associated with pro-apoptotic pathways.

Desensitization of Beta-adrenoreceptors

β_1- and β_2-adrenoreceptor subtypes also differ in terms of the processes by which they undergo desensitization during continuous and prolonged activation (**Fig. 3**). Two patterns of rapid desensitization have been characterized for G-protein-coupled receptors [9]. Homologous desensitization mainly involves G-protein-coupled receptor kinases and arrestins; heterologous desensitization is executed mainly through PKA and protein kinase C (PKC) [10]. Persistent agonist activation of β_1-adrenoreceptors results in desensitization by reducing the number of available receptors on the cell surface [10]. Degradation of receptors after internalization, together with a decrease in receptor mRNA provide the mechanisms whereby the reduction persists. β_1-adrenoreceptors are desensitized when agonist-occupied receptors are phosphorylated by PKA and by G protein-coupled receptor kinase 2 (GRK2), which is also called beta-adrenergic receptor kinase 1 (betaARK1) [10]. The cellular expression of GRK2 increases during continuous β_1-adrenoreceptor stimulation. Following receptor phosphorylation, binding of a small protein, known as β-arrestin, sterically blocks G protein activation; beta-arrestin binding also directs the internalization of desensitized receptors. Studies of mice over-expressing β_1-adrenoreceptors suggest that continuous β_1-adrenoreceptor stimulation leads to cardiomyocyte toxicity [4]. Studies in which the β_1/β_2 agonist, isoproterenol, was administered for prolonged periods of time to β_2-adrenoreceptor knockout mice also support this finding [11].

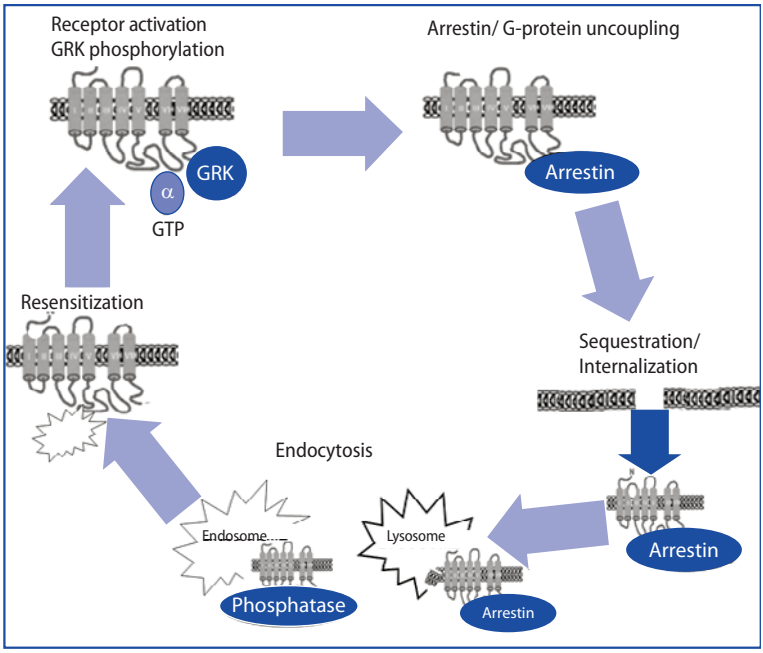

Fig. 3. The β_2-adrenoreceptor as a model for β-adrenoreceptor downregulation. Following binding of the β_2 agonist, G protein receptor kinases (GRKs) phosphorylate the receptor. Arrestin proteins bind to the phosphorylated β_2-adrenoreceptor, causing uncoupling from G proteins. Arrestins may also enable the delivery of the β_2-adrenoreceptor to clathrin-coated pits for endocytosis by endosomes or lysosomes. In endosomes, dissociation of arrestin and phosphatase mediated dephosphorylation resensitizes the β_2-adrenoreceptor, permitting it to recycle back to the plasma membrane. Alternatively, lysosomes degrade the β_2-adrenoreceptor arrestin complex.

The desensitization of β-adrenoreceptors during critical illness is associated with poorer clinical outcome. Preservation of cardiac and metabolic responses to exogenously administered dobutamine, dopamine, and epinephrine are associated with markedly better survival [12]. Experimental and clinical data have demonstrated that lactate production in the muscle is linked to epinephrine-β_2 receptor mediated stimulation of the Na^+, K^+-ATPase pump, independent of tissue hypoxia [13]. The ability to produce, and clear, more lactate following catecholamine administration in stable, non-lactatemic patients is associated with higher survival rates [14].

Catecholamine-induced Immune Dysregulation

Adrenoreceptor desensitization is a central mechanism involved in catecholamine-induced immune dysregulation. Sympathetic/adrenomedullary activity controls the expression of peripheral adrenoreceptors in target tissues, including immune cells [15]. Through direct communication via sympathetic nerve fibers that innervate lymphoid organs, catecholamines modulate mouse lymphocyte proliferation, differentiation, and cytokine production of rodent T cells and human peripheral blood mononuclear cells [15]. These interactions are facilitated by adrenergic receptors

expressed on a range of immune cells, across species [15]. T cells, macrophages, and neutrophils, when stimulated, can synthesize and release catecholamines *de novo*. Catecholamines released from these immune cells act in a complex autocrine/paracrine manner to regulate cytokine mediator release differentially via the full complement of adrenergic receptors, including both β_1- and β_2-adrenoreceptor subtypes [16] .

At the onset of critical illness (sepsis, burns), pronounced increases in natural killer cells and CD8 lymphocytes occur, with moderate changes in B cells or CD4+lymphocytes [17]. An increasing body of evidence indicates that the prolonged neurohormonal response to critical illness contributes to the inhibition of pro-inflammatory/T-helper 1 (Th1) responses and up-regulation of anti-inflammatory/T-helper 2 (Th2) responses through complex effects on innate/adaptive immune cells [18]. Sustained catecholamine infusion in rats results in splenocyte apoptosis and decreases in natural killer cells, T and B lymphocytes. By contrast, acutely administered β-adrenoreceptor agonists, such as isoproterenol, suppress the expression of endotoxin-induced cytokines, experimental allergic encephalomyelitis and collagen/adjuvant-induced arthritis [18]. Although acutely administered non-specific β-blockers augment pro-inflammatory cytokine production in experimental studies, such responses are not seen in a variety of clinical, pro-inflammatory scenarios. Indeed, a direct, innate link between epinephrine and immune function has been demonstrated in both humans and rat strains with high and low endogenous basal levels of epinephrine. Lewis rats exhibit markedly lower baseline epinephrine levels and responsiveness to isoproterenol-induced cytokine inhibition compared to F344 rats [19]. Thus, low basal adrenomedullary activity confers enhanced immune responsiveness.

β-adrenoreceptor mediated immunosuppression by the sympathetic nervous system may also be dependent on the source of inflammation [20]. Under bacteria-free conditions, tumor necrosis factor (TNF)-α secretion is low, while interleukin (IL)-6 secretion is α_2-adrenoreceptor dependent. In the presence of *Pseudomonas* bacteria, TNF-α and IL-6 secretion increase, but IL-6 secretion is reduced by β-adrenoreceptor blockade with propranolol. This α- to β switch of IL-6 inhibition in the presence of bacteria adds a further layer of complexity to the immunomodulatory role of β-adrenoreceptors [20]. In addition to immunosuppression, catecholamine inotropes directly stimulate bacterial growth [21], mediated by removal of iron from lactoferrin and transferrin by the catechol moiety and its subsequent acquisition by bacteria.

Amelioration of lymphocyte apoptosis is a cardinal event in determining outcomes in experimental sepsis [22]. Catecholamines are likely to contribute to this during the systemic response to inflammation, since they directly increase apoptosis in various lymphoid populations [23], through both α- and β-adrenoreceptor subtypes. Treatment of splenic lymphocytes with a non-selective β-adrenoreceptor antagonist (propranolol) inhibited apoptosis as a consequence of hemorrhagic shock [24]. The precise contribution of each receptor subtype, and their roles in specific organs, is unclear with huge potential for intra- and inter-organ effects (**Fig. 4**).

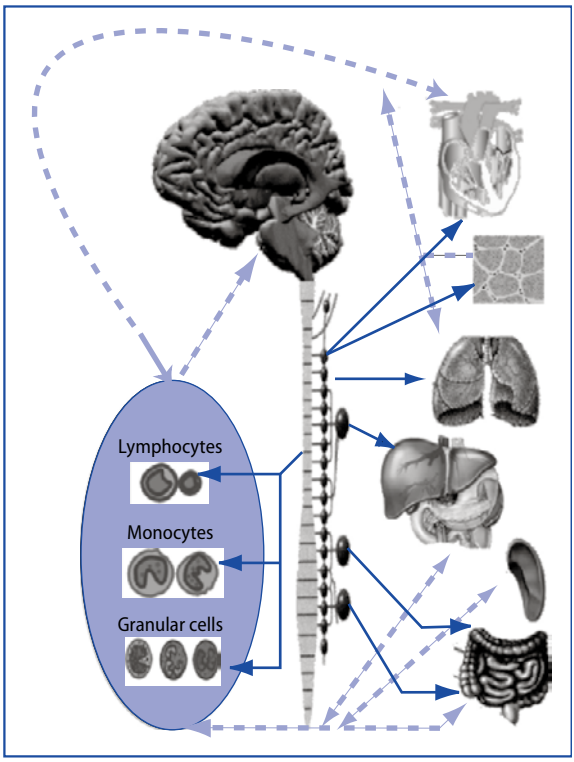

Fig. 4. Despite the intimate temporal, anatomical and physiological relationship between catecholamine release and key pathophysiological changes that occur during critical illness, the β-adrenoreceptor plays a largely ill-defined role in mediating the interaction between sympathetic nervous system outflow (solid blue lines), immune function (blue dotted lines), and organ dysfunction. Expression of β-adrenoreceptor on different lymphoid cells and their coupling to intracellular pathways is likely to differ according to their stage of maturation, differentiation, tissue localization and concurrent pathological changes. The bidirectional links (blue dotted lines/arrows) demonstrate potential links between β-adrenoreceptor-mediated catecholamine actions and inflammatory, neural, metabolic, and circulatory changes, which are likely to be compartmentalized between and perhaps within organs.

Beta-adrenoreceptor-mediated Metabolic Effects of Critical Illness

As well as impaired immune function, the metabolic hallmarks of critical illness physiology include hyperglycemia, marked net protein loss, insulin resistance, and peripheral lipolysis [25]. Excess catecholamines drive many of these processes directly through the stimulation of glycogenolysis in skeletal muscle and lipolysis in peripheral adipose tissue. The resultant increased production of lactate, alanine, glycerol, and free fatty acids, further fuels hepatic gluconeogenesis, augmenting glucose levels already driven higher through hepatic glycogenolysis triggered directly by higher circulating levels of norepinephrine and epinephrine. The seminal work of Herndon and colleagues has demonstrated in the pediatric burn population that administration of propranolol reduces energy expenditure, muscle protein catabolism, and peripheral lipolysis [26]. The reduction in peripheral lipolysis and free fatty acid oxidation shifts metabolism towards increased glucose oxidation. Human studies have revealed a net decrease in plasma glucose concentrations in patients receiving non-selective beta-blockade using propranolol during states of stress [27], due to a decrease in glucose production without any change in glucose clearance. Given the deleterious role of hyperglycemia in critically ill patients and the beneficial effects of glucose control [28], the targeting of β-adrenoreceptor mediated catecholamine-induced metabolic dysregulation is an attractive target to ameliorate the deleterious metabolic effects of critical illness.

Beta-adrenoreceptor-mediated Effects on Barrier Gut Function

There are compelling reasons to support the contention that the gut should be regarded as the motor of critical illness [29]. Loss of intestinal lymphocytes in the mucosal layer is likely to play a critical role in host defence [30] because these cells are exposed to a vast array of environmental antigens. Intestinal lymphocyte apoptosis triggered through the systemic release of catecholamines following sympathetic activation or tissue trauma may lead to the overgrowth of endogenous Gram-negative bacteria [31]. Catecholamines directly induce intestinal lymphocyte apoptosis [32], an effect that is ameliorated after exercise-induced lymphocytosis by nadolol, a non-specific β-adrenoreceptor antagonist [33].

Specific Beta-adrenoreceptor-mediated Roles in Common Critical Illness Pathophysiology

Traumatic Head Injury

Applied experimental critical illness models, such as head injury, where prolonged excessive catecholamine stimulation occurs, demonstrate the potential importance of β-adrenoreceptor biology in mediating clinical benefits. In a murine model of stroke, an immune deficient state characterized by the extensive apoptotic loss of lymphocytes and a shift from Th1 to Th2 cytokine production, rapidly leads to spontaneous systemic bacterial infection. Mortality and bacterial infections were prevented by propranolol-mediated inhibition of sympathetic nervous activity but not by steroid receptor blockade [34]. The positive effect of propranolol on immune profile and clinical outcome was identical to both the adoptive transfer of T and natural killer cells and administration of interferon (IFN)-γ, the archetypal Th1 cytokine. Recent clinical data support the idea that ß-blockade (albeit poorly defined) may be protective in isolated head trauma [35].

Cardiovascular Dysfunction during Critical Illness

The mammalian heart contains three β-adrenoreceptor subtypes: β_1-, β_2-, and β_3-adrenoreceptors. The β_1- and β_2-adrenoreceptor subtypes dominate the cardiac response to adrenergic stimulation. Differences in cell signaling between β_1- and β_2-adrenoreceptors with regard to activation of cytotoxic versus cytoprotective pathways (**Fig. 2.**) explain why continuous β_1-adrenoreceptor stimulation causes myocyte injury while continuous β_2-adrenoreceptor stimulation does not [36]. These differences may also help to explain why relatively β_1-adrenoreceptor selective antagonists produce favorable outcomes in ischemic heart disease and cardiac failure [37]. Both β_1- and β_2-adrenoreceptor polymorphisms are associated with an increased risk of adverse cardiovascular outcomes [38, 39].

Cardiac dysfunction during sepsis, though usually reversible, is associated with poorer clinical outcomes [40]. Sepsis induces a disruption at various levels of the β-adrenoreceptor signaling cascade. Since myocardial responses to increased extracellular calcium ion concentrations remain normal, disruption of G-protein signal transduction seems critical [41]. Gs proteins were decreased in endotoxemic rabbits [42], whereas Gi proteins were increased in non-survivors of septic shock [43]. These changes result in decreased activity of adenylyl cyclase and reduced levels of cAMP. β_3 receptors, linked to Gi proteins, are upregulated during human sepsis [44].

Clinically, a blunted contractile response to dobutamine during critical illness is associated with an increase in mortality (45).

Acute Lung injury

β_2-adrenoreceptors are expressed on different cell types in the lung, including respiratory epithelial cells, smooth muscle cells, and macrophages. Inhalation of propranolol enhances lipopolysaccharide (LPS)-induced lung inflammation and activation of coagulation pathways in mice, without altering neutrophil recruitment [46], suggesting a protective role for β-adrenoreceptors in lung injury. Experimental and preliminary clinical studies in acute lung injury (ALI) also support a therapeutic role for β_2 agonists [47], indicating multiple protective mechanisms, including an anti-inflammatory action [48].

Limitations of Current Experimental/clinical Data

Four important limitations preclude further interpretation of this literature with regard to the precise role of specific β-adrenoreceptor subtypes. First, most studies have employed non-specific β-blockers, thereby precluding specific insights into which subtype is important. Typically, propranolol has been used, which also possesses significant local anesthetic and serotonergic receptor actions that could contribute to immune regulation amongst other physiologic actions [49]. Second, both the timing and duration of administration, as well as agonist load, may influence the immune response through desensitization and switching of of subcellular mechanisms. Third, the uncontrolled systemic effects of β-adrenoreceptor agonism/antagonism on cardiac and peripheral vascular physiology may also introduce confounding factors that alter cytokine expression indirectly (e.g., hypotension). Lastly, tissue, pathogen and host (gender, age) specific differences in β-adrenoreceptor response in mediating inflammation may be important confounding factors. For example, experimental data suggest the route of administration of β-antagonists in ALI may be crucial in conferring protective β_2-mediated effects [46]. Furthermore, the recent Peri-Operative ISchemic Evaluation (POISE) trial, where perioperative cardiac injury was reduced yet overall mortality increased due to sepsis and stroke, provides a pivotal example as to how β-adrenoreceptor modulation may yield disparate clinical outcomes [50]. The apparently negative result of this landmark perioperative trial may be explained in part by the contention that the *acute* immuno-modulatory role of β_1-adrenoreceptor antagonism is detrimental, thereby influencing clinical outcome adversely independent of cardioprotective mechanisms.

Conclusion

β-adrenoreceptors play an important role in several pathophysiological processes familiar to critical care physicians. Nevertheless, the clinical utilization of β-adrenoreceptor agonists and antagonists is a mainstay of critical care, despite studies that highlight several potentially detrimental effects. The complex and apparently counteracting roles of catecholamines, either endogenous or exogenous, in different organs/systems demonstrates the further need to understand local and systemic consequences of critical illness on β-adrenoreceptor physiology. The roles of β-adre-

noreceptor subtypes and β-adrenoreceptor downregulation/desensitization are central to an enhanced understanding of the complexity of the contribution of β-adrenoreceptors in critical illness.

References

1. Guimarães S, Moura D (2001) Vascular adrenoreceptors: an update. Pharmacol Rev. 53: 319 – 356
2. Xiao RP, Avdonin P, Zhou YY, et al (1999) Coupling of beta2-AR to Gi proteins and its physiological relevance in murine cardiac myocytes. Circ Res 84: 43 – 52
3. Xiao RP, Cheng H, Zhou YY, Kuschel M, Lakatta EG (1999) Recent advances in cardiac beta2-adrenergic signal transduction. Circ Res 85: 1092 – 1100
4. Engelhardt S, Hein L, Wiesmann F, Lohse MJ (1999) Progressive hypertrophy and heart failure in beta1-adrenergic receptor transgenic mice. Proc Natl Acad Sci USA 96: 7059 –7064
5. Milano CA, Allen LF, Rockman HA, et al (1994) Enhanced myocardial function in transgenic mice overexpressing the beta2-adrenergic receptor. Science 264: 582 – 586
6. Communal C, Singh K, Sawyer DB, Colucci WS (1999) Opposing effects of beta1-and beta2-adrenergic receptors on cardiac myocyte apoptosis: role of a pertussis toxin-sensitive G protein. Circulation 100: 2210 –2212
7. Xiao RP, Zhu W, Zheng M, et al (2006) Subtype-specific beta1 and beta2 adrenoreceptor Signaling in the Heart. Trends Pharmacol Sci 27: 330 – 337
8. Richter W, Day P, Agrawal R, et al (2008) Signaling from beta1 and beta2 adrenergic receptors is defined by differential interactions with PDE4. EMBO J 27: 384 – 393
9. Bünemann M, Lee KB, Pals-Rylaarsdam R, Roseberry AG, Hosey MM (1999) Desensitization of G-protein-coupled receptors in the cardiovascular system. Annu Rev Physiol 61: 169 – 192
10. Reiter E, Lefkowitz RJ (2006) GRKs and beta-arrestins: roles in receptor silencing, trafficking and signaling. Trends Endocrinol Metab 17: 159 – 165
11. Patterson AJ, Zhu W, Chow A, et al (2004) Protecting the myocardium: A role for the beta2 adrenergic receptor in the heart. Crit Care Med 32: 1041 – 1048
12. Collin S, Sennoun N, Levy B (2008) Cardiovascular and metabolic responses to catecholamine and sepsis prognosis: a ubiquitous phenomenon? Crit Care12: 118
13. Levy B, Gibot S, Franck P, Cravoisy A, Bollaert PE (2005) Relation between muscle Na+K+-ATPase activity and raised lactate concentrations in septic shock: a prospective study. Lancet 365: 871 – 875
14. Levraut J, Ichai C, Petit I, Ciebiera JP, Perus O, Grimaud D (2003) Low exogenous lactate clearance as an early predictor of mortality in normolactatemic critically ill septic patients. Crit Care Med 31: 705 – 710
15. Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES (2000) The sympathetic nerve--an integrative interface between two supersystems: the brain and the immune system. Pharmacol Rev. 52: 595 – 638
16. Flierl MA, Rittirsch D, Huber-Lang M, Sarma JV, Ward PA (2008) Catecholamines-crafty weapons in the inflammatory arsenal of immune/inflammatory cells or opening pandora's box? Mol Med 14: 195 – 204
17. Sanders VM, Straub RH (2002) Norepinephrine, the beta-adrenergic receptor, and immunity. Brain Behav Immun 16: 290 – 332
18. Elenkov IJ, Chrousos GP (1999) Stress hormones, Th1/Th2 patterns, pro/anti-inflammatory cytokines and susceptibility to disease. Trends Endocrinol Metab 10: 359 – 368
19. Elenkov IJ, Kvetnansky R, Hashiramoto A, et al (2008) Low- versus high-baseline epinephrine output shapes opposite innate cytokine profiles: presence of Lewis- and Fischer-like neurohormonal immune phenotypes in humans? J Immunol 181: 1737 – 1745
20. Straub RH, Linde HJ, Männel DN, Schölmerich J, Falk W (2000) A bacteria induced switch of sympathetic effector mechanisms augments local inhibition of TNF-alpha and IL-6 secretion in the spleen. FASEB J 14: 1380 – 1388
21. Lyte M, Freestone PP, Neal CP, et al (2003) Stimulation of *Staph epidermidis* growth and biofi lm formation by catecholamine inotropes. Lancet 361: 130 – 135
22. Coopersmith CM, Stromberg PE, Dunne WM, et al (2002) Inhibition of intestinal epithelial

apoptosis and survival in a murine model of pneumonia-induced sepsis. JAMA 287: 1716 – 1721
23. Stevenson JR, Westermann J, Liebmann PM, et al (2001) Prolonged alpha-adrenergic stimulation causes changes in leukocyte distribution and lymphocyte apoptosis in the rat. J Neuroimmunol 120: 50 – 57
24. Oberbeck R, van Griensven M, Nickel E, Tschernig T, Wittwer T, Pape HC (2002) Influence of beta-AR antagonists on hemorrhage-induced cellular immune suppression. Shock 18: 331 – 335
25. Norbury WB, Jeschke MG, Herndon DN (2007) Metabolism modulators in sepsis: propranolol. Crit Care Med 35: S616 – 620
26. Herndon DN, Hart DW, Wolf SE, Chinkes DL, Wolfe RR (2001) Reversal of catabolism by beta-blockade after severe burns. N Engl J Med 345: 1223 – 1229
27. Shaw JH, Holdaway CM, Humberstone DA (1988) Metabolic intervention in surgical patients: The effect of alpha- or beta-blockade on glucose and protein metabolism in surgical patients receiving total parenteral nutrition. Surgery 103: 520 – 525
28. Langouche L, Vanhorebeek I, Van den Berghe G (2007) Therapy insight: the effect of tight glycemic control in acute illness. Nat Clin Pract Endocrinol Metab 3: 270 – 278
29. Ackland G, Grocott MP, Mythen MG (2000) Understanding gastrointestinal perfusion in critical care: so near, and yet so far. Crit Care 4: 269 – 281
30. Husain KD, Coopersmith CM (2003) Role of intestinal epithelial apoptosis in survival. Curr Opin Crit Care 9: 159 – 163
31. Lyte M, Bailey MT (1997) Neuroendocrine-bacterial interactions in a neurotoxin-induced model of trauma. J Surg Res 70: 195 – 201
32. Marra S, Burnett M, Hoffman-Goetz L (2005) Intravenous catecholamine administration affects mouse intestinal lymphocyte number and apoptosis. J Neuroimmunol 158: 76 – 85
33. Marra S, Hoffman-Goetz L (2004) Beta-adrenergic receptor blockade during exercise decreases intestinal lymphocyte apoptosis but not cell loss in mice. Can J Physiol Pharmacol 82: 465 – 473
34. Prass K, Meisel C, Höflich C, et al (2003) Stroke-induced immunodeficiency promotes spontaneous bacterial infections and is mediated by sympathetic activation reversal by poststroke T helper cell type 1-like immunostimulation. J Exp Med 198: 725 – 736
35. Inaba K, Teixeira PG, David JS, et al (2008) Beta-blockers in isolated blunt head injury. J Am Coll Surg 206: 432 – 438
36. Patterson AJ, Zhu W, Chow A, et al (2004) Protecting the myocardium: a role for the beta2 adrenergic receptor in the heart. Crit Care Med 32: 1041 – 1048
37. Lohse MJ, Engelhardt S, Eschenhagen T (2003) What is the role of beta-adrenergic signaling in heart failure? Circ Res 93: 896 – 906
38. Small KM, Wagoner LE, Levin AM, Kardia SL, Liggett SB (2002) Synergistic polymorphisms of beta1- and alpha2C-adrenergic receptors and the risk of congestive heart failure. N Engl J Med 347: 1135 – 1142
39. Heckbert SR, Hindorff LA, Edwards KL, et al (2003) Beta2-adrenergic receptor polymorphisms and risk of incident cardiovascular events in the elderly. Circulation 107: 2021 – 2024
40. Rudiger A, Singer M (2007) Mechanisms of sepsis-induced cardiac dysfunction. Crit Care Med 35:1599 – 608
41. Matsuda N, Hattori Y, Akaishi Y, et al (2000) Impairment of cardiac [beta]-AR cellular signaling by decreased expression of Gs[alpha] in septic rabbits. Anesthesiology 93:1465 – 1473
42. Chung MK, Gulick TS, Rotondo RE, et al (1990) Mechanism of cytokine inhibition of beta-adrenergic agonist stimulation of cyclic AMP in rat cardiac myocytes. Impairment of signal transduction. Circ Res 67: 753 – 763
43. Böhm M, Kirchmayr R, Gierschik P, et al (1995) Increase of myocardial inhibitory G-proteins in catecholamine-refractory septic shock or in septic multiorgan failure. Am J Med 98: 183 – 186
44. Moniotte S, Belge C, Sekkali B, et al (2007) Sepsis is associated with an upregulation of functional beta3 ARs in the myocardium. Eur J Heart Fail 9: 1163 – 1171
45. Rhodes A, Lamb FJ, Malagon I, Newman PJ, Grounds RM, Bennett ED (1999) A prospective study of the use of a dobutamine stress test to identify outcome in patients with sepsis, severe sepsis, or septic shock. Crit Care Med 27: 2361 – 2366
46. Giebelen IA, Leendertse M, Dessing MC, et al (2008) Endogenous beta-adrenergic receptors

inhibit lipopolysaccharide-induced pulmonary cytokine release and coagulation. Am J Respir Cell Mol Biol 39: 373 – 379
47. Wiener-Kronish JP, Matthay MA (2006) Beta-2-agonist treatment as a potential therapy for acute inhalational lung injury. Crit Care Med 34: 1841 – 1842
48. Lovén J, Svitacheva N, Jerre A, Miller-Larsson A, Korn SH (2007) Anti-inflammatory activity of beta2-agonists in primary lung epithelial cells is independent of glucocorticoid receptor. Eur Respir J 30: 848 – 856
49. Green AR, Grahame-Smith DG (1976) (-)-Propranolol inhibits the behavioral responses of rats to increased 5-hydroxytryptamine in the central nervous system. Nature 262: 594 – 596
50. POISE Study Group (2008) Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomized controlled trial. Lancet 371: 1839 – 1847