



# Metabolism and secretion mechanism of catecholamine syndrome and related treatment strategies

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**Abstract:** Catecholamine syndrome, also known as pheochromocytoma, is a kind of tumor that originate from adrenal or extra-adrenal chromaffin tissue, secreting a large amount of catecholamines. Some typical gene mutations such as VHL, RET and NF1 play roles in the development of pheochromocytoma. Besides, headache, sweating, and palpitations are the usual manifestations of pheochromocytoma. Most clinical symptoms such as hypertension, headache, sweating and palpitation are related to excessive catecholamine secretion. Though preoperative pretreatment with  $\alpha$ -blockers was routine before pheochromocytoma surgery, it showed a lot of limitations because the blockage took effect after catecholamine releasing. Thus, blocking catecholamine production before its releasing shows great significance. For this purpose, in this review, we described the synthesis and metabolic process of catecholamines, the ion channels associated with catecholamine secretion and the influencing factors of the secretion of catecholamine. We then discussed the related treatment strategies which based on the metabolism and secretion of catecholamine to lay a foundation for the clinical medication of pheochromocytoma.

**Keywords:** Catecholaminergic syndrome; pheochromocytoma; catecholamine; metabolism

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## Introduction

Pheochromocytoma is a kind of tumor that originated in the adrenal medulla, the sympathetic ganglia and other parts of the chromaffin cells, secreting a large number of catecholamines (epinephrine, norepinephrine and dopamine) which act on the adrenergic receptors and cause high blood pressure (1). It is usually associated with paroxysmal or sustained hypertension, recurrent headaches, sweating, palpitations as well as weight loss (2,3). Severe cases can even be complicated by shock, heart failure, intracranial hemorrhage, ventricular fibrillation as well as myocardial infarction (4). If not diagnosed in time, the delaying treatment can cause serious damages in heart,

blood vessel, brain and even death.

Pheochromocytoma is a kind of rare tumor. Its prevalence is not exactly known but has been estimated to be 1:6,500–1:2,500 in the United States (5). However, the autopsy results have even revealed that the prevalence was as high as 1:2,000, 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).

The same as most tumors, the etiology of sporadic pheochromocytoma has not been fully explained, but the familial pheochromocytoma is related to heredity. The

occurrence of pheochromocytoma is usually along with the mutations of PHD2, VHL, SDHx, IDH, HIF2A, MDH2 and FH which are involved in the hypoxic pathway as well as RET, NF1, KIF1B $\beta$ , MAX and TMEM127 which are involved in the activating kinase signaling pathways. In addition, GDNF, GNAS, H-ras, K-ras, CDKN2A (p16), p53, BRCA1&2, BAP1, ATRX and KMT2D mutations also play roles in the development of pheochromocytoma (16-27).

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).

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  $\alpha$ -adrenergic receptor blockers, the perioperative mortality was even as high as 50% in some researches (34,35) while after the introduction of  $\alpha$ -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  $\alpha$ -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

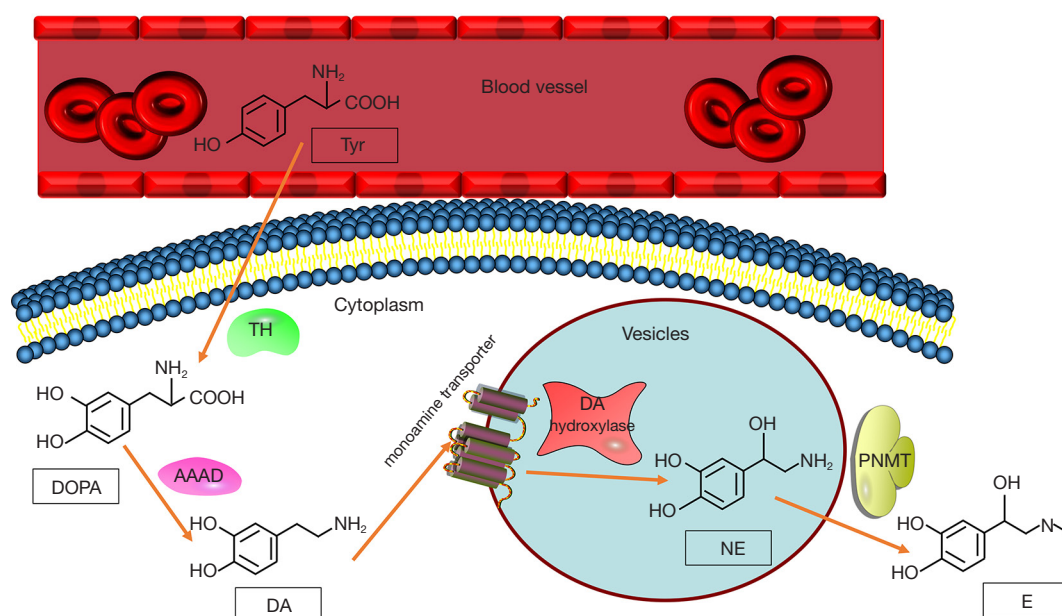
the reception of catecholamines at the  $\alpha$ -receptor level may show significant clinical effect in the treatment of pheochromocytoma.

