

Peer Review File

Article information: <http://dx.doi.org/10.21037/jxym-20-88>.

Reviewer A:

Comment 1: Paragraph in introduction part refer to epidemiology of PPGLs which is not close to the topic should be shorten.

Reply 1: we have shortened the related paragraph which is not close to the topic. (see Page 3, line 4-10)

Changes in the text: Pheochromocytoma is a kind of rare tumor. Its prevalence is not exactly known but has been estimated to be 1:6500-1:2500 in the United States.(5) However, the autopsy results have even revealed that the prevalence was as high as 1:2000, suggesting that many pheochromocytoma were not diagnosed before death.(6) Besides, it is reported that the annual incidence is 2-10:100,000 individuals/year.(7-9) Tumors can occur in all ages, but the highest incidence happens in 40 to 50 years old, with the basically same gender distribution.(10-15)

Comment 2: References should be added to paragraph from page 4 to page 5 about clinical manifestations of PPGLs.

Reply 2: References have been added to the paragraph about clinical manifestations of PPGLs. (see Page 3, line 19-25 and Page 4, line 1-9)

Changes in the text: The clinical manifestation of this disease is heterogeneous mainly related to predominate catecholamine secretions. Catecholamines can act on the heart, increasing heart rate, contractions, and blood pressure.(28, 29) Typical paroxysmal attack is often characterized by sudden high blood pressure even reaching 200-300/130-180 mmHg with severe headache, excess sweating and palpitations.(30) Besides, prolonged, persistent hypertension can lead to left ventricular hypertrophy, cardiac enlargement and heart failure. As for metabolization, high concentration of epinephrine acts on central nervous system, especially sympathetic nervous system to make oxygen consumption increase and basal metabolization rate heighten, resulting in calorific and emaciation.(31) Liver glycogen decomposition is accelerated and insulin secretion is inhibited to decrease glucose tolerance and increase liver glycogen dysplasia. For other performances, too many catecholamines reduce peristalsis and tension of the intestine, leading to constipation, intestinal dilatation, intestinal necrosis, bleeding and perforation. Under the action of large amounts of epinephrine, the blood cells are redistributed, making the white blood cell count in the peripheral blood increase, and sometimes the red blood cell may also increase.(32)

Comment 3: Though the history and disadvantages of receptor blockers are important, it should be shortened in the introduction part or included in the main manuscript.

Reply 3: we have shortened the introduction part about the receptor blockers. (see Page 4, line 10-23)

Changes in the text: Significant advances have been remarked in pheochromocytoma management since the tumor was first removed successfully by Roux and Mayo in

1926.(33) Before the use of α -adrenergic receptor blockers, the perioperative mortality was even as high as 50% in some researches(34, 35) while after the introduction of α -blockers, the mortality range between 0%-3%.(33) Until now, surgical resection of tumors has been usually the first choice for the clinical use to control blood pressure and heart rate, treat arrhythmias, reduce circulating plasma volume, and prevent cardiovascular complications caused by excessive catecholamines in perioperative and intraoperative period.(36, 37) However, although treatments with α -blockers preoperatively seem to show some effect in many cases,(38-40) limitations and side effects also appear along with them.(41-47) Generally speaking, treatment therapies combining decreasing the producing of catecholamines upstream and the reception of catecholamines at the α -receptor level may show significant clinical effect in the treatment of pheochromocytoma.

Comment 4: It not so convinced that Calcium channel blockers control the BP by block the secretion since Calcium channel blockers is commonly used for patents with hypertension and maintain the BP by decrease the pressure of peripheral vessels. Authors should be carefully present their opinions here. (page 19)

