Western University Scholarship@Western

Paediatrics Publications

Paediatrics Department

1-1-2014

Mechanisms of propranolol action in infantile hemangioma

Jina J.Y. Kum Schulich School of Medicine & Dentistry

Zia A. Khan Schulich School of Medicine & Dentistry, zia.khan@schulich.uwo.ca

Follow this and additional works at: https://ir.lib.uwo.ca/paedpub

Citation of this paper: Kum, Jina J.Y. and Khan, Zia A., "Mechanisms of propranolol action in infantile hemangioma" (2014). *Paediatrics Publications*. 2187. https://ir.lib.uwo.ca/paedpub/2187





Dermato-Endocrinology

ISSN: (Print) 1938-1980 (Online) Journal homepage: https://www.tandfonline.com/loi/kder20

Mechanisms of propranolol action in infantile hemangioma

Jina JY Kum & Zia A Khan

To cite this article: Jina JY Kum & Zia A Khan (2014) Mechanisms of propranolol action in infantile hemangioma, Dermato-Endocrinology, 6:1, e979699, DOI: 10.4161/19381980.2014.979699

To link to this article: https://doi.org/10.4161/19381980.2014.979699

6

© 2014 The Author(s). Published with license by Taylor & Francis Group, LLC© Jina JY Kum and Zia A Khan



Published online: 26 Jan 2015.

Submit your article to this journal 🕑

Article views: 1647



View related articles



View Crossmark data



Citing articles: 9 View citing articles 🗹

Mechanisms of propranolol action in infantile hemangioma

Jina JY Kum¹ and Zia A Khan^{1,2,3,*}

¹Department of Pathology and Laboratory Medicine; Schulich School of Medicine & Dentistry; Western University; London, Ontario Canada; ²Metabolism and Diabetes Research Program; Lawson Health Research Institute; London, Ontario Canada; ³Division of Genetics and Development; Children's Hospital Research Institute; London, Ontario Canada

Keywords: adrenergic receptors, angiogenesis, apoptosis, endothelial cells, infantile hemangioma, propranolol, stem cells

Abbreviations: Akt, protein kinase B; ADR, adrenergic receptor; bm-MPC, bone marrow mesenchymal progenitor cell; cAMP, cyclic adenosine monophosphate; CREB, cAMP response element binding protein; EC, endothelial cell; EPAC, exchange protein activated by adenylyl cyclase; Glut-1, glucose transporter-1; hemECs, hemangioma-derived endothelial cells; hemSCs, hemangioma-derived stem cells; hemPericytes, hemangioma-derived pericytes; IH, infantile hemangioma; IL, interleukin; MAPK, mitogen-activated protein kinase; MMP, matrix metalloproteinase; mTOR, mammalian target of rapamycin; PKA, protein kinase A; PPAR, peroxisome proliferator-activated receptor; VEGF, vascular endothelial growth factor

Infantile hemangioma is a common tumor of infancy. Although most hemangiomas spontaneously regress, treatment is indicated based on complications, risk to organ development and function, and disfigurement. The serendipitous discovery of propranolol, a non-selective β-adrenergic receptor blocker, as an effective means to regress hemangiomas has made this a first-line therapy for hemangioma patients. Propranolol has shown remarkable response rates. There are, however, some adverse effects, which include changes in sleep, acrocyanosis, hypotension, and hypoglycemia. Over the last few years, researchers have focused on understanding the mechanisms by which propranolol causes hemangioma regression. This has entailed study of cultured vascular endothelial cells including endothelial cells isolated from hemangioma patients. In this article, we review recent studies offering potential mechanisms of how various cell types found in hemangioma may respond to propranolol.

Infantile Hemangioma

Infantile hemangioma (IH) is the most common vascular tumor of infancy.¹ For reasons unknown, IH affects more females than males, and is also more prevalent in premature and Caucasian babies, ultimately affecting up to 10% of infants.^{2,3} IH is often noticed soon after birth, when a bright red lesion appears.⁴ Approximately 80% of these lesions are found in the head and neck regions, but they can be located elsewhere in the

*Correspondence to: Zia A Khan; Email: zia.khan@schulich.uwo.ca

Submitted: 08/19/2014; Accepted: 10/20/2014

http://dx.doi.org/10.4161/19381980.2014.979699

body.^{5,6} It has been well-established that IH follows 3 developmental phases.^{7,8} The first phase entails expansion of undifferen-tiated stem/progenitor cells.^{9,10} These stem/progenitor cells differentiate into atypical vascular endothelial cells (ECs) characteristic of IH. Uniquely, IH endothelium exhibits robust expression of glucose transporter-1 (Glut-1).^{11,12} This proliferating stage is completed by 8 months of age in most cases.¹⁰ In the following involuting phase, the differentiation process continues as hemangioma-initiating cells differentiate into ECs and pericytes.^{13,14} This involuting phase, like the proliferating phase, is a continuum of cellular and molecular changes with the end result being appearance of adipocytes and fibrofatty residuum.^{7,8,14} Most IHs resolve spontaneously and do not require treatment.¹⁵ However, therapeutic intervention is necessary in cases where the lesion grows in certain locations and to sizes that could result in life-threatening complications. An example of such a situation is the growth of IH in the airway to obstruct the respiratory system.¹⁶

Current Treatment Options for IH

Although a number of attempts have been made, the treatment guidelines for IH are not fully clear due to the differential effects of various therapeutic options, the differences in the location, stage and size of the tumors, and the age of patients.¹⁵ Treatment is typically initiated during the early proliferative stage of the tumor at which point many treatment options are available such as surgery, laser, and corticosteroids.¹⁷⁻²⁰ Corticosteroids represented a common treatment option for IH patients, however, there are severe side effects including severe growth retardation in children when used over an extended period of time at high doses.²¹ Propranolol, a synthetic β-adrenergic receptor (ADR) antagonist that is widely used to treat myocardial complications, was accidentally discovered to be a promising treatment for IH.²² This non-selective β-blocker proved to be more effective with fewer adverse events when compared to corticosteroids, such that it is now the first-line treatment option.²³ Despite its

[©] Jina JY Kum and Zia A Khan

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

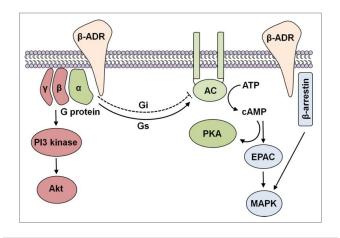


Figure 1. Schematic illustrating -adrenergic receptor signaling. Ligand binding to β -adrenergic receptors (β -ADRs) results in Gs-mediated activation of adenylyl cyclase (AC) and subsequent conversion of ATP into cAMP. Intracellular cAMP activates PKA to phosphorylate multiple target proteins. cAMP may also activate exchange protein activated by adenylyl cyclase (EPAC) leading mitogen-activated protein kinase signaling pathway and downstream effects on cellular processes. Another pathway activated by β -ADRs is the PI3 kinase and protein kinase B (Akt) pathway which may be initiated through dissociated G $\beta\gamma$ complex. In addition to G protein-mediated signaling, β -ADRs may also participate in G protein-independent signaling through β -arrestin and MAPK.

effectiveness, a major challenge remains in understanding the therapeutic mechanism of propranolol in regressing IH.