Therefore, understanding the metabolism of catecholamines in pheochromocytoma and reducing its secretion by using drugs is a good way to guide the preoperative medication and treatment of pheochromocytoma. Our review summarized the literature to describe the synthesis and metabolic process of catecholamines in pheochromocytoma, the ion channels associated with catecholamine secretion and the influencing factors of the secretion of catecholamine. The related treatment strategies are then summarized based on the metabolism and secretion of catecholamine.

### Pathways of catecholamines synthesis and metabolism in pheochromocytoma

The first step in catecholamine synthesis is converting tyrosine to 3,4-dihydroxyphenyl alanine (DOPA) by the rate-limiting enzyme, tyrosine hydroxylase (48). DOPA is then converted to dopamine by L-aromatic amino acid decarboxylase which is a kind of enzyme distributing widely in cells. After that, the vesicular monoamine transporter translocates dopamine into storage vesicles (49), in which dopamine  $\beta$ -hydroxylase converts dopamine to norepinephrine (50). Phenylethanolamine N-methyltransferase (PNMT) is an enzyme that primarily locate in the adrenal medullary chromaffin cells, and its action results in the conversion of norepinephrine to epinephrine (*Figure 1*). Since PNMT locates in cytoplasmic, the synthesis of epinephrine is dependent on the metabolism of norepinephrine, which leaks from the inner vesicles of the noradrenaline synthesis to the cytoplasm (51). Pheochromocytoma which produces catecholamines shows considerable differences in catecholamine levels based on biosynthetic enzyme expression (52-56). Most pheochromocytomas produce mainly norepinephrine, some produce norepinephrine and epinephrine, and few produce epinephrine. However, there are some extremely rare cases have been reported producing mainly dopamine (56,57).

Catecholamines are metabolized by a variety of enzymes, such as monoamine oxidase (MAO), catechol-O methyltransferase (COMT), as well as sulfotransferase. There are also other enzymes participating glycol and acid deamination metabolites such as aldose or aldehyde reductase and aldehyde dehydrogenase. In addition, alcohol dehydrogenase has contribution to the formation of the final product of catecholamine metabolism. Thus, the



**Figure 1** The synthesis pathway of catecholamines. Tyr, tyrosine; DOPA, 3,4-dihydroxyphenyl alanine; TH, tyrosine hydroxylase; AAAD, aromatic amino acid decarboxylase; DA, dopamine; NE, norepinephrine; PNMT, phenylethanolamine N-methyltransferase; E, epinephrine.

multiple different metabolic pathways produce amounts of different metabolites (51).