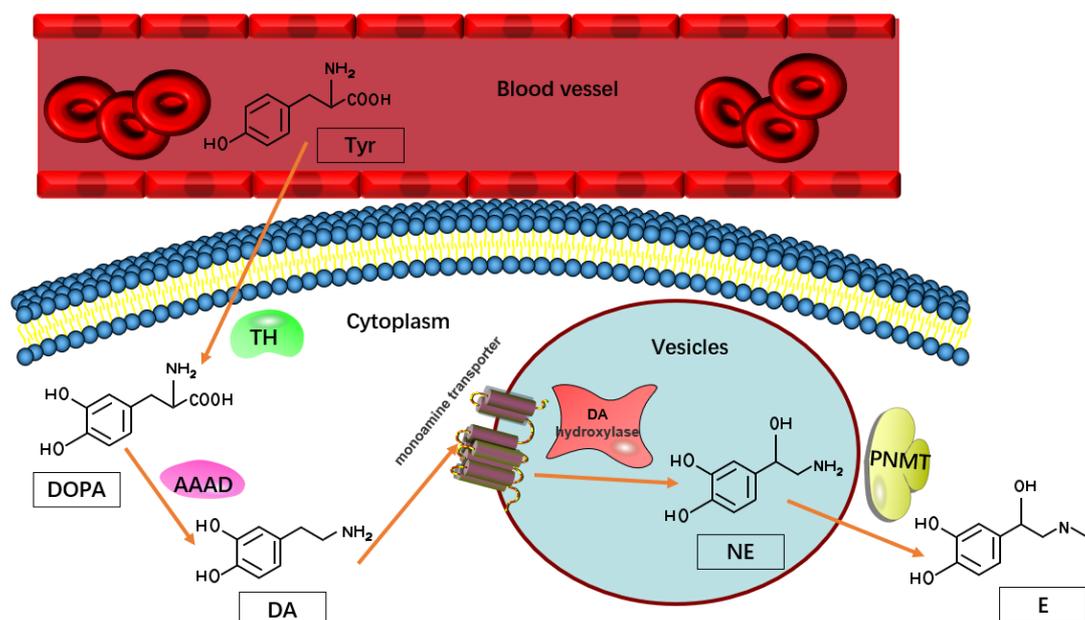
Reply 4: The related paragraph has been presented more carefully. (see Page 14, line 23-25 and Page 15, line 1-2)

Changes in the text: Calcium channel blockers is commonly used for patents with hypertension and maintain the blood pressure by decreasing the pressure of peripheral vessels. While in some studies, calcium channel blockers may inhibit norepinephrine-mediated calcium fluxes into vascular smooth muscle cells for the purpose of controlling blood pressure and arrhythmia.

Comment 5: Figure 1 look great! But it's PNMT not PNMI in the image.

Reply 5: We have modified Figure 1. (see Figure 1)

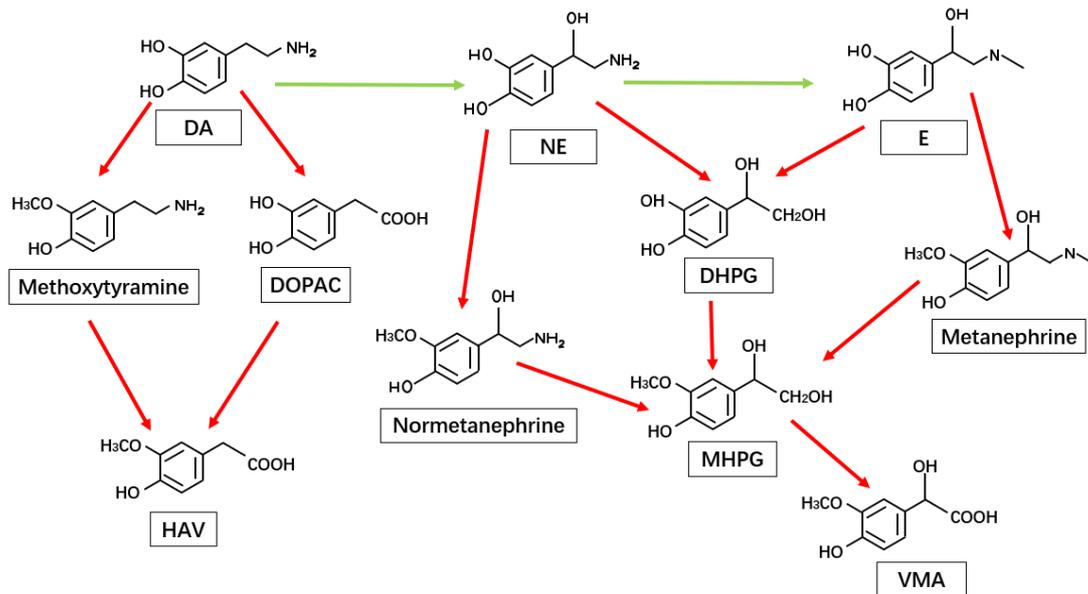
Changes in the text:



Comment 6: There is connections between dopamine with norepinephrine and epinephrine, but it not looks like so in Figure 2. Catecholamines are biochemical structure, while MNs were presented with name though with similar structures. They should be presented in the same style

Reply 6: We have modified Figure 2. (see Figure 2)

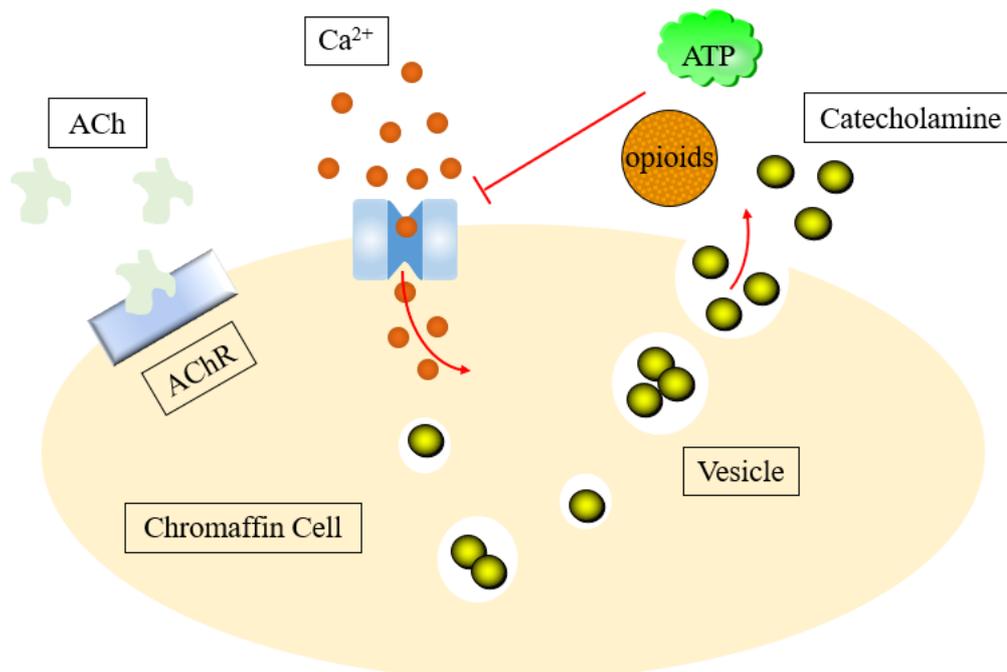
Changes in the text:



Comment 7: A vivid figure illustrating the ‘channel’ dependent catecholamine secretion will be appreciated.

Reply 7: We have added Figure 3. (see Figure 3)

Changes in the text:



Comment 8: Language should be improved.

Reply 8: We have modified our text as advised, and here are some examples. (see Page 2, line 6-8 and Page 3, line 19-20)

Changes in the text: Most clinical symptoms such as hypertension, headache, sweating and palpitation are related to excessive catecholamine secretion.

The clinical manifestation of this disease heterogeneous mainly related to predominate catecholamine secretions.

Reviewer B

Comment 1: The sections of the review needed to be numbered to make the readers easier to follow the ideas.

Reply 1: We have numbered the sections in the review as advised. (see Page 5, line 7-8; Page 7, line 18; Page 8, line 7,19; Page 9, line 23; Page 11, line 11,12; Page 14, line 6; Page 15, line 14-15,21;)

Changes in the text:

1 Pathways of catecholamines synthesis and metabolism in pheochromocytoma

2 Ion channel and catecholamine secretion

2.1 Na⁺ channels

2.2 Ca²⁺ channels

3 The influencing factors of the secretion of catecholamine

4 Treatment strategies for metabolism and secretion mechanisms

4.1 The treatment of pheochromocytoma with metyrosine (Table 1)

4.2 The treatment of pheochromocytoma with Calcium channel blockers

4.3 Use of magnesium sulfate during the perioperative period of pheochromocytoma

4.4 Reducing tyrosine-rich food intake

Comment 2: The discussion section will be better if it is revised to expectations and conclusion.

Reply 2: We have revised the discussion section to expectations and conclusion. (Page 16, line 2-25 and Page 17, line 1-12)

Changes in the text:

Conclusion and Expectations

Synthesis, conversion, release, as well as type of catecholamines produced are heterogeneous among patients with pheochromocytoma. These differences in

catecholamine precursors, metabolites and their accompanying variations can offer useful information about pheochromocytoma, which includes potential mutations, locations either inside or outside the adrenal gland, tumor size and the degree of metastasis.(51)

Catecholamines are catalyzed by tyrosine via tyrosine hydroxylase to produce DOPA, and then gradually reacts to produce dopamine, norepinephrine and epinephrine. Catecholamines are metabolized mainly through MAO and COMT pathways. Understanding its related characteristics and pay attention to the protection show good effect on the nursing and treatment of pheochromocytoma.

Preoperative pretreatment with α -blockers was routine before pheochromocytoma surgery, which showed a good result in improving the perioperative progression and reducing arrhythmias. (38-40) However, there are a lot of limitations in the use of α -blockers. In our review, we summarized the articles that tried the therapies using metyrosine or combining α -blocker and metyrosine, the results showed remarkable clinical effect in the treatment of pheochromocytoma. However, there are still some limitations in the use of metyrosine and the clinical trials are insufficient. More prospective randomized trials need to be done to provide more evidence proving the effect of metyrosine.

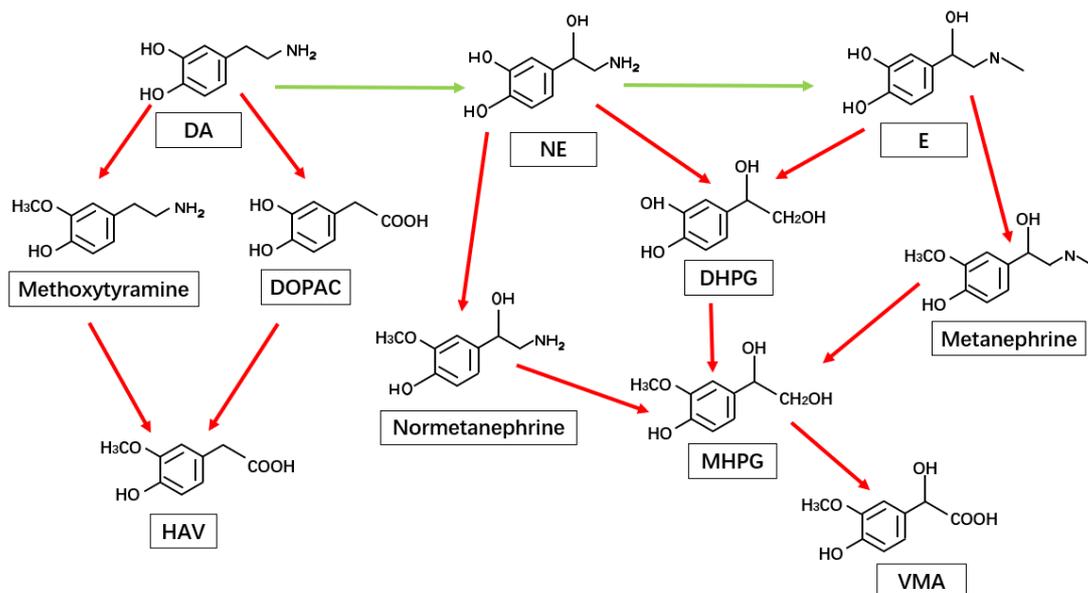
When the cell membrane increases the permeability of extracellular Ca^{2+} by different causes, the intracellular Ca^{2+} concentration increases and the catecholamine is secreted afterward. Calcium channel blockers show good effect in these cases and can use in company with or replace the α -blocker. Magnesium sulfate can also be used for perioperative hypotension or anesthesia with the mechanism of relaxing vascular smooth muscle, inhibiting catecholamine secretion, and inhibiting catecholamine receptors.

As for catecholamine metabolism, there are still many unexplained mechanisms and many potential metabolic targets. For example, do different gene mutations cause different levels of catecholamine secretion, and what are the mechanisms involved? There are many important enzymes in catecholamine metabolism pathway. Can useful drugs be developed to inhibit the production of catecholamines or accelerate their metabolism so as to reduce the incidence of hypertension in patients with pheochromocytoma before operation? These are expected to be addressed in future studies.

Comment 3: If the chemicals in Figure 2 show their chemical structures, it will be better.

Reply 3: We have modified Figure 2. (see Figure 2)

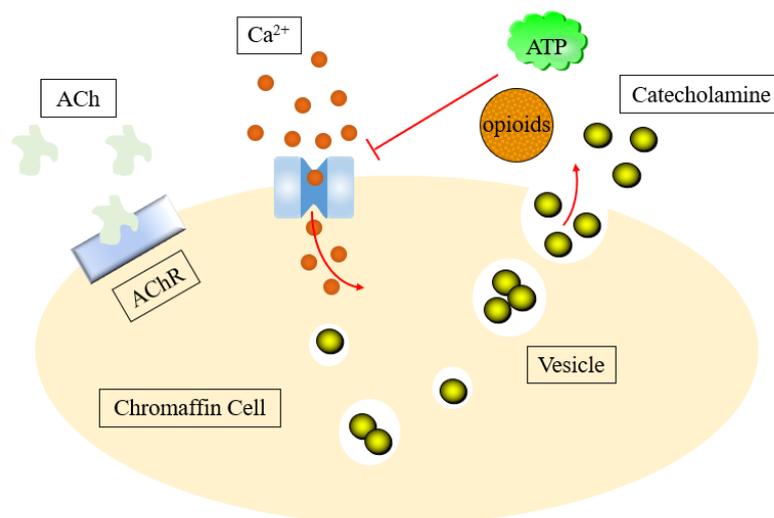
Changes in the text:



Comment 4: If the authors add a figure showing catecholamines secretion associated with ion channels in pheochromocytoma, it will be easier for readers to follow the ideas.

Reply 4: We have added Figure 3. (see Figure 3)

Changes in the text:



Comment 5: Table 1 have no references.

Reply 5: We have added references in Table 1. (see Table 1)

Changes in the text:

Table 1: Studies on the use of metyrosine

Author	Year	Study	Drugs	Efficacy
Renato Mariani-Costantini	2019	Paraganglioma: A Multidisciplinary Approach (139)	metyrosine and α -blocker	providing remarkable hemodynamic stability during operation

Mitsuhide Naruse	2018	Efficacy and Safety of Metyrosine in Pheochromocytoma/Paraganglioma: A Multi-center Trial in Japan (46)	metyrosine and α -blocker	improving symptoms of chronic excess catecholamine in metastatic and unresectable paraganglioma patients
Roger. R. Perry	1990	Surgical Management of Pheochromocytoma with the Use of Metyrosine (33)	metyrosine and phenoxybenzamine	controlling blood pressure, reducing the blood loss and the need for intraoperative fluid replacement
Heather Wachtel	2015	Preoperative Metyrosine Improves Cardiovascular Outcomes for Patients Undergoing Surgery for Pheochromocytoma and Paraganglioma (140)	metyrosine and phenoxybenzamine	improving the hemodynamic stability during operation and decreasing the cardiovascular-specific complications rates
Jaime Steinsapir	1997	Metyrosine and Pheochromocytoma (141)	metyrosine and phenoxybenzamine	controlling blood pressure and reducing the need for antihypertensive drugs or pressor
Karl Engelman	1968	Biochemical and Pharmacologic Effects of α -Methyltyrosine in Man (132)	metyrosine	a wide range of catecholamine synthesis reduction
Omar Serri	1984	Reduction in the Size of a Pheochromocytoma Pulmonary Metastasis (142)	metyrosine	shrinking the size of the functional metastasis in lung of a paraganglioma patients

Comment 6: The English writing is needed to be modified to make more fluent.

Reply 6: We have modified our text as advised, and here are some examples. (see Page 2, line 6-8 and Page 3, line 19-20)

Changes in the text: Most clinical symptoms such as hypertension, headache, sweating and palpitation are related to excessive catecholamine secretion.

The clinical manifestation of this disease heterogeneous mainly related to predominate catecholamine secretions.