Propranolol usage has shown remarkable efficacy.²³ There are some adverse effects associated with propranolol use, which include sleep disturbances, acrocyanosis, hypotension, and hypoglycemia.^{24,25} In addition, there are also reports of IH regrowth following cessation of treatment in as many as 20% of the cases.^{26,27} Therefore, greater understanding of the potential mechanisms underlying the therapeutic effect is needed to develop better and safer treatment options. Many mechanisms have been proposed, though only tested in culture studies, to explain the therapeutic mechanism of propranolol in treating IH. Theories involving vasoconstriction,²⁸ EC apoptosis via β-ADR signaling^{29,30} and the caspase pathway,^{31,32} and inhibition of angiogenesis via the modulation of vascular growth factors^{30,33,34} have been suggested. This review will emphasize the diverse mechanisms implicated with the therapeutic action of propranolol in the various cell types found in IH.

β-adrenergic Receptor Signaling

β-adrenergic receptors (β-ADRs) are a family of G proteincoupled receptors that mediate physiological responses to adrenaline and noradrenaline. To date, 3 subtypes of β-ADRs have been identified: β1-3 ADRs. Although a putative β4 subtype has been suggested, the function and localization remains unknown. There is limited information available on β1-3 ADR distribution at the cellular as well as the tissue level. Highest levels of β1-ADR are believed to be found in the heart and brain.³⁵ β2-ADR shows a wide spread distribution pattern.³⁶ β3-ADR is believed to be predominantly expressed in adipose tissue consistent with its lipolytic function.³⁷ In the blood vessels, studies have utilized β -ADR antagonist binding and shown sites in all cellular layers of vessels.^{38,39} Predominant ADR subtypes in vessels include β 1 and β 2 as confirmed by β -ADR subtype knockout studies.³⁸ Using immunohistochemistry, β 1 and β 2 ADR protein has been localized to IH endothelium (co-localized to CD31-positive cells) as well as perivascular cells (co-localized to α -smooth muscle actin-positive cells).^{40,41} In addition, β 3 ADR has also been reported in all phases of IH.³⁴ Given that β -ADRs are present in normal vessels and IH vessels, the question arises as to the role of β -ADRs in vessel function and the effect of β -ADR blockade in IH resolution.

β1 and β3 generally couple with Gs (stimulatory) proteins, whereas $\beta 2$ may couple with Gs or Gi (inhibitory) (Fig. 1). In the unstimulated state, the trimeric G protein is bound to GDP. Activation of ADRs promotes exchange of GDP for GTP. The G protein's a subunit with bound GTP then dissociates from the β and γ subunits to phosphorylate adenylate cycles (AC) and increase intracellular cyclic adenosine monophosphate (cAMP) levels. Gi may counteract this increase by inhibiting AC. Intracellular cAMP activates cAMP-dependent protein kinase A (PKA) which may have multiple cellular consequences.⁴² For example, PKA has been shown to be involved in elaboration of angiogenic factors through cAMP response element-binding protein (CREB).⁴³ In addition to PKA-mediated signaling, activated AC may also activate mitogen activated protein kinase (MAPK) pathway through exchange protein activated by adenylyl cyclase (EPAC).^{44,45} Dissociated G $\beta\gamma$ may also lead to activation of phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3 kinase) and Akt/protein kinase B. In addition, ADR signaling may entail a G protein independent signaling pathway. A well-characterized example is the B-arrestin-mediated activation of MAPK pathways.^{46,47} These pathways indicate that inhibiting β-ADR by propranolol in IH may, indeed, have beneficial effects by reducing cell survival as well as inhibiting angiogenesis. In support, Zhang et al have shown that propranolol does regulate MAPK pathway and activity of CREB in pancreatic cancer cells.⁴⁸

Cell-type Dependent Effect of Propranolol in Infantile Hemangioma

Hemangioma-derived endothelial cells (HemECs)

Culture of hemangioma-derived ECs (HemECs) in the presence of propranolol causes apoptosis.⁴⁹ This is evident upon exposure to 100 μ mol/L propranolol in the culture media.^{32,49,50} Ji et al. also found significant increases in caspase-3 and -9 cleavage products, but not caspase-8 cleavage following propranolol exposure.⁴⁹ These results are suggestive of an intrinsic apoptotic pathway mediated by propranolol. However, other studies have found an increase in protein and mRNA levels of caspase-8³², indicative of both intrinsic and extrinsic involvement of the apoptotic pathway. At the mRNA level, it was reported that propranolol induces expression of apoptotic genes, such as Bax, p53, caspase-8, and cytochrome c in hemECs that may be responsible for its apoptotic effect.^{32,49} It should be noted that these studies have essentially examined the effect of propranolol without the addition of β -ADR stimulation. This may suggest a constitutively active β -ADR pathway. Stress hormones or growth factors in serum may also play a role. Interestingly, propranolol's effect is not specific to hemECs, as it has been shown to cause apoptosis in a similar manner with other EC types as well.^{29,50,51}

Many studies have gone in-depth with analyzing the expression levels of the different β -ADR subtypes. It has been shown that hemECs and other EC types express both β 1- and β 2-ADRs at very similar levels, but not β 3.^{52,53} We have shown that normal ECs express all 3 β -ADRs, with β 1-ADR expression being significantly higher when compared to the other subtypes.⁵⁰ Despite the various β -ADRs expressed, it is believed that the main mechanism of action of propranolol in hemECs may involve β 1 and/or 2-ADR pathway. A recent report by Ji et al. have shown that ICI-118551 (a selective β 2-ADR antagonist) was more effective than metaprolol (selective β 1-antagonist) in inhibiting hemECs proliferation.⁵⁴

In addition to caspase-mediated apoptosis, propranolol may block phosphorylation of vascular endothelial growth factor receptor 2 (VEGFR-2).⁵² It was found that when hemECs were challenged with higher concentrations of propranolol (50 and 100 μ mol/L), the expression of VEGF at the protein level was reduced in a dose-dependent manner.^{49,55} This reduction in the level of activated VEGFR-2 receptors and VEGF protein upon propranolol exposure was a critical element that affected the survivability of these hemECs.^{52,56} In addition, decrease in key cyclin levels and an increase in cell cycle inhibitor levels were observed.⁵² This suggested that cell cycle regulation is also another mechanism involved in mediating propranolol's therapeutic effect. HemECs show a greater proportion of cells in the G1 phase than the S/G2 phase when treated with propranolol.^{29,52} This was further confirmed with decreased expression of cyclin proteins such as cyclins A1, A2, B2, D1, D2, D3,^{29,50,52} while cell cycle inhibitor proteins p15, p21, p27,52 were upregulated.