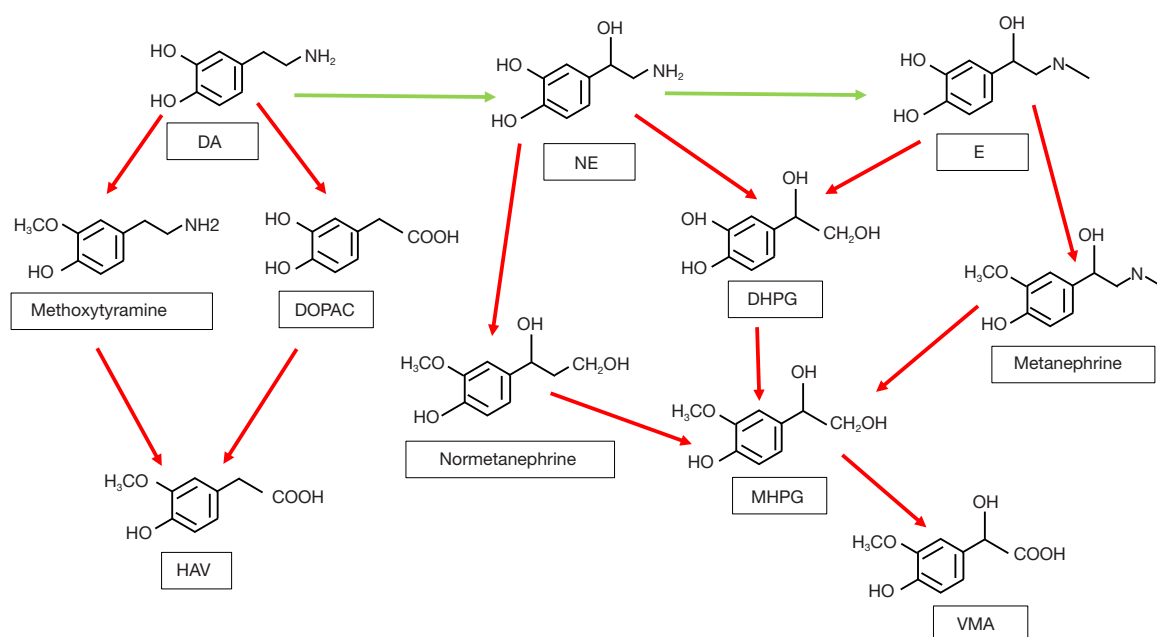
MAO deamination stands for the more important one of the two major pathways on catecholamine metabolism. MAO has two isozymes, MAO-A and MAO-B, encoded by adjacent genes on the same chromosome (58). Both norepinephrine and epinephrine are metabolized by MAO in combination with aldose or aldehyde reductase into the deaminated glycol metabolite, 3,4 dihydroxyphenylglycol (DHPG). Besides, the aldehyde intermediate formed by the deamination of dopamine is preferentially metabolized by aldehyde dehydrogenase to 3,4 dihydroxyphenylacetic acid (DOPAC) (59-61).

The second major enzyme of catecholamine metabolism is COMT, which catalyze O-methylation of dopamine to methoxytyramine, epinephrine to metanephrine, and norepinephrine to normetanephrine. COMT also has two isozymes encoded by the same gene, which are membrane-bound and soluble COMT (62,63). Furthermore, the metabolites catalyzed by MAO can be metabolized by COMT sequentially. DHPG is metabolized to 3-methoxy-4-hydroxyphenylglycol (MHPG) by COMT, while DOPAC can be metabolized to high homovanillic acid (HVA), which is the major end product of dopamine metabolism. Vanillic acid (VMA) is the major end product of human

norepinephrine and epinephrine metabolism (64). VMA is mainly produced by MHPG oxidation, which is catalyzed by alcohol dehydrogenase (65-67). Except for the VMA, all catecholamines and their metabolites are metabolized into sulfate conjugates, representing other end products of catecholamine metabolism (51).

The activities of enzymes in catecholamine synthesis steps including tyrosine hydroxylase, L-aromatic amino acid decarboxylase and dopamine  $\beta$ -hydroxylase are found higher in pheochromocytoma than that in normal adrenal medulla, which may be the cause of excessive catecholamine production in pheochromocytoma (57,68,69). Another study found the similar results and came to the conclusion that catecholamines in the normal adrenal medulla may have a negative feedback mechanism through tyrosine hydroxylase, which not appears in pheochromocytoma. In addition, the increase in catecholamine degradation metabolism pathway of pheochromocytoma turns out to be unstable comparing with the normal adrenal medulla (70).

