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Opinion

Why Is Epinephrine Preferred for Cardiac Arrest? The Answer May Lie in β_2-Adrenergic Receptor Activation

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Abstract

Epinephrine (Epi, adrenaline) is routinely used during cardiopulmonary resuscitation (CPR) for cardiac arrest and is a first line treatment according to the international advanced life support (ALS) guidelines, which recommend 1 mg Epi be administered every 3–5 minutes during CPR. However, specific pharmacological factors that may distinguish Epi from other vasopressor agents used during CPR are unclear. This opinion article argues that one such factor, perhaps even the most important, is the activation of the β_2-adrenergic receptor (AR) subtype, which only Epi, among all vasopressor hormones, can induce. β_2AR activation equips Epi with more robust capabilities for pulse generation in the pacemaker cells (sinoatrial node) for the heart and of restoring contractile function in ischemic/hypoxic cardiomyocytes via sodium/potassium pump activation, compared to all other vasopressor hormones, including the closely related catecholamine norepinephrine (NE, noradrenaline). These additional actions of Epi via the β_2AR, which are probably not shared by NE or other vasopressor agents, may make it particularly useful in situations where simple blood pressure elevation is insufficient, such as cardiac arrest.

Keywords: adrenaline (epinephrine); beta-adrenergic receptors; cardiac arrest; catecholamine; noradrenaline (norepinephrine); return of spontaneous circulation (ROSC); sodium-potassium pump

1. Introduction

The best choice of therapeutic agent(s) to improve outcomes of cardiopulmonary resuscitation (CPR) during cardiac arrest is still a matter of debate. Circulating hormone epinephrine (Epi, adrenaline), produced and secreted by the chromaffin cells of the adrenal medulla, with contributions from the sympathetic nervous system neurotransmitter norepinephrine (NE, noradrenaline), is responsible for generating the "fight-or-flight" response of our bodies to environmental stressful stimuli or traumatic insults [1–3]. Epi and NE exert their effects in cells via adrenergic receptors (ARs), all nine subtypes of which are class A (rhodopsin-like) G protein-coupled receptors (GPCRs) [4]: three α_1-ARs (α_{1A}, α_{1B}, α_{1D}), primarily exerting vasopressor actions [5]; three α_2-ARs (α_{2A}, α_{2B}, α_{2C}), primarily functioning as sympatho-inhibitory autoreceptors in central and peripheral nervous systems [6]; and three βARs (β_1, β_2, β_3), primarily coupling to adenylyl cyclase (AC) stimulation and cyclic adenosine monophosphate (cAMP) signaling [7]. The βAR subtypes share some actions, e.g., in adipocytes [7], but have very distinct functions, as well: for instance, while both β_1- and β_2ARs exert positive inotropy, chronotropy, dromotropy, and lusitropy in the myocardium, β_3AR exerts negative inotropy [8]. In addition, β_1- and β_3ARs are almost exclusively located at sites receiving direct sympathetic innervation, and thus, are ideally placed to respond to neuronally released NE [4]. Conversely, β_2AR is located at various peripheral organs and tissues that usually lack sympathetic innervation, and thus, is ideally suited to respond to the circulating hormone Epi.

NE and Epi activate all α_1ARs, all α_2ARs, and the β_1AR equipotently. Whereas Epi is more potent at β_1AR & β_2AR activation than at αAR activation [9], NE is more potent at β_3AR activation than Epi is and, in fact, β_3AR is the only AR subtype for which Epi has low affinity [10]. The exact opposite is true for the β_2AR: NE has by far the lowest affinity for this AR subtype, much lower than that of Epi. In this opinion article, we argue that this is exactly what makes Epi much more efficacious in the treatment of cardiac arrest.

2. Why Epi Is the Sole Endogenous β_2AR Agonist Hormone: The Answer is Tyr308

NE has ~10–15-fold lower affinity for human β_2AR than Epi [11]; yet, both NE and Epi make contacts with the exact same amino acid residues in the agonist binding (orthosteric) pockets of both β_2AR and β_1AR [12,13]. Yet, Epi displays far superior potency and efficacy at the human β_2AR over NE, as measured in a cAMP accumulation assay in human lymphocytes [14]. In human atrial and ventricular tissue biopsies from patients, NE displayed 20-fold lower affinity for β_2AR over β_1AR [15]. This, coupled

with the fact that β_1AR, which both NE and Epi activate equipotently, is much (~10-fold) less efficacious at producing cAMP in human heart than β_2AR is [15], translates into a significantly (5-fold) higher potency for Epi over NE at stimulating cardiac contractility: 1 µM of NE produces the same degree of positive inotropy as 200 nM of Epi in human atrial myocardium [15]. It is thus clear that NE, at normal physiological concentrations, does not really activate the β_2AR subtype, similarly to dopamine [14], and thus, Epi is essentially the only endogenous catecholamine that activates the β_2AR, at least at physiological concentrations.

The only structural difference between NE and Epi is the presence of one methyl group on the positively charged (protonated)-NH_2 group, absent in NE (Fig. 1A, Ref. [16]). This methyl substitution increases the basicity (protonation) of Epi's nitrogen atom (secondary amines like Epi are generally more basic than primary amines like NE). It also increases ligand affinity for the human β_2AR dramatically: when this N-methyl group is added to NE, affinity for the β_2AR increases ~60-fold [17]. How exactly this N-methyl group confers this dramatic difference in β_2AR affinity is still under investigation. However, the orientation of the catecholamine in the orthosteric pocket, a "groove" formed by Asp113 of TM3 & Asn312 of TM7 on one end, and Ser203/Ser204/Ser207 of TM5 on the other (Fig. 1A), gives some crucial hints [16]. The N-methyl group is well positioned to interact with the extracellular top of TM7 at the extracellular "lid" of the pocket. Although it does not contact the agonist in the pocket directly, Tyr308 of TM7 is in close proximity (within 8 Å) to amino acids that do contact the ligand, specifically Asn312 (Fig. 1A) [18]. Notably, all other AR subtypes, the β_1AR included, have phenylalanine ($F^{7.35}$) at this TM7 position (position 7.35 based on the Ballesteros-Weinstein numbering) [13]. Given that tyrosine forms both polar (hydrogen bond) interactions via its hydroxyl group and hydrophobic (Van der Waals) interactions via its phenyl group (Fig. 1A), Tyr308 is ideally placed to coordinate the entry of the N-methyl group of Epi into the pocket and to stabilize binding (prevent dissociation) to the β_2AR (Fig. 1A). This is because the N-methyl group also makes polar, via the protonated amino group (-$^+NH_2$), and hydrophobic, via the methyl group (-CH_3), interactions. Indeed, the "on" (receptor association) rate of Epi for the β_2AR has been estimated to be ~14-fold faster than that of NE [11], and Tyr308 of the β_2AR has been documented to be the main determinant of β_2AR-selective affinity for βAR agonists via both hydrophobic (with the phenyl) and polar (with the -OH group) interactions [19]. Importantly, Tyr308 both increases the association and decreases the dissociation rates of Epi on the β_2AR [19]. In contrast, by lacking this N-methyl substitution, NE is probably incapable of interacting with Tyr308 (the NE molecule is not long enough to sterically reach Tyr308 for strong interaction) and thus, quickly dissociates from the β_2AR's orthosteric pocket. Hence, only very high NE concentrations can activate the β_2AR [14]. Interestingly, Tyr308 has been reported to be essential for the Gs protein-"biased" agonism of the β_2AR, as well [20]. β_2AR's $Tyr^{7.35}$ appears necessary for efficient activation of the Gs/AC/cAMP signaling pathway by the receptor. Since β_1AR has Phe instead of Tyr at this position, this could underlie, in part, the reduced efficacy, versus β_2AR, of β_1AR at producing cAMP [15]. The significantly larger (by 27 amino acids) third intracellular loop of β_1AR, compared to that of β_2AR, is another reason postulated for this reduced efficacy [15]. Taken together, Tyr308 controls both orthosteric agonist affinity (potency) and, partly, cAMP signaling efficiency (agonist efficacy) at the human β_2AR.

3. Epi in Cardiac Arrest: β_2AR Activation is Key

3.1 Clinical Evidence for the Use of Epi in Cardiac Arrest

Their α_1AR-dependent vasopressor actions form the basis for the use of catecholamines in cardiac arrest (or asystole) and during CPR [21]. In cardiac arrest, coronary artery perfusion pressure drops precipitously because the heart has stopped beating, and, since coronary perfusion pressure is defined as the difference between aortic and right atrial blood pressures, vasopressors that acutely raise arterial blood pressure are indicated to enhance coronary perfusion and restart the heart, i.e., to induce the so-called "return of spontaneous circulation" (ROSC) [22]. Thus, alongside NE and Epi, potent vasopressors, such as vasopressin and phenylephrine, are sometimes used during CPR. Epi has historically been the agent of choice for cardiac arrest/CPR with several studies/meta-analyses supporting its utility in this medical emergency setting [23–27], showing consistent increases in ROSC and return of pulse in CPR-receiving subjects, as well as in survival to hospital admission and even hospital discharge. Indeed, the latest American Heart Association's guidelines recommend administering 1 mg of epinephrine intravenously (IV) or intraosseously (IO) every 3–5 minutes for adult cardiac arrest [27]. Epi can also augment the effect of vasopressin and other vasopressors on ROSC and survival rate in cardiac arrest [26]. However, a few trials have cast doubt on the actual benefit of Epi for long term cardiac arrest outcomes, particularly with respect to neurological recovery [21,23]. Indeed, β_2AR activation by Epi can substantially increase myocardial oxygen consumption to meet the demands of significantly enhanced contractility, which may lead to non-favorable long term survival outcomes, especially in ischemic heart disease patients [21,28]. In addition, β_2AR activation leads to vasodilation, which may affect local microcirculation negatively, particularly in the brain, due to perturbations in small vessel (arterioles/capillaries)-mediated tissue perfusion [28]. Nevertheless, other studies have failed to demonstrate any inferiority of Epi in cardiac arrest compared to NE [29] and the overall picture regarding Epi's utility in cardiac arrest is still fuzzy. This is probably because: (a) each

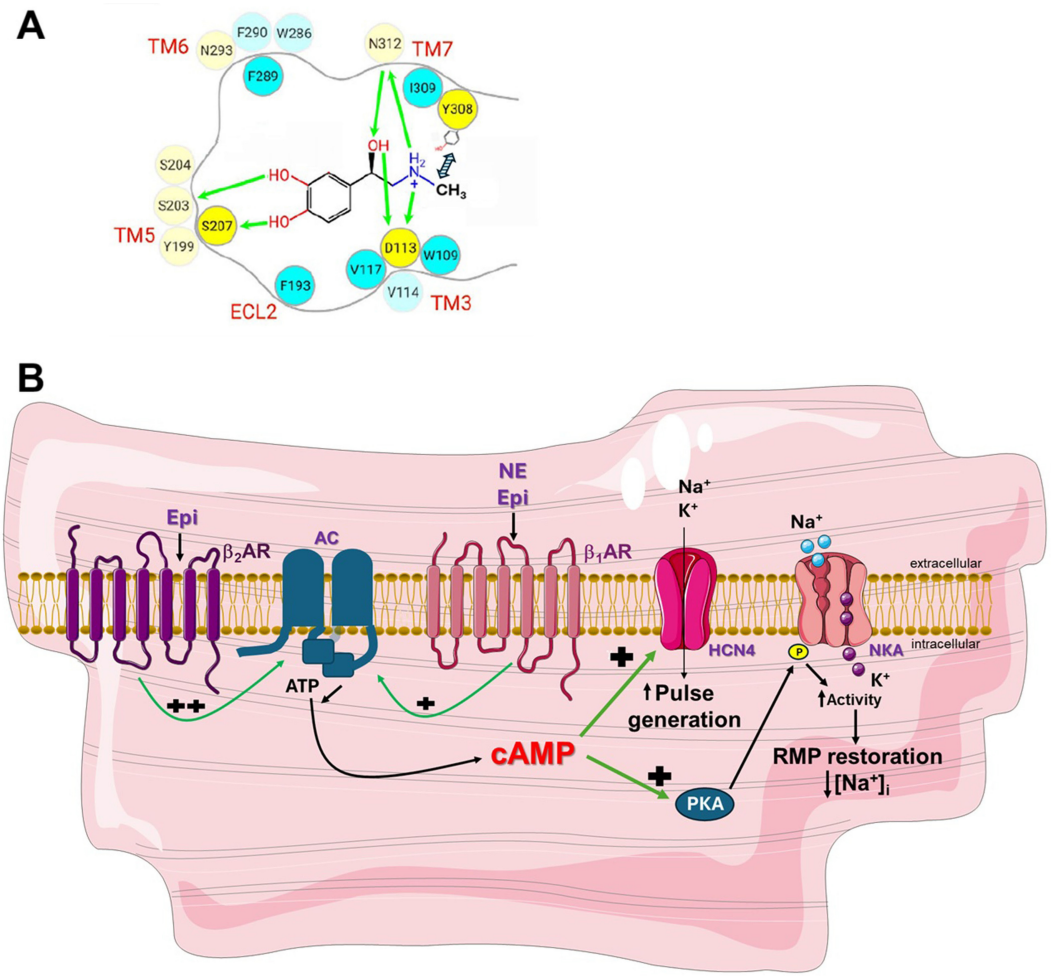

Fig. 1. β_2AR activation boosts the efficacy of Epi in cardiac arrest. (A) The amino acids of the orthosteric pocket of the human β_2AR occupied by the Epi molecule, including Tyr7.35 (Y308). Y308 does not contact Epi directly in the pocket but nevertheless facilitates its docking and binding to the pocket thanks to proper coordination of the N-methyl group. In contrast, this methyl group is absent in NE and thus, Y308 cannot do the same for NE. The green arrows indicate polar (hydrogen bond or ionic) interactions. Fig. 1A is modified with permission from Ref. [16]. (B) Beneficial actions in cardiac arrest of cardiomyocyte-residing β_2ARs via cAMP towards pulse generation and contractile function restoration. Because Epi activates the β_2AR, in addition to the β_1AR, and β_2AR is more potent at generating cAMP (i.e., at activating AC) than β_1AR is, Epi activates HCN4 channels in SA nodal cardiomyocytes to increase pulse generation, and NKA in working (contracting) cardiomyocytes to restore resting membrane potential & excitability, more robustly than NE does. "++" denotes higher potency than "+". AC, Adenylyl cyclase; AR, Adrenergic receptor; ATP, Adenosine triphosphate; cAMP, Cyclic adenosine monophosphate; ECL, Extracellular loop; Epi, Epinephrine; HCN4, Hyperpolarization-activated cyclic nucleotide-gated channel-4; $[Na^+]_i$, Intracellular Na^+ concentration; NE, Norepinephrine; NKA, Na^+/K^+-ATPase; P, Phosphorylation (of phospholemman); PKA, Protein kinase A; RMP, Resting membrane potential; TM, Transmembrane helix. Fig. 1B was created using images from Servier Medical Art Commons Attribution 3.0 Unported License.

study's findings may not be generalizable to all patients; (b) there are several factors, unrelated to Epi's effects, affecting neurological outcomes in cardiac arrest survivors, as well as methodological problems in some of the studies [24]; and, perhaps most importantly, (c) since Epi increases the chances of post-cardiac arrest survival, the total number of survivors having received Epi during CPR is higher, which can skew the number of survivors that do not recover neurologically towards Epi in an unfavorable manner. In other words, the main goal of Epi administration in cardiac arrest is ROSC and return of pulse, so the patient can escape instant death and hopefully survive either to hospital admission or, if already hospitalized, to discharge.

3.2 Physiological Mechanisms of Epi in Cardiac Arrest

Apart from Epi-activated α_1AR-mediated vasoconstriction that enhances coronary perfusion, Epi-activated β_2ARs in the airways dilate the bronchi and lungs, an action crucial not only in treatment of anaphylactic shock but also during CPR to improve blood oxygenation [30]. In

addition, cAMP elevation inside cardiomyocytes by Epi-activated β_1ARs and β_2ARs affords two additional important benefits in cardiac arrest. One of these benefits is stimulation of the sinoatrial (SA) node, the natural pacemaker of the myocardium, to increase the I*f* current via enhanced opening of hyperpolarization-activated cyclic nucleotide-gated (HCN)-4 channels [31,32]. These channels are directly bound and operated by cAMP and their opening results in increased beating frequency, i.e., elevated heart rate (Fig. 1B). It is well established that β_2ARs are abundant in the SA node (in fact, more abundant than in the rest of the atria) and mediate HCN4 channel activation and positive chronotropy alongside β_1ARs [33–35]. Given that cardiac β_2ARs are 10 times more potent at cAMP synthesis than their β_1AR counterparts [15] and that Epi activates both subtypes equipotently, unlike NE that activates the β_1AR but not the β_2AR subtype at normal concentrations, it follows that Epi can stimulate the pacemaker activity of the SA nodal cardiomyocytes much more robustly than NE (Fig. 1B). This would be consistent with the long-reported greater potency of Epi over NE at stimulating contractility, as well (higher heart rate normally leads to increased contractility) [15]. Being able to stimulate pacemaker activity more robustly via greater cAMP production driven by both β_1- and β_2ARs gives Epi a unique ability to generate heartbeats (pulse), and thus, a significant advantage over NE (and other vasopressors) in treatment of cardiac arrest.

Finally, the other cAMP-dependent benefit that is therapeutically exploited by using Epi in cardiac arrest is stimulation of the sodium-potassium pump (Na^+/K^+-ATPase, NKA) (Fig. 1B). Protein kinase A (PKA), the main effector of cAMP, activates NKA via phosphorylation of FXYD1 (also known as phospholemman, PLM), a protein that physically interacts with NKA reducing its affinity for intracellular Na^+ and thus, its activity [36,37]. PKA-dependent phosphorylation releases PLM inhibition of NKA, robustly increasing NKA activity [37,38]. Since NKA-dependent Na^+ efflux and K^+ influx are essential for restoration of the resting membrane potential and gradients of these two cations, NKA activation is an integral part of the adrenergic "fight-or-flight" response [37] (Fig. 1B). It is also essential for reduction of intracellular [Ca^{2+}] (via the Na^+/Ca^{2+} exchanger) [38] (Fig. 1B). High intracellular [Na^+] suppresses excitability of working cardiomyocytes due to perturbation (suppression) of normal Na^+ currents, on which fast depolarization (Phase 0 of the action potential) depends [39]. Therefore, NKA stimulation by cAMP is crucial for maintaining cardiac function, particularly in ischemic (hypoxic) cardiomyocytes, where NKA activity is low due to energy (ATP) depletion. β_2AR, probably again due to its greater potency at increasing cAMP, stimulates NKA activity more robustly than β_1AR does: the β_2AR-selective agonist salbutamol is equipotent to Epi but 100-fold more potent than a β_1AR-selective agonist at stimulating NKA in rat soleus muscle [40]. Together with activation of both β_1- and β_2ARs, this means that Epi stimulates cardiomyocyte NKA more robustly than NE does (Fig. 1B), which is also consistent with the well-documented, clinically, Epi-induced hypokalemia (due to high NKA activity) [41]. In conclusion, Epi stimulates cardiac NKA more robustly than NE and other vasopressors used in cardiac arrest, which is another crucial beneficial mechanism by which Epi can restore cardiac pulse and contraction, i.e., increase ROSC.

4. Conclusions & Future Perspectives

Epi is a particularly useful drug (the agent of choice) in cardiac arrest thanks to its unique, among vasopressor hormones/agents, activation of cardiac β_2ARs. β_2AR activation results in profound increases in potency and efficacy of Epi, compared to NE and other non-catecholamine vasopressors, towards pulse generation in the SA node and contractility restoration in the working myocardium via NKA activation. Of course, other important mechanisms for cardiomyocyte homeostasis, such as NCX and sarco(endo)plasmic reticulum Ca^{2+}-ATPase (SERCA) activation [42], may also mediate Epi's superior potency & efficacy. Being able to exert this lifesaving action in the extremely dire situation of cardiac arrest via β_2AR activation might be one of the reasons why only the β_1AR (not the β_2AR) is downregulated in human chronic heart failure; however, β_2AR may also be desensitized and dysfunctional in this disease [43]. It could also explain why circulating Epi, contrary to NE, is not elevated in chronic human heart failure [44]: perhaps the body keeps Epi levels low in this disease state, so it can increase them to activate the β_2AR only at moments of absolute life-or-death emergencies, such as cardiac arrest or asphyxiation due to acute airway obstruction.

Abbreviations

AC, Adenylyl cyclase; AR, Adrenergic receptor; Epi, Epinephrine; NE, Norepinephrine; cAMP, Cyclic adenosine monophosphate; HCN4, Hyperpolarization-activated cyclic nucleotide-gated channel-4; NCX, Na^+/Ca^{2+} exchanger; NKA, Na^+/K^+-adenosine triphosphatase (ATPase); PKA, Protein kinase A; ROSC, Return of spontaneous circulation; SA, Sinoatrial; SERCA, Sarco(endo)plasmic reticulum Ca^{2+}-ATPase.

Author Contributions

AL conceived the article, performed literature research, and wrote the manuscript. AJM, RAS, and VLA assisted with literature research and contributed to the writing of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used Gemini for assistance with literature search. No AI tool was used for drafting of the manuscript. The authors take full responsibility for the content of the publication.

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