Hemangioma-derived stem cells (HemSCs)

We have shown that IHs are derived from multipotential stem cells termed hemangioma stem cells (hemSCs).9 Clonally expanded hemSCs produce Glut-1 positive microvessels in immunodeficient mice. Boscolo and colleagues have shown that binding of VEGF-A and VEGF-B to VEGFR-1 expressed on the surface of hemSCs is required for the induction of hemSC to EC differentiation, and for blood vessel formation.⁵⁷ Interestingly, immunostaining of IH specimens shows co-labeling of EC markers and stem cell markers indicative of an immature EC phenotype in IH.^{14,50} Since IHs regrow in a significant proportion of patients that discontinue propranolol treatment,²⁶ it is possible that hemSCs, unlike hemECs and normal vascular ECs, are not susceptible to propranolol-induced apoptosis. This may explain why recurrence of these tumors often occurs following cessation of treatment. We have recently shown that propranolol causes significantly reduced cell number.⁵⁰ To determine whether the decrease in hemSCs was due to changes in the cell viability as

expected from studies utilizing ECs, caspase-3 was measured. Unlike ECs, the levels of activated caspase-3 were significantly reduced in hemSCs.⁵⁰ This indicates that hemSCs do not undergo apoptosis upon propranolol exposure. However, propranolol exposure significantly decreased cyclin-D1 levels in hemSCs, similar to its effect in ECs,⁵⁰ suggesting that the decrease in hemSCs cell number upon propranolol exposure is not due to apoptosis, but rather the inhibition of cell cycle progression. Furthermore, Zhang and colleagues have shown that propranolol reduces VEGF expression in hemSCs, that later suppresses angiogenesis.⁵⁸ At the protein level, the quantity of VEGF produced by hemSCs decreased in a dose-dependent manner, showing a significant reduction even at a very low concentration (0.02 µmol/L) of propranolol.⁵⁸ This decrease in VEGF levels from hemSCs may also contribute to their quiescent state, rather than apoptosis, upon propranolol treatment.

The difference in propranolol response between hemECs and hemSCs may be related to β-ADR subtype expression. Studies have shown that β 1-ADR and β 2-ADR have opposing effects on regulating apoptosis.⁵⁹⁻⁶¹ HemSCs express β2 and β3-ADRs, whereas ECs predominantly express β1-ADR.⁵⁰ This suggests that propranolol may mediate its apoptotic effect in ECs through β 1-ADR, and cell cycle arrest in hemSCs through β 2-ADR. A novel mechanism we have observed in hemSCs is a significant induction of anti-apoptotic genes following exposure to propranolol.⁵⁰ Although these inductions were significantly higher in hemSCs, anti-apoptotic genes were also evident, but to a lesser degree, in normal bone marrow-derived mesenchymal progenitor cells (bm-MPCs).⁵⁰ This indicated that upon propranolol exposure, these stem/progenitor cells trigger a mechanism that induces anti-apoptotic genes to provide these cell types with an apoptotic escape route, unlike ECs.

IH ends its continuous developmental phase when adipocytes replace majority of the tumor lesion. Yu and colleagues first reported presence of cells with adipogenic differentiation potential in proliferating phase IH.⁶² More recently, we have shown that clonally derived hemSCs produce human adipocytes when implanted in immunodeficient mice.⁹ Culturing hemSCs in the presence of propranolol enhances adipogenesis and this may offer another possible mechanism of the beneficial effects of propranolol in IH resolution. Continuous culture of hemSCs in adipogenic differentiation media supplemented with propranolol causes cell death.³¹ These results suggested that propranolol treatment accelerated the dysregulated differentiation process in hemSCs that ultimately resulted in increased apoptosis of adipocytes derived from hemSCs.³¹ It is possible that differentiation of hemSCs causes a shift in β -ADR expression profile and an increase in β 1-ADR which may induce apoptosis. We have found that upon adipogenic differentiation in hemSCs, all 3 β -ADR subtypes are significantly increased. Therefore, changing β -ADR profile may increase cell's susceptibility to apoptosis, in a manner similar to that of propranolol-treated ECs.

Hemangioma-derived pericytes (HemPericytes)

Pericytes are cells that control EC proliferation and survival by stabilizing the vasculature wall and releasing pro-survival signals.⁶³ In IH, pericytes are also believed to be derived from hemSCs.⁶⁴ When hemSCs are in direct cell contact with ECs, hemSCs can also differentiate into pericytes through the JAG-GED1 signaling.⁶⁴ It is known that addition of β -ADR agonists and cAMP analogs can induce relaxation of pericytes.⁶⁵ When hemPericytes were exposed to propranolol, epinephrine-induced relaxation in hemPericytes was prevented.⁶⁶ Furthermore, the proliferative capacity of hemPericytes was also reduced. These pericytes also expressed B2-ADRs on their cell surface.⁶⁶ With knockdown of B2-ADR, hemPericytes lost epinephrine-induced relaxation and propranolol had no effect.⁶⁶ This suggested that β2-ADR is involved with relaxation and contractility of hemPericytes in response to propranolol.⁶⁶ In addition, when hemPericytes co-implanted with hemECs were exposed to propranolol, propranolol decreased the vascular volume indicative of increased vasoconstriction.⁶⁶ This may be suggestive of a possible mechanism by which propranolol causes increased constriction of the vasculature in IH to reduce the blood flow to the tumor, limiting its growth.

Effect of Propranolol in Other Human Neoplasms

The progression of various cancers has been associated with alteration of β -ADR signaling pathways. Hence, β -blockers have been proposed as therapeutic agents for various cancers. Pediatric melanoma is a rare disease but its incidence has increased in the young population. Melanoma is accountable for up to 3% of all pediatric malignancies.⁶⁷ Similarly to IH, melanoma cases are more commonly diagnosed in Caucasian and female patients,⁶⁸ and almost 20% of malignant melanoma occurs in the head and neck region.⁶⁹ Melanocyte stem cells (MSCs) generate melanocytes that produce melanin-pigment throughout adult life. When MSCs undergo mutation and transform, it can result in melanoma.^{70,71} The pathogenesis of melanoma is still subject to debate, but many have suggested mutations involving the cell cycle and apoptosis pathways, such as tumor protein p53 pathways, and stressors that increase catecholamines are involved in tumor progression.72,73

The increase in norepinephrine and epinephrine primarily modulates the β-ADR pathways, through PKA and MAPK signaling mechanisms, ultimately affecting the growth and progression of melanoma.⁷⁴ Additionally, increases in the expression of VEGF, interleukin (IL) -6 and IL-8 after catecholamine stimulation correlates with the aggressiveness of the tumor.74,75 Similar to IH, melanoma cells express $\beta 1$ and $\beta 2$ -receptors with $\beta 1$ -ADR expression being weaker relative to \$2-ADR.72,74 Recently, B3-ADRs have been proposed to be involved with melanoma growth and vascularization.⁷⁶ The use of β -blockers in malignant melanoma decreased the risk of progression.⁷⁷ Although the exact mechanism underlying the effectiveness of these medications in reducing tumor progression is unknown, it has been suggested that β-blockers reduce angiogenic factors and metastatic progression.⁷⁷ It is thought that β -blockers inhibit angiogenesis by reducing VEGF activity via MAPK signaling. In addition, *B*-blockers also modulate matrix metalloproteinases (MMPs) that can alter the tumor microenvironment involved with angiogenesis to further inhibit the formation of new blood vessels.⁷⁸ Recently, specific inhibition of β 3-ADRs in melanoma cells was found to impair cell growth and induce apoptosis.⁷⁶

β-ADR has also been implicated in breast cancer. Breast cancer cells express both β1- and β2- ADRs,^{79,80} and the polymorphisms of β-ADR subtypes may be associated with breast cancer susceptibility.⁸¹ Breast cancer patients who received propranolol for hypertension displayed reduced metastasis and cancer recurrence.⁸² This may be due β-ADR signaling involvement that alters gene expression within the primary tumor.⁸³ Further investigation of β-ADR signaling provided evidence that the β-ADR pathway controls the stimulation of the arachidonic acid cascade.⁸⁴ In breast cancer development, arachidonic acid is a critical molecule that has been shown to activate mTOR and increase the activity of VEGF.⁸⁵ mTOR and VEGF seem to be a common pathway in breast cancer and in hemECs, involving enhanced angiogenesis.

Direct and Indirect Effects of Propranolol

Although propranolol treatment and B-ADR antagonism seems promising for IH as well as a number of other human cancers, there is quite a bit of knowledge gap. This essentially involves understanding whether propranolol mediates the effects through blocking B-ADR or another indirect mechanism. There are possibilities that need to be explored: 1) involvement of receptor dimerization and α -ADR signaling, and 2) involvement of serotonin (5HT) signaling. Although data is limited, propranolol does stereoselectively bind and inhibit α-ADR in the heart.⁸⁶ Immunoprecipitation studies also show that β 1-ADR and α 2-ADR heterodimerize when co-expressed.⁸⁷ This interaction changes the pharmacological properties of B1-ADR as shown by ligand binding assays. β1- and β2- ADR have also been shown to heterodimerize.^{88,89} These findings suggest that the profile of ADR may have functional cellular consequence and represents an area of significant future research interest. In addition to ADRs, propranolol may also mediate its effects through serotonin (5HT) receptors.^{90,91} The interaction between propranolol and 5HT occurs with high affinity as well as low affinity 5HT receptors.⁹⁰ There is also experimental evidence that propranolol acts as a 5HT1A antagonist and a 5HT1B agonist in the rat cortex.92 Treatment with propranolol also inhibited basal cAMP and steroidogenesis in rat leydig cells, with effects evident at 0.1 µmol/L.⁵

Concluding Remarks

Propranolol has shown promising effects in IH resolution and many studies have sought to understand the mechanism of propranolol as an effective treatment. Recent clinical studies have also suggested that the use of β -blockers is effective in treating several tumors and cancers. β -ADR subtypes are associated with cancer growth and progression by increasing angiogenic, migratory, and invasive factors in tumor cells. In culture studies, propranolol causes apoptosis in ECs, as well as reduces VEGF to decrease angiogenesis. However, different responses are seen in perivascular cells and hemangioma derived stem cells. β -ADR-associated proteins may exhibit distinct tissue localization and underlie the differential activity of propranolol. Identification of cytoplasmic regulatory proteins in IH-derived cells that interact with β -ADRs may represent an attractive future research area for the development of cell-type specific therapies.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Funding

The authors would like to acknowledge support from the Canadian Institutes of Health Research (ZAK; MOP 97783) and Lawson Health Research Institute (ZAK). ZAK is a recipient of a New Investigator Award from the Heart and Stroke Foundation of Canada (Great-West Life and London Life New Investigator Award).

Contributor's Statement

JJYK drafted the manuscript. ZAK edited and finalized the manuscript.

References

- Mulliken JB, Glowacki J. Hemangiomas and vascular malformations in infants and children: a classification based on endothelial characteristics. Plast Reconstr Surg 1982; 69:412-22; PMID:7063565; http://dx.doi. org/10.1097/00006534-198203000-00002
- Haggstrom AN, Drolet BA, Baselga E, Chamlin SL, Garzon MC, Horii KA, Lucky AW, Mancini AJ, Metry DW, Newell B, et al. Prospective study of infantile hemangiomas: demographic, prenatal, and perinatal characteristics. J Pediatr 2007; 150:291-4; PMID:17307549; http://dx. doi.org/10.1016/j.jpeds.2006.12.003
- Amir J, Metzker A, Krikler R, Reisner SH. Strawberry hemangioma in preterm infants. Pediatr Dermatol 1986; 3:331-2; PMID:3774653; http://dx.doi.org/ 10.1111/j.1525-1470.1986.tb00535.x
- Bruckner AL, Frieden IJ. Hemangiomas of infancy. J Am Acad Dermatol 2003; 48:477-93; quiz 94-6; PMID:12664009; http://dx.doi.org/10.1067/mjd.2003. 200.
- Chiller KG, Passaro D, Frieden IJ. Hemangiomas of infancy: clinical characteristics, morphologic subtypes, and their relationship to race, ethnicity, and sex. Arch Dermatol 2002; 138:1567-76; PMID:12472344; http://dx.doi.org/10.1001/archderm.138.12.1567
- Waner M, North PE, Scherer KA, Frieden IJ, Waner A, Mihm MC, Jr. The nonrandom distribution of facial hemangiomas. Arch Dermatol 2003; 139:869-75; PMID:12873881; http://dx.doi.org/10.1001/archderm. 139.7.869
- Enjolras O, Mulliken JB. The current management of vascular birthmarks. Pediatr Dermatol 1993; 10:311-3; PMID:8302734; http://dx.doi.org/10.1111/j.1525-1470.1993.tb00393.x
- Ritter MR, Butschek RA, Friedlander M, Friedlander SF. Pathogenesis of infantile haemangioma: new molecular and cellular insights. Expert Rev Mol Med 2007; 9:1-19; PMID:18045510; http://dx.doi.org/ 10.1017/S146239940700052X
- Khan ZA, Boscolo E, Picard A, Psutka S, Melero-Martin JM, Bartch TC, Mulliken JB, Bischoff J. Multipotential stem cells recapitulate human infantile hemangioma in immunodeficient mice. J Clin Invest 2008; 118:2592-9; PMID:18535669
- Chang LC, Haggstrom AN, Drolet BA, Baselga E, Chamlin SL, Garzon MC,Horii KA, Lucky AW, Mancini AJ, Metry DW, et al. Growth characteristics of infantile hemangiomas: implications for management. Pediatrics 2008; 122:360-7; PMID:18676554; http:// dx.doi.org/10.1542/peds.2007-2767
- North PE, Mihm MC, Jr. Histopathological diagnosis of infantile hemangiomas and vascular malformations. Facial Plast Surg Clin North Am 2001; 9:505-24; PMID:17590939

- Smolinski KN, Yan AC. Hemangiomas of infancy: clinical and biological characteristics. Clin Pediatr (Phila) 2005; 44:747-66; PMID:16327961
- Boscolo E, Bischoff J. Vasculogenesis in infantile hemangioma. Angiogenesis 2009; 12:197-207; PMID:19430954; http://dx.doi.org/10.1007/s10456-009-9148-2
- Kleiman A, Keats EC, Chan NG, Khan ZA. Evolution of hemangioma endothelium. Exp Mol Pathol 2012; 93:264-72; PMID:22565125; http://dx.doi.org/ 10.1016/j.yexmp.2012.04.020
- Frieden JJ, Eichenfield LF, Esterly NB, Geronemus R, Mallory SB. Guidelines of care for hemangiomas of infancy. American Academy of Dermatology Guidelines/Outcomes Committee. J Am Acad Dermatol 1997; 37:631-7; PMID:9344205; http://dx.doi.org/ 10.1016/S0190-9622(97)70183-X
- Durr ML, Meyer AK, Huoh KC, Frieden IJ, Rosbe KW. Airway hemangiomas in PHACE syndrome. Laryngoscope 2012; 122:2323-9; PMID:22865344; http://dx.doi.org/10.1002/lary.23475
- Clemis JD, Briggs DR, Changus GW. Intramuscular hemangioma in the head and neck. Can J Otolaryngol 1975; 4:339-46; PMID:1139430
- Apfelberg DB, Maser MR, Lash H. Argon laser treatment of cutaneous vascular abnormalities: progress report. Ann Plast Surg 1978; 1:14-8; PMID:569453; http://dx.doi.org/10.1097/00000637-197801000-00005
- Edgerton MT. The treatment of hemangiomas: with special reference to the role of steroid therapy. Ann Surg 1976; 183:517-32; PMID:776106
- Kveton JF, Pillsbury HC. Conservative treatment of infantile subglottic hemangioma with corticosteroids. Arch Otolaryngol 1982; 108:117-9; PMID:7059313; http:// dx.doi.org/10.1001/archotol.1982.00790500053013
- Goyal R, Watts P, Lane CM, Beck L, Gregory JW. Adrenal suppression and failure to thrive after steroid injections for periocular hemangioma. Ophthalmology 2004; 111:389-95; PMID:15019396; http://dx.doi. org/10.1016/S0161-6420(03)00833-9
- Leaute-Labreze C, Dumas de la Roque E, Hubiche T, Boralevi F, Thambo JB, Taieb A. Propranolol for severe hemangiomas of infancy. N Engl J Med 2008; 358:2649-51; PMID:18550886; http://dx.doi.org/ 10.1056/NEJMc0708819
- Price CJ, Lattouf C, Baum B, McLeod M, Schachner LA, Duarte AM, Connelly EA. Propranolol vs corticosteroids for infantile hemangiomas: a multicenter retrospective analysis. Arch Dermatol 2011; 147:1371-6; PMID:21844428; http://dx.doi.org/10.1001/ archdermatol.2011.203
- Drolet BA, Frommelt PC, Chamlin SL, Haggstrom A, Bauman NM, Chiu YE, Chun RH, Garzon MC, Holland KE, Liberman L, et al. Initiation and use of

propranolol for infantile hemangioma: report of a consensus conference. Pediatrics 2013; 131:128-40; PMID:23266923; http://dx.doi.org/10.1542/peds. 2012-1691

- Marqueling AL, Oza V, Frieden IJ, Puttgen KB. Propranolol and infantile hemangiomas four years later: a systematic review. Pediatr Dermatol 2013; 30:182-91; PMID:23405852; http://dx.doi.org/10.1111/pde. 12089
- Bagazgoitia L, Hernandez-Martin A, Torrelo A. Recurrence of infantile hemangiomas treated with propranolol. Pediatr Dermatol 2011; 28:658-62; PMID:22082463; http://dx.doi.org/10.1111/j.1525-1470.2011.01644.x
- Xiao Q, Li Q, Zhang B, Yu W. Propranolol therapy of infantile hemangiomas: efficacy, adverse effects, and recurrence. Pediatr Surg Int 2013; 29:575-81; PMID:23519547; http://dx.doi.org/10.1007/s00383-013-3283-y
- Bingham MM, Saltzman B, Vo NJ, Perkins JA. Propranolol reduces infantile hemangioma volume and vessel density. Otolaryngol Head Neck Surg 2012; 147:338-44; PMID:22691693; http://dx.doi.org/ 10.1177/0194599812451570
- Lamy S, Lachambre MP, Lord-Dufour S, Beliveau R. Propranolol suppresses angiogenesis in vitro: inhibition of proliferation, migration, and differentiation of endothelial cells. Vascul Pharmacol 2010; 53:200-8; PMID:20732454; http://dx.doi.org/10.1016/j.vph.2010. 08.002
- Hogeling M, Adams S, Wargon O. A randomized controlled trial of propranolol for infantile hemangiomas. Pediatrics 2011; 128:e259-66; PMID:21788220; http://dx.doi.org/10.1542/peds.2010-0029
- Wong A, Hardy KL, Kitajewski AM, Shawber CJ, Kitajewski JK, Wu JK. Propranolol accelerates adipogenesis in hemangioma stem cells and causes apoptosis of hemangioma endothelial cells. Plast Reconstr Surg 2012; 130:1012-21; PMID:23096601; http://dx.doi.org/ 10.1097/PRS.0b013e318267d3db
- Tu JB, Ma RZ, Dong Q, Jiang F, Hu XY, Li QY, Pattar P, Zhang H. Induction of apoptosis in infantile hemangioma endothelial cells by propranolol. Exp Ther Med 2013; 6:574-8; PMID:24137229
- Richter GT, Friedman AB. Hemangiomas and vascular malformations: current theory and management. Int J Pediatr 2012; 2012:645678; PMID:22611412; http:// dx.doi.org/10.1155/2012/645678
- Chisholm KM, Chang KW, Truong MT, Kwok S, West RB, Heerema-McKenney AE. β-Adrenergic receptor expression in vascular tumors. Mod Pathol 2012; 25:1446-51; PMID:22743651; http://dx.doi. org/10.1038/modpathol.2012.108
- Frielle T, Collins S, Daniel KW, Caron MG, Lefkowitz RJ, Kobilka BK. Cloning of the cDNA for the human

 β 1-adrenergic receptor. Proc Natl Acad Sci U S A 1987; 84:7920-4; PMID:2825170; http://dx.doi.org/ 10.1073/pnas.84.22.7920

- 36. Dixon RÅ, Kobilka BK, Strader DJ, Benovic JL, Dohlman HG, Frielle T, Bolanowski MA, Bennett CD, Rands E, Dichl RE, et al. Cloning of the gene and cDNA for mammalian β-adrenergic receptor and homology with rhodopsin. Nature 1986; 321:75-9; PMID:3010132; http://dx.doi.org/10.1038/321075a0
- Emorine LJ, Marullo S, Briend-Sutten MM, Patey G, Tate K, Delavier-Klutchko C, Strosberg AD. Molecular characterization of the human β 3-adrenergic receptor. Science 1989; 245:1118-21; PMID:2570461; http:// dx.doi.org/10.1126/science.2570461
- Chruscinski A, Brede ME, Meinel L, Lohse MJ, Kobilka BK, Hein L. Differential distribution of β-adrenergic receptor subtypes in blood vessels of knockout mice lacking β(1)- or β(2)-adrenergic receptors. Mol Pharmacol 2001; 60:955-62; PMID:11641423
- Lipe S, Summers RJ. Autoradiographic analysis of the distribution of β-adrenoceptors in the dog splenic vasculature. Br J Pharmacol 1986; 87:603-9; PMID:3026541; http://dx.doi.org/10.1111/j.1476-5381.1986.tb10203.x
- Boucek RJ, Jr., Kirsh AL, Majesky MW, Perkins JA. Propranolol responsiveness in vascular tumors is not determined by qualitative differences in adrenergic receptors. Orolaryngol Head Neck Surg 2013; 149:772-6; PMID:24009211; http://dx.doi.org/ 10.1177/0194599813503445
- Hadaschik E, Scheiba N, Engstner M, Flux K. High levels of beta2-adrenoceptors are expressed in infantile capillary hemangiomas and may mediate the therapeutic effect of propranolol. J Cutan Pathol 2012; 39:881-3; PMID:22764832; http://dx.doi.org/10.1111/ j.1600-0560.2012.01937.x
- Freedman NJ, Lefkowitz RJ. Desensitization of G protein-coupled receptors. Recent Prog Horm Res 1996; 51:319-51; discussion 52-3; PMID:8701085
- Al-Wadei HA, Ullah MF, Al-Wadei MH. Intercepting neoplastic progression in lung malignancies via the β adrenergic (β-AR) pathway: implications for anti-cancer drug targets. Pharmacol Res 2012; 66:33-40; PMID:22487140; http://dx.doi.org/10.1016/j.phrs. 2012.03.014
- de Rooij J, Zwartkruis FJ, Verheijen MH, Cool RH, Nijman SM, Wittinghofer A, Bos JL. Epac is a Rap1 guanine-nucleotide-exchange factor directly activated by cyclic AMP. Nature 1998; 396:474-7; PMID:9853756; http://dx.doi.org/10.1038/24884
- Breckler M, Berthouze M, Laurent AC, Crozatier B, Morel E, Lezoualc'h F. Rap-linked cAMP signaling Epac proteins: compartmentation, functioning and disease implications. Cell Signal 2011; 23:1257-66; PMID:21402149; http://dx.doi.org/10.1016/j.cellsig. 2011.03.007
- Audet M, Bouvier M. Insights into signaling from the beta2-adrenergic receptor structure. Nat Chem Biol 2008; 4:397-403; PMID:18560432; http://dx.doi.org/ 10.1038/nchembio.97
- Luttrell LM, Ferguson SS, Daaka Y, Miller WE, Maudsley S, Della Rocca GJ, Lin F, Kawakatsu H, Owada K, Luttrell DK, et al. Beta-arrestin-dependent formation of beta2 adrenergic receptor-Src protein kinase complexes. Science 1999; 283:655-61; PMID:9924018; http://dx.doi.org/10.1126/science. 283:5402.655
- Zhang D, Ma QY, Hu HT, Zhang M. beta2-adrenergic antagonists suppress pancreatic cancer cell invasion by inhibiting CREB, NFkappaB and AP-1. Cancer Biol Ther 2010; 10:19-29; PMID:20424515; http:// dx.doi.org/10.4161/cbt.10.1.11944
- Ji Y, Li K, Xiao X, Zheng S, Xu T, Chen S. Effects of propranolol on the proliferation and apoptosis of hemangioma-derived endothelial cells. J Pediatr Surg 2012; 47:2216-23; PMID:23217879; http://dx.doi.org/ 10.1016/j.jpedsurg.2012.09.008

- Kum JJY, Khan ZA. Propranolol inhibits growth of hemangioma-initiating cells but does not induce apoptosis. Pediatr Res 2014; 75:381-8; PMID:24296797; http://dx.doi.org/10.1038/pr.2013.231
- Sommers Smith SK, Smith DM. Beta blockade induces apoptosis in cultured capillary endothelial cells. In Vitro Cell Dev Biol Anim 2002; 38:298-304; PMID:12418927
- Stiles J, Amaya C, Pham R, Rowntree RK, Lacaze M, Mulne A, Bischoff J, Kokta V, Boucheron LE, Mitchell DC, et al. Propranolol treatment of infantile hemangioma endothelial cells: A molecular analysis. Exp Ther Med 2012; 4:594-604; PMID:23170111
- Ji Y, Chen S, Li K, Xiao X, Zheng S, Xu T. The role of β-adrenergic receptor signaling in the proliferation of hemangioma-derived endothelial cells. Cell Div 2013; 8:1; PMID:23286511; http://dx.doi.org/10.1186/ 1747-1028-8-1
- 54. Ji Y, Chen S, Li K, Xiao X, Xu T, Zheng S. Upregulated autocrine vascular endothelial growth factor (VEGF)/VEGF receptor-2 loop prevents apoptosis in haemangioma-derived endothelial cells. Br J Dermatol 2014; 170:78-86; PMID:24033364; http://dx.doi.org/ 10.1111/bjd.12592
- Chim H, Armijo BS, Miller E, Gliniak C, Serret MA, Gosain AK. Propranolol induces regression of hemangioma cells through HIF-1alpha-mediated inhibition of VEGF-A. Ann Surg 2012; 256:146-56; PMID:22580939; http://dx.doi.org/10.1097/SLA. 0b013e318254ce7a
- Zhang L, Lin X, Wang W, Zhuang X, Dong J, Qi Z, Hu Q. Circulating level of vascular endothelial growth factor in differentiating hemangioma from vascular malformation patients. Plast Reconstr Surg 2005; 116:200-4; PMID:15988268; http://dx.doi.org/ 10.1097/01.PRS.0000170804.80834.5F
- Boscolo E, Mulliken JB, Bischoff J. VEGFR-1 mediates endothelial differentiation and formation of blood vessels in a murine model of infantile hemangioma. Am J Pathol 2011; 179:2266-77; PMID:21945324; http:// dx.doi.org/10.1016/j.ajpath.2011.07.040
- Zhang L, Mai HM, Zheng J, Zheng JW, Wang YA, Qin ZP, Li KL. Propranolol inhibits angiogenesis via down-regulating the expression of vascular endothelial growth factor in hemangioma derived stem cell. Int J Clin Exp Pathol 2014; 7:48-55; PMID:24427325
- Communal C, Singh K, Sawyer DB, Colucci WS. Opposing effects of β(1)- and β(2)-adrenergic receptors on cardiac myocyte apoptosis: role of a pertussis toxin-sensitive G protein. Circulation 1999; 100:2210-2; PMID:10577992; http://dx.doi.org/10.1161/01. CIR.100.22.2210
- Zaugg M, Xu W, Lucchinetti E, Shafiq SA, Jamali NZ, Siddiqui MA. Beta-adrenergic receptor subtypes differentially affect apoptosis in adult rat ventricular myocytes. Circulation 2000; 102:344-50; PMID:10899100; http:// dx.doi.org/10.1161/01.CIR.102.3.344
- Shizukuda Y, Buttrick PM. Subtype specific roles of β-adrenergic receptors in apoptosis of adult rat ventricular myocytes. J Mol Cell Cardiol 2002; 34:823-31; PMID:12099721; http://dx.doi.org/10.1006/jmcc. 2002.2020
- Yu Y, Fuhr J, Boye E, Gyorffy S, Soker S, Atala A, Mulliken JB, Bischoff J. Mesenchymal stem cells and adipogenesis in hemangioma involution. Stem Cells 2006; 24:1605-12; PMID:16456130; http://dx.doi.org/10. 1634/stemcells.2005-0298
- 63. Grad YH, Lipsitch M, Griggs AD, Haas BJ, Shea TP, McCowan C, Montmayeur A, FitzGerald M, Wortman JR, Krogfelt KA, et al. Support for a bottleneck in the 2011 Escherichia coli O104:H4 outbreak in Germany. Proc Natl Acad Sci U S A 2012; 109:E3629-30.
- 64. Boscolo E, Stewart CL, Greenberger S, Wu JK, Durham JT, Herman IM, Mulliken JB, Kitajewski J, Bischoff J. JAGGED1 signaling regulates hemangioma stem cell-to-pericyte/vascular smooth muscle cell differentiation. Arterioscler Thromb Vasc Biol 2011;

31:2181-92; PMID:21757656; http://dx.doi.org/ 10.1161/ATVBAHA.111.232934

- Kelley C, D'Amore P, Hechtman HB, Shepro D. Vasoactive hormones and cAMP affect pericyte contraction and stress fibres in vitro. J Muscle Res Cell Motil 1988; 9:184-94; PMID:2458383; http://dx.doi.org/10.1007/ BF01773740
- Lee D, Boscolo E, Durham JT, Mulliken JB, Herman IM, Bischoff J. Propranolol Targets Contractility of Infantile Hemangioma-derived Pericytes. Br J Dermatol 2014; 171:1129-37; PMID: 24720697
- Linabery AM, Ross JA. Trends in childhood cancer incidence in the US (1992-2004). Cancer 2008; 112:416-32; PMID:18074355
- Strouse JJ, Fears TR, Tucker MA, Wayne AS. Pediatric melanoma: Risk factor and survival analysis of the surveillance, epidemiology and end results database. J Clin Oncol 2005; 23:4735-41; PMID:16034049; http://dx. doi.org/10.1200/JCO.2005.02.899
- Medina JE, Ferlito A, Brandwein MS, Fisher SR, Pellitteri PK, Shaha AR, Pitman KT, Robbins KT, Rinaldo A, Silver CE, et al. Current management of cutaneous malignant melanoma of the head and neck. Acta Otolaryngol 2002; 122:900-6; PMID:12542213; http:// dx.doi.org/10.1080/0036554021000028067
- Buac K, Pavan WJ. Stem cells of the melanocyte lineage. Cancer Biomark 2007; 3:203-9; PMID:17917150
- Regad T. Molecular and cellular pathogenesis of melanoma initiation and progression. Cell Mol Life Sci 2013; 70:4055-65; PMID:23532409
- 72. Yang EV, Kim SJ, Donovan EL, Chen M, Gross AC, Webster Marketon JI, Barsky SH, Glaser R. Norepinephrine upregulates VEGF, IL-8, and IL-6 expression in human melanoma tumor cell lines: implications for stress-related enhancement of tumor progression. Brain Behav Immun 2009; 23:267-75; PMID:18996182; http://dx.doi.org/10.1016/j.bbi.2008.10.005
- 73. Mills O, Messina JL. Pediatric melanoma: a review. Cancer Control 2009; 16:225-33; PMID:19556962
- Moretti S, Massi D, Farini V, Baroni G, Parri M, Innocenti S, Cecchi R, Chiarugi P. β-adrenoceptors are upregulated in human melanoma and their activation releases pro-tumorigenic cytokines and metalloproteases in melanoma cell lines. Lab Invest 2013; 93:279-90; PMID:23318885; http://dx.doi.org/10.1038/ labinvest.2012.175
- Mahabeleshwar GH, Byzova TV. Angiogenesis in melanoma. Semin Oncol 2007; 34:555-65; PMID:18083379; http://dx.doi.org/10.1053/j.seminoncol.2007.09.009
- Dal Monte M, Casini G, Filippi L, Nicchia GP, Svelto M, Bagnoli P. Functional involvement of beta3-adrenergic receptors in melanoma growth and vascularization. J Mol Med (Berl) 2013; 91:1407-19; PMID:23907236
- De Giorgi V, Grazzini M, Gandini S, Benemei S, Lotti T, Marchionni N, Gepetti P. Treatment with β-blockers and reduced disease progression in patients with thick melanoma. Arch Intern Med 2011; 171:779-81; PMID:21518948
- Lens M. Do β-blockers slow down melanoma progression? Arch Intern Med 2011; 171:1686-7; author reply 7; PMID:21987205
- Lang K, Drell TLt, Lindecke A, Niggemann B, Kaltschmidt C, Zaenker KS, Entschladen F. Induction of a metastatogenic tumor cell type by neurotransmitters and its pharmacological inhibition by established drugs. Int J Cancer 2004; 112:231-8; PMID:15352035; http://dx.doi.org/10.1002/ijc.20410
- Shi M, Liu D, Duan H, Qian L, Wang L, Niu L, Zhang H, Yong Z, Gong Z, Song L, et al. The beta2adrenergic receptor and Her2 comprise a positive feedback loop in human breast cancer cells. Breast Cancer Res Treat 2011; 125:351-62; PMID:20237834; http:// dx.doi.org/10.1007/s10549-010-0822-2
- Huang XE, Hamajima N, Saito T, Matsuo K, Mizutani M, Iwata H, Iwase T, Miura S, Mizuno T, Tokudome S, et al. Possible association of beta2- and beta3-adrenergic receptor gene polymorphisms with susceptibility

to breast cancer. Breast Cancer Res 2001; 3:264-9; PMID:11434877; http://dx.doi.org/10.1186/bcr304

- Powe DG, Voss MJ, Žanker KS, Habashy HO, Green AR, Ellis IO, Entschladen F. Beta-blocker drug therapy reduces secondary cancer formation in breast cancer and improves cancer specific survival. Oncotarget 2010; 1:628-38; PMID:21317458
- Sloan EK, Priceman SJ, Cox BF, Yu S, Pimentel MA, Tangkanangnukul V, Arevalo JM, Morizono K, Karanikolas BD, Wu L, et al. The sympathetic nervous system induces a metastatic switch in primary breast cancer. Cancer Res 2010; 70:7042-52; PMID:20823155; http://dx. doi.org/10.1158/0008-5472.CAN-10-0522
- Cakir Y, Plummer HK, 3rd, Tithof PK, Schuller HM. Beta-adrenergic and arachidonic acid-mediated growth regulation of human breast cancer cell lines. Int J Oncol 2002; 21:153-7; PMID:12063562
- 85. Wen ZH, Su YC, Lai PL, Zhang Y, Xu YF, Zhao A, Yao GY, Jia CH, Lin J, Xu S, et al. Critical role of

arachidonic acid-activated mTOR signaling in breast carcinogenesis and angiogenesis. Oncogene 2013; 32:160-70; PMID:22349822; http://dx.doi.org/ 10.1038/onc.2012.47

- Stauber RE, Heinemann A. Propranolol stereoselectively inhibits α-adrenoceptor-mediated vasoconstriction in mesenteric arterial beds of rats. J Auton Pharmacol 1996; 16:125-9; PMID:8884459
- Xu J, He J, Castleberry AM, Balasubramanian S, Lau AG, Hall RA. Heterodimerization of α 2A- and β 1adrenergic receptors. J Biol Chem 2003; 278:10770-7; PMID:12529373; http://dx.doi.org/10.1074/jbc. M207968200
- Mercier JF, Salahpour A, Angers S, Breit A, Bouvier M. Quantitative assessment of β 1- and β 2-adrenergic receptor homo- and heterodimerization by bioluminescence resonance energy transfer. J Biol Chem 2002; 277:44925-31; PMID:12244098; http://dx.doi.org/ 10.1074/jbc.M205767200
- Lavoie C, Mercier JF, Salahpour A, Umapathy D, Breit A, Villeneuve LR, Zhu WZ, Xiao RP, Lakatta EG, Bouvier M, et al. Beta 1/β 2-adrenergic receptor heterodimerization regulates β 2-adrenergic receptor internalization and ERK signaling efficacy. J Biol Chem 2002; 277:35402-10; PMID:12140284; http://dx.doi. org/10.1074/jbc.M204163200
- Nishio H, Nagakura Y, Segawa T. Interactions of carteolol and other β-adrenoceptor blocking agents with serotonin receptor subtypes. Arch Int Pharmacodyn Ther 1989; 302:96-106; PMID:2576893
- Tinajero JC, Fabbri A, Dufau ML. Serotonergic inhibition of rat Leydig cell function by propranolol. Endocrinology 1993; 133:257-64; PMID:8391422
- Pierson ME, Lyon RA, Titeler M, Schulman SB, Kowalski P, Glennon RA. Design and synthesis of propranolol analogues as serotonergic agents. J Med Chem 1989; 32:859-63; PMID:2539480; http://dx.doi.org/ 10.1021/jm00124a021