What's more, in pheochromocytoma patients, more than 94% of elevated plasma metanephrines concentrations are caused by metabolism of catecholamines through COMT (71). The metabolism happens in pheochromocytoma tumor cells, rather than in the *blood* circulation by the extra-adrenal COMT (52). This suggests that in pheochromocytoma



**Figure 2** The metabolism pathway of catecholamines. DA, dopamine; NE, norepinephrine; E, epinephrine; DOPAC, 3,4 dihydroxyphenylacetic acid; HVA, homovanillic acid; DHPG, 3,4 dihydroxyphenylglycol; MHPG, 3-methoxy-4-hydroxyphenylglycol; VMA, Vanillic acid.

patients, most of the elevated levels of catecholamine metabolites are produced within the tumor rather than released outside the tumor (51) (See in *Figure 2*).

### **Ion channel and catecholamine secretion**

Generally, the trigger for catecholamine secretion is the activity of the visceral nerve, which releases acetylcholine from nerve endings in the adrenal medulla, close enough to chromaffin cells that rapid synaptic potentials can be observed (72). The direct response to acetylcholine release is nicotinic receptors activation (73,74), which depolarizes chromaffin cells and allows  $\text{Ca}^{2+}$  to flow through the nicotinic receptors (75). This produces cellular depolarization, action potential discharges, as well as catecholamine secretion on the other hand (76).

Although neuro-induced catecholamine release is critical (77) the intrinsic electrical activity of catecholamines is also an important possibility that contributes to catecholamine secretion in some situations. Consistently, recent studies have revealed that chromaffin cells exhibit series of intrinsic excitatory patterns, including slow-wave burst which is potentially important for the secretion of catecholamines (78-83). Some ion channels are related to

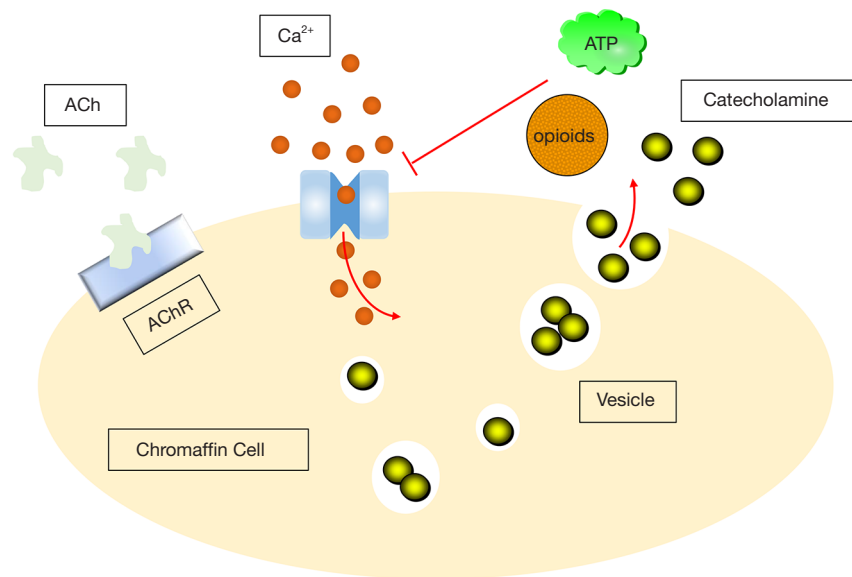
the secretion of catecholamine.

### ***Na<sup>+</sup> channels***

Chromaffin cells in almost all mammalian species show obvious voltage-dependent  $\text{Na}^+$  ( $\text{Nav}$ ) current (83,84). It is reported that  $\text{Na}^+$  current in chromaffin cells is caused by  $\text{Nav1.7}$  (85-87), while the evidence is still limited. The recent report shows that  $\text{Nav1.3}$  and  $\text{Nav1.7}$  both contribute to mouse chromaffin cells, with  $\text{Nav1.3}$  subtype taking the predominance (83). However, the activation as well as the steady-state inactivation of  $\text{Nav}$  whole cell current seem to be consistent with only one type of channel (83). According to the research on the heterologous expression of  $\text{Nav1.3}$  and  $\text{Nav1.7}$ , the two channels usually have similar functional characteristics, but compared with  $\text{Nav1.7}$ , the  $\text{Nav1.3}$  semi-inactivated voltage *usually* shifts to the right (88,89). In mouse chromaffin cells,  $\text{Nav}$  current seems to be the most consistent with  $\text{Nav1.3}$  channel (76).

### ***Ca<sup>2+</sup> channels***

Chromaffin cells release catecholamines into the circulation via a calcium-dependent extracellular mechanism (90).



**Figure 3** Catecholamine releasing via a calcium-dependent extracellular mechanism. Ach, acetylcholine; AChR, acetylcholine receptor.

Acetylcholine released by splanchnic-chromaffin cells causes cell depolarization and the opening of L- (91), N- (92), and P/Q-type (93) voltage-dependent calcium channels.  $\text{Ca}^{2+}$  enters the cell through these channels and triggers the fusion of vesicles with the plasma membrane, as well as releasing catecholamines (94). Therefore, the effectiveness of  $\text{Ca}^{2+}$  may be a possible control of the extent and rate of the secretion. ATP (95-97) and opioids (98) are co-released with catecholamines, inhibiting calcium channel currents through these three type channels (99-102) with a pathway delimited by G-protein-coupled membranes. This may form the basis of autoinhibitory mechanism for the entry of  $\text{Ca}^{2+}$ , which has been shown to exist in different animal species (97,99-102), including human chromaffin cells (103). This  $\text{Ca}^{2+}$  entry control can therefore be used to modulate the release of catecholamines (*Figure 3*).

To illuminate the important  $\text{Ca}^{2+}$ -dependent steps required for catecholamine secretion, chromaffin cells have been extensively studied to understand how cytosolic  $\text{Ca}^{2+}$  transients are coupled to exocytosis (104,105). Evidence differs from the different reports on whether a particular  $\text{Ca}^{2+}$  channel subtype plays a specific role in the coupling of catecholamine secretion, or exerts other subtype-specific effects (106-110).

In addition, the  $\text{Ca}^{2+}$  channel also takes a crucial part in regulating chromaffin cell excitability, which is triggered by the activation of inward and outward  $\text{Ca}^{2+}$  current, through

the nearby BK channel or farther SK channel (111,112). It has been reported that there may exist a mechanism of tight coupling of  $\text{Ca}^{2+}$  and BK channels in some neuroendocrine cells. To support this suggestion, the P/Q-type channel and N-type channel have turned out to couple with BK channel activation (113,114). It seems that all  $\text{Ca}^{2+}$  channels can drive BK current in chromaffin cells, in which L-type may preferentially co-locate with it, especially when transient depolarization is in use (115,116). For longer depolarizing stimuli, secretion (117) and activation of the BK channels are both activated by a global elevation of  $\text{Ca}^{2+}$  from all  $\text{Ca}^{2+}$  channels (116,117).

### The influencing factors of the secretion of catecholamine

The secretion of catecholamine and the accompanying hypertension are affected by many factors such as the triggers, tumor location, genetic background and so on. Catecholamines are stored in separate vesicles along with adenosine triphosphate, chromogranin and dopamine  $\beta$ -hydroxylase. Stress, pain, cold, heat, asphyxia, hypotension, hypoglycemia, and sympathetic excitation during hyponatremia increase the release of catecholamines (118). After preganglionic sympathetic excitation, the vesicle contents can be released by exocytosis (119). In addition, in some cases, catecholamines can be released not through



**Table 1** Studies on the use of metyrosine

Author	Year	Study	Drugs	Efficacy
Renato Mariani-Costantini	2019	Paraganglioma: A Multidisciplinary Approach (129)	Metyrosine and $\alpha$ -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 $\alpha$ -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 (130)	Metyrosine and phenoxybenzamine	Improving the hemodynamic stability during operation and decreasing the cardiovascular-specific complications rates
Jaime Steinsapir	1997	Metyrosine and Pheochromocytoma (131)	Metyrosine and phenoxybenzamine	Controlling blood pressure and reducing the need for antihypertensive drugs or pressor
Karl Engelman	1968	Biochemical and Pharmacologic Effects of a -Methyltyrosine in Man (132)	Metyrosine	A wide range of catecholamine synthesis reduction
Omar Serri	1984	Reduction in the Size of a Pheochromocytoma Pulmonary Metastasis (133)	Metyrosine	Shrinking the size of the functional metastasis in lung of a paraganglioma patients

sympathetic excitation and exocytosis.

Paraganglioma derived from extra-adrenal chromaffin tissues in sympathetic paravertebral ganglia of thoracic cavity, abdomen and pelvis. It also originates from parasympathetic ganglia located near the glossopharyngeal and vagus nerves in the neck and skull base (120) which is not able to produce catecholamines. About 80–85% of chromaffin-cell tumors are pheochromocytomas, while 15–20% are paragangliomas (121).

Pheochromocytoma has been proven to exhibit highly evident gene expression profiles in MEN2 and VHL syndrome which usually caused by the mutation of RET and VHL respectively (122,123). Although VHL tumors show activation of the hypoxia-angiogenic signaling pathway, the expression of many components associated with the catecholamine-related pathway is decreased compared to MEN2. For example, MEN2 tumors express phenylethanolamine N-methyltransferase, which converts norepinephrine to epinephrine and is not expressed in VHL tumors (56). The reason of the more symptomatic character of pheochromocytoma in MEN 2 than in VHL syndrome is considered to be the relative amount of norepinephrine and epinephrine produced by the two tumors and the different effects on  $\alpha$  and  $\beta$  adrenergic receptors (56,124-126).

Furthermore, Tumors associated with SDHAF2,

SDHC, and SDHD mutations are usually located in the head and neck, originating from the parasympathetic ganglia. As mentioned earlier, they often do not secrete catecholamines. As for NF1-related pheochromocytoma, it usually shows elevated norepinephrine and catecholamine metabolites (127). The biochemical features of SDHB mutant tumors are similar to those of norepinephrine predominance VHL patients, but they also show high methoxytyramine (a metabolite of dopamine) excretion as the increased biochemical marker (127). Last but not least, the biochemical features of tumors associated with SDHA, TMEM127, and MAX mutations have not been well determined (128).

What's more, when cases like compression of the tumor during massage; direct trauma; eating foods rich in tyramine; and taking potentially stimulating drugs such as histamine, glucagon, tetraethylamine happen, high blood pressure may occur.

### **Treatment strategies for metabolism and secretion mechanisms**

#### *The treatment of pheochromocytoma with metyrosine (Table 1)*

Metyrosine specifically inhibits tyrosine hydroxylase

which catalyzes the conversion from tyrosine to DOPA, the first and rate-limiting step in the pathway of catecholamine synthesis (134). Clinical trials have proved that metyrosine can inhibit the synthesis of catecholamines thus improves the symptoms caused by catecholamine excess such as hypertension (132,135-138). In 1979, metyrosine was approved by the United States Food and Drug Administration for preoperative preparation of surgical patients, management of patients during surgical contraindications, and treatment of patients with metastatic pheochromocytoma (139). However, at that time, the clinical researches could neither meet the regulatory standards of evaluating the efficacy and safety, nor provide sufficient evidence for them (140). Metyrosine was recommended for long-term treatment for patients with metastatic pheochromocytoma in 1981 (141).

As described in the book *Paraganglioma-A Multidisciplinary Approach*, using metyrosine could provide remarkable hemodynamic stability during operation because of the inhibition of excessive catecholamine production, as a result, it can prevent potential fluctuations in blood pressure during tumor resection. Because the storage of catecholamines is usually exhausted within 3 days of surgery, for those with metastatic pheochromocytoma or high catecholamine levels, metyrosine is especially useful. Due to incomplete exhaustion of the catecholamines, no matter how much the dose is required, it is desirable to use metyrosine in combination with other  $\alpha$ -blockers. This combination medication reduces the instability of blood pressure control, the blood loss and the need for volume replacement perioperatively, as compared to using  $\alpha$ -blockers alone (129).

A Japanese study showed the efficacy and safety of metyrosine in patients with malignant and unresectable pheochromocytoma to improve symptoms related to catecholamine excess. It showed that the combination of metyrosine and  $\alpha$ -blocker may be one of the optional treatments in pheochromocytoma patients (46).

Perry *et al.* reviewed 25 cases of consecutive patients undergoing pheochromocytoma surgery. Among them, 19 patients were prepared preoperatively with phenoxybenzamine and metyrosine while the other 6 patients were only given phenoxybenzamine. Although this study was a retrospective review rather than a prospective randomized trial, the results could explain that for surgical pheochromocytoma patients, management with both phenoxybenