β -Adrenoceptor Blockade for Infantile Hemangioma Therapy: Do β_3 -Adrenoceptors Play a Role?

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Keywords

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Abstract

Infantile hemangiomas (IH) are frequent (4–5% of the childhood population) benign vascular tumors that involve accumulation, proliferation, and differentiation of aberrant vascular cells. Typically, IH are innocuous and spontaneously disappear, but they represent a potential risk for harmful effects in the body (e.g., permanent disfigurement) and health (e.g., ulcerations) in some patients. From a serendipitous discovery, the nonselective β -adrenoceptor blocker propranolol (which blocks β_1 -adrenoceptors, β_2 -adrenoceptors, and β_3 -adrenoceptors) emerged as an alternative therapy to treat this pathology and it quickly became a first-line treatment for IH. Nevertheless, its specific mechanisms of action remain thus far unknown. In this respect, several studies have suggested that β_1 -adrenoceptors and β_2 -adrenoceptors play a role in proliferative and angiogenic mechanisms. However, current basic research studies suggest that β_3 -

adrenoceptors could be also involved. Notably, β_3 -adrenoceptors stimulate multiple intracellular pathways related to vascular function (e.g., blood flow, angiogenesis, etc.). This review compiles some lines of evidence suggesting that β_3 -adrenoceptors may: (1) play a role in the pathophysiology of IH and (2) represent a potential therapeutic target for IH treatment. Hence, clinical evidence is mandatory to decide whether incorporation of β_3 -adrenoceptor blockers into the therapeutic armamentarium may increase effectiveness in the treatment of IH and other vascular anomalies.

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Introduction

Among proliferative vascular anomalies in pediatric patients, infantile hemangiomas (IH) are common and usually harmless [1–3]. The International Society for the Study of Vascular Anomalies (ISSVA) defines IH as benign and frequent vascular tumors that affect principally babies, children, and young adults [3]. To classify IH, the

Fig. 1. Chemical structures of the most relevant β -adrenoceptor blockers currently used in clinical practice (**a**) and some selective and potent β_3 -adrenoceptor blockers (**b**). Their relative selectivity (rank order) over the 3 different β -adrenoceptors is depicted. Data were taken from Alexander et al. [101] and Law et al. [102]. Values in parentheses are expressed as pK_i constants. FDA, Food and Drug Administration; IH, infantile hemangiomas.

ISSVA [3] uses the following main patterns: (1) focal, (2) multifocal, (3) segmental, and (4) indeterminate. These patterns of IH differ in terms of the anomaly extent (i.e., superficial, deep, mixed, reticular, and others). Clearly, to identify all of these differences it is important to achieve a more precise diagnosis and treatment [3].

From an epidemiological perspective, IH are prevalent in 4–5% of the childhood population [4–7], mainly in female Caucasians, and generally do not require therapy. Nevertheless, in 10–15% of patients diagnosed with IH some complications may occur and, consequently, effective therapy is necessary (see below) [6]. Although IH are

Table 1. Affinity of some drugs for β -adrenoceptors

Drug	β_1 -Adrenoceptor	β_2 -Adrenoceptor	β_3 -Adrenoceptor
Nevibolol	9.1 pK _D ¹	7.9 pK _D ¹	7.0 pK _D ¹
Propranolol	8.16 pK _D ²	9.1 pK _D ²	6.9 pK _D ²
Timolol	8.3 pK _D ²	9.7 pK _D ²	6.8 pK _D ²
Carvedilol	8.75 pK _D ²	9.4 pK _D ²	8.3 pK _D ²
Carazolol	9.7 pK _D ¹	10.5 pK _D ¹	8.3 pK _D ¹
L-748337	5.44 pK _D ¹	6.47 pK _D ¹	6.2–8.6 pK _D ¹
Atenolol	6.6 pK _D ²	5.9 pK _D ²	4.1 pK _D ²

β_3 -Adrenoceptor blockade as a potential therapeutic target against infantile haemangioma. ¹ Data taken from Baker [63].

² Data taken from Baker [54].

mainly detected in the head and neck [3], they can appear in other parts of the body such as the airways [8–10] and, depending on the location of the lesions, some patients can present dramatic disfigurement, ulcerations, visual compromise, airway and auditory canal obstruction, hypothyroidism, amblyopia, scarring, blindness, and liver or cardiac failure [11–13]. In the most dramatic cases, when the lesions invade systemic arteries, the life of the patient may be compromised [14], but only rare cases of death associated with complications in treating IH have been documented [15]. Indeed, the size of the lesions can vary from very small isolated tumors to large and progressive tumors that could compromise the function of the affected tissues/organs [16].

General Pathophysiology

Although abnormal levels of some biomarkers have been detected during pathophysiology progression [17, 18], the specific pathogenesis of IH is not deeply understood [19, 20]. In general, the tumors include aberrant agglutination of immature vascular endothelial cells, pericytes, glial and adipocytes [2, 21] that in IH result in dysregulation of vasculogenesis and angiogenesis [6]. One hypothesis that requires further investigation suggests that these cell types start to work aberrantly in part because they were submitted to a hypoxic stress that consequently induces overexpression of angiogenic factors (e.g., vascular endothelial growth factor; VEGF) [2, 22]. In any case, during IH progression there are active processes related to signaling pathways of vasculogenesis, angiogenesis, and tumorigenesis [19, 23]. Notably, the risk factors associated with IH include: (1) a low birth weight and/or premature birth; (2) Caucasian origin, (3) familial

antecedents for this pathology, (4) female sex, (5) advanced maternal age, and (6) in vitro fertilization [24–28]. Other factors that have been associated with the incidence of IH are: progesterone therapy during early pregnancy, prenatal maternal vaginal bleeding, multiple gestation pregnancy, low levels of maternal education, maternal engagement in manual labor, preeclampsia and placental anomalies, chorionic villus sampling, and amniocentesis [21, 27, 29, 30].

Commonly, it is possible to detect the following 3 phases during IH progression: (i) a proliferative period of tumor expansion of undifferentiated stem progenitor cells that subsequently differentiate into atypical vascular endothelial cells [31–33], (2) a second involution stage that usually occurs after age 1 year and is experienced in about 90% of IH sufferers (this stage encompasses a spontaneous decrease in the volume of lesions), and lastly (3) a resolution phase where biological changes occur, resulting in a fibro-fatty residuum and adipocytes [33–35].

The proliferative phase normally takes place during the first year of life [31, 33–36]. Macrophages from the M2 group may be involved by promoting the proliferation of aberrant cells [37], which in turn promote differentiation of tumor cells into endothelial cells and pericytes [38]. On the other hand, the regressive phase seems to include the participation of macrophages from the M1 group [39]. Finally, the resolution phase may last 5–10 years [35].

Multiple and diverse experimental therapies have been used in an attempt to find an effective treatment against different types of IH. These include electrocautery [40], interferon- α -2A [26], steroids, and CO₂ laser, among others unspecific treatments [41]. More recently, the antihypertensive agent propranolol (a nonselective β -adrenoceptor blocker with a higher affinity for block $\beta_1 \geq \beta_2 > \beta_3$; Fig. 1; Table 1) has been reported to be a successful specific treatment for IH [1]. Indeed, propranolol was recently approved by the Food and Drug Administration (FDA) for the treatment of this pathology [42], and in few years it became a first-line treatment for IH [43]. In view of the casual discovery of propranolol as an agent with properties against IH [1], the therapeutic mechanisms of action by which propranolol exerts its anti-IH action are partially understood. Certainly, the β -adrenoceptor family consists of β_1 -adrenoceptor, β_2 -adrenoceptor, and β_3 -adrenoceptor subtypes [33] and propranolol can interact with the 3 receptor subtypes (Fig. 1a). Current research on the role of the different subtypes on IH pathophysiology remains ambiguous and there are opposite findings sup-

porting the specific (if any) β -adrenoceptor subtype(s) involved in the different phases of IH. In this respect, some in vitro results suggest that β_3 -adrenoceptors are not involved in IH [44], whereas others suggest that all β -adrenoceptor subtypes contribute to this pathology [45]. On this basis, the present review was set up to further assess the literature supporting the potential role of the β_3 -adrenoceptor subtype in the pathophysiology and therapeutics of IH.

β -Blockers as a First-Line Treatment for IH

Pharmacology of β -Adrenoceptors and Transductional Mechanisms

The β -adrenoceptors (β_1 , β_2 , and β_3) are G-stimulatory protein-coupled (G_s -coupled) receptors that canonically promote the guanosine-triphosphate pathway [33] and the adenylate cyclase pathway which increases the levels of intracellular cyclic adenosine monophosphate (cAMP) [46]. Interestingly, the β_3 -adrenoceptor subtype has been reported to be functionally coupled to both G_s and G_i proteins simultaneously (at least in adipocytes) [47]. Moreover, some proliferative actions of selective β_3 -adrenoceptor agonists (i.e., ZD7114) involve the activation of phospholipase C, PKC, and the calcium/calmodulin complex [48]. Clearly, the β_3 -adrenoceptor is a highly complex subtype whose actions under physiological and pathological conditions remain unclear.

Under physiological conditions, the autonomic nervous system can carry out a suitable regulation of structure and cardiovascular function via several mechanisms mediated by β_1 -adrenoceptors and β_2 -adrenoceptors, whereas the role of β_3 -adrenoceptors has been associated with negative feedback that inhibits sympathetic hyperactivity (e.g., via the release of anticontractile molecules from adipocytes) [49] and/or with compensatory mechanisms under pathological or specific conditions such as pregnancy [50, 51]. Certainly, β_3 -adrenoceptors are expressed in blood vessels, the heart, and adipocytes [52], but they have been useless as therapeutic targets in clinical practice because of their complex pharmacological profile (see above).

The typical G-protein pathway that all β -adrenoceptors activate in smooth muscle cells (including the β_3 -adrenoceptor subtype) [53] seems to be the G_s protein that activates the adenylate cyclase enzyme for augmenting cAMP which, in turn, produces relaxation (in the case of vascular tissues, this pathway leads to an increase in blood flow). Accordingly, the β -blockers are among the

most widely used drugs in clinical practice to treat cardiovascular diseases such as hypertension, heart failure, and cardiac arrhythmias, and they may exert cardioprotection after myocardial infarction, migraines, anxiety, tremors, glaucoma, etc. [54, 55], where vasodilatation plays a key role in the pathophysiology. Typical actions of β -adrenoceptor blockers (or β -blockers) include: (1) bradycardia by blocking the β_1 -adrenoceptors mainly located in heart and (2) bronchoconstriction by blocking β_2 -adrenoceptors [56].

Propranolol as a First-Line Treatment for IH

From this point of view, ever since its discovery as an anti-IH, one of propranolol's therapeutic mechanisms of action has been associated with its vasoconstrictor effect considering that immediately after treatment a visible change in the color (due to vascular irrigation) of the hemangioma was observed [1]. That clinical report [1] showing propranolol's spectacular results on IH treatment not only promoted several studies that tested the efficacy of propranolol and other β -blockers for the treatment of IH but also encouraged research on the role of β -adrenoceptors in the pathophysiology of this disease [12, 57, 58].

It is important to note that some β -blockers used to treat IH show little differences in their pharmacological profiles for blocking their β -adrenoceptor subtypes (Fig. 1). This lack of selectivity makes it difficult to determine the specific β -adrenoceptor subtype directly associated with its therapeutic action. Whatever the case, β -adrenoceptor blockers seem to be effective therapeutic tools for managing IH, for example: (1) propranolol induced a decrease in redness, size, and latency to resolution in IH patients [57–59], (2) atenolol induced regression of IH at 4 weeks of treatment in 93.4% of patients [12], (3) acetobutolol was efficient against subglottic IH without side effects [60], and (4) timolol was also effective against superficial IH using 0.5% gel administered topically [61]. Furthermore, positive effects against IH have been seen by combining β -blockers such as oral propranolol plus timolol gel. This combination showed a positive response in 100% of the patients with few side effects [62].

On the other hand, despite the arsenal of β -adrenoceptor blockers to block $\beta_1/\beta_2/\beta_3$ -adrenoceptor subtypes, the lack of selectivity for β_3 -adrenoceptors is a general characteristic of these drugs [54, 63]. This lack of selectivity has made it difficult to ascertain the potential role of β_3 -adrenoceptors in the therapeutics of IH. This notwithstanding, some lines of evidence suggest that β_3 -adrenoceptors may be involved (see below).

β -adrenoceptor activation. Certainly, β -adrenoceptor activation facilitates diseases involved in abnormal cell growth [103, 104], an effect reverted by β_3 -adrenoceptor blockade [68, 90]. Furthermore, the mRNA expression of β_3 -adrenoceptors was significantly higher in a population of propranolol-responsive IH, suggesting a clinical relevance of the use of selective β -blockers [105]. Akt, protein kinase B; cAMP, cyclic adenosine monophosphate; GRK, G protein-coupled receptor kinase; EGFR, epidermal growth factor receptor; HIF-1 α , hypoxia-inducible factor-1 α ; mTOR, mammalian target of rapamycin; NF- κ B, nuclear factor κ -light-chain enhancer of activated B cells; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PKA, protein kinase A; Src, proto-oncogene tyrosine-protein kinase Src; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

As shown in Figure 2, the activation of all β -adrenoceptors may induce mechanisms that lead to differentiation of hemangioma-derived endothelial cells [45, 64]. Indeed, β -adrenoceptors have been associated with the promotion and development of diverse tumors such as adenocarcinomas, squamous cell carcinomas [64], colon cancer, hepatocellular carcinoma, lung adenocarcinoma,

prostate cancer, and breast cancer [65]. Moreover, activation of β -adrenoceptors induces synthesis of VEGF and basic fibroblast growth factor, which are proangiogenic factors that activate the mitogen-activated protein kinase (MAPK) cascade leading to angiogenesis [45]. ERK and MAPK regulate the expression of various genes and nuclear transcription factors involved in cell proliferation [64]. In this respect, during the proliferative phase of IH, a high expression of β_2 -adrenoceptors and β_3 -adrenoceptors has been reported [45]. Moreover, Dal

Monte et al. [66] reported that β_3 -adrenoceptors are involved in angiogenesis induced by hypoxia. It is important to highlight that hypoxia may be a determinant factor for the development of IH [67]. In contrast, apoptosis as the therapeutic mechanism of action of β -blockers in IH remains unclear [33, 68, 69].

On the other hand, the capability of β_3 -adrenoceptors (which are expressed in blood vessels, the heart, and adipocytes) [52] to control blood flow at a local level may be another plausible mechanism that requires further research. Certainly, peripheral β_3 -adrenoceptors seem to induce direct and indirect vasodilatation [70], but they produce no clear effects on systemic blood pressure [71]. However, some studies have confirmed the role of β_3 -adrenoceptors in some vascular actions, e.g., (1) vasodilatation in brown adipose tissue [72], (2) regulation of the retinal blood flow with no detectable actions on systemic hemodynamic variables [73], and (3) vasodilatation in mesenteric and aortic arteries [74]. These findings, coupled with the high expression of β_3 -adrenoceptors in different vascular cells during all phases of IH [45], suggest an important participation of β_3 -adrenoceptors in IH. In agreement with this suggestion, β_3 -adrenoceptors can induce proliferative and migrative actions (e.g., in retinal endothelial cells) [75] and vasodilatation (e.g., at the ophthalmic level) [73]. On this basis, β_3 -adrenoceptors may represent a novel pharmacological target for different vascular ophthalmic disorders (including IH).

In addition to vascular actions, β_3 -adrenoceptors are expressed in the mammalian cardiac system, where their functions seem to be related with ventricular relaxation and cardioprotection [76, 77]. Interestingly, β_3 -adrenoceptors are overexpressed during hyperglycemia, hypertension, and heart failure [78, 79]. Altogether, these findings suggest that β_3 -adrenoceptors could be a kind of auto-break for the sympathetic tone and a homeostatic promoter under some pathological conditions.

Basic Research: Lines of Evidence Supporting the Potential Clinical Usefulness of β_3 -Adrenoceptor Blockers in the Treatment of IH

As previously pointed out: (1) β_3 -adrenoceptors play a physiological role in the control of several vascular functions (both proliferation/differentiation and blood flow in some tissues), and (2) the pharmacological profile of propranolol [54, 63] guarantees a reasonable blockade of all β -adrenoceptor subtypes, with a rank order of antagonist potency of β_2 -adrenoceptors > β_1 -adrenoceptors >

β_3 -adrenoceptors [80] (Fig. 1). Thus, it may seem reasonable to suggest that some therapeutic effects of propranolol may result from blocking β_3 -adrenoceptors (Fig. 2). In keeping with this suggestion, refractory cancer may be successfully treated with β -adrenoceptor blockers combined with chemotherapy [81], but the mechanisms of action beyond specific β -adrenoceptor subtype blockade are not evident. For example, Chang et al. [82] showed that EGF-induced AP-1 transactivation: (i) remained unaffected by atenolol (a β -blocker with a very low affinity for β_3 -adrenoceptors) [54, 63] at any dose tested (which is required for tumor promotion) and (2) was prevented by carvedilol (a nonselective β -blocker with a high affinity for β_3 -adrenoceptors; Table 1). The simplest interpretation of these findings may be that, apart from the β_1 / β_2 -mediated actions, some affinity for β_3 -adrenoceptors may be a *conditio sine qua non* for their antiproliferative actions. Clearly, this speculation requires further experimental evidence.

Furthermore, since β_3 -adrenoceptors may be involved in the local control of vasodilatation in some tissues (e.g., at ophthalmic level) [52, 70, 73], another mechanism of action by which β_3 -adrenoceptor blockers could be useful in therapeutics of IH may be via local vasoconstriction. Of course, further experiments are required to confirm this possibility. The above findings point to a potential therapeutic utility for β_3 -adrenoceptors as a target in the treatment of vascular proliferative anomalies. Indeed, novel β -adrenoceptor blockers with a higher affinity/selectivity for β_3 -adrenoceptors should and could be tested experimentally to explore their utility in the pathophysiology of IH and other vascular diseases. In addition, at the ophthalmic level, β_3 -adrenoceptor blockers may represent a very selective option for treating vascular proliferative disorders. Certainly, in the case of propranolol, the FDA initially approved this drug to treat angina [83] and lately it has been widely used in the treatment of hypertension, myocardial infarction, anxiety disorders, migraines, tremor, and, more recently, IH [42, 84]. However, a local vascular regulator (i.e., a selective β_3 -adrenoceptor blocker) with no systemic actions on blood pressure may be more useful than propranolol. It could even be used at lower doses if administered in combination with other antiproliferative agents to treat IH more effectively and perhaps with fewer side effects than those related to the current use of propranolol (e.g., hypoglycemia, hypotension, bronchial hyperreactivity, restless sleep, constipation, and cold extremities) [85].

Selective β_3 -adrenoceptor antagonists such as L-748337 [86] have shown beneficial actions in heart failure in ex-

perimental dogs [87]. Hence, it is not unreasonable to suggest that a novel application for selective β_3 -adrenoceptor antagonists may include IH and other vascular anomalies. In keeping with this suggestion, a decrease in nitric oxide (NO) levels, VEGF, and the release of proangiogenic factors was observed after β_3 -adrenoceptor blockade (with SR59230A and L-748337) in hypoxic retinal explants [66, 88]. Moreover, treatment with L-748337 showed a reduction in tumor weight, volume, and growth via a decrease in cell proliferation, iNOS expression, and VEGF production and an increase in apoptosis [89–91]. The above findings, taken together, suggest that targeting β_3 -adrenoceptors might be relevant in the treatment of IH, since this receptor seems to be involved in the pathophysiology of IH.

Main Side Effects Resulting from β -Adrenoceptor Blockade

As previously stated, propranolol and other β -adrenoceptor antagonists have long been used in the treatment of various diseases, but important side effects include, among others: light-headedness, drowsiness, nausea, cold extremities, fatigue, bradycardia, bronchospasm, indigestion, and diarrhea [92, 93]. In the specific case of propranolol-based treatment for IH, some patients have reported side effects such as: hypoglycemia, hypotension, bradycardia, bronchial hyperreactivity, restless sleep, constipation, cold extremities, gastrointestinal problems, and diarrhea [57, 85]. As propranolol exerts 10-fold and 100-fold more affinity for β_1 -adrenoceptors and β_2 -adrenoceptors, respectively, than for β_3 -adrenoceptors (Table 1), these side effects may be mediated via blockade of β_1 -adrenoceptors and β_2 -adrenoceptors rather than β_3 -adrenoceptors.

In the case of carvedilol (a nonselective β -adrenoceptor blocker with a rank order of antagonist potency of $\beta_1 \gg \beta_2 \geq \beta_3$; Table 1), the most common side effects are dizziness and hypotension [94]. Also, in the treatment of pediatric heart failure, side effects such as dizziness, hypotension, dyspnea, fatigue, and headache have been reported, with the latter being most common in children [95]. Besides, bradycardia has been found to be a side effect related to the use of carvedilol in the treatment of chronic heart failure [96]. However, in general, carvedilol presents a tolerable profile in different kinds of patients [97].

The side effects produced by tertatolol include fatigue, headache, and hot flushes [98]. Evidently, as these drugs are not selective β -adrenoceptor blockers, the specific ad-

renoceptors involved in all of these side effects have not been determined. Nevertheless, in agreement with their expression and pharmacological profile, it is possible that side effects follow a rank order of antagonist potency of: β_1 -adrenoceptor > β_2 -adrenoceptor > β_3 -adrenoceptor. The great expression of β_1 -adrenoceptors in the heart and of β_2 -adrenoceptors in multiple-tissue smooth muscle cells may be also involved in explaining some side effects associated with propranolol and other nonselective β -adrenoceptor antagonists. The above lines of evidence, in conjunction with all basic research data (see Basic Research: Lines of Evidence Supporting the Potential Clinical Usefulness of β_3 -Adrenoceptor Blockers in the Treatment of Infantile Hemangiomas), make it logical to explore the potential therapeutic participation of β_3 -adrenoceptor blockade (if any) in IH. Following this line of reasoning, an eventual anti-IH drug with a predominant affinity for β_3 -adrenoceptor (and a secondary affinity for β_1 -adrenoceptors and β_2 -adrenoceptors) might induce its therapeutic effects faster and in a way that is better tolerated than propranolol. Undoubtedly, these are just theoretical speculations that require many experimental findings in order to be proven.

Notably, Watkins et al. [99] showed that nonselective β -adrenoceptor antagonist therapies seemed to be associated with a longer overall survival in patients with ovarian cancer compared to those receiving selective β_1 -adrenoceptor antagonist therapies. Similarly, Montoya et al. [100] demonstrated that selective β_1 -adrenoceptor antagonist therapies were less effective against proliferation of tumors than nonselective ones. The above lines of evidence, in a simplistic interpretation, may be explained in 2 main ways: (1) it is mandatory to induce the blockade of more than one β -adrenoceptor type, and/or (2) β_1 -adrenoceptor blockade alone is not responsible for the therapeutic effects in these cases. This, again, is a field that requires further research.

Importantly, the potential adverse side effects induced by any selective β_3 -adrenoceptor antagonist have not yet been reported. Hence, additional toxicological studies are required to explore the potential side effects produced by selective β_3 -adrenoceptor antagonists before any attempt is made to explore their clinical effects.

Conclusions

Propranolol is an effective therapeutic tool for treating IH. Nevertheless, as it is a nonselective β -adrenoceptor blocker, it is difficult to determine the specific contribu-

tion of each β -adrenoceptor subtype. Knowledge of this may be useful for selecting a more appropriate β -adrenoceptor blocker which, in turn, could: (1) reduce the therapy time and side effects and (2) increase therapeutic efficacy. Since basic research data seem to support the participation of β_3 -adrenoceptors in the pathophysiology of IH, we hope that this review will motivate clinical research groups to analyze the potential therapeutic use-

fulness and toxicological risks of β_3 -adrenoceptor antagonists (as they may be useful against IH and other vascular abnormalities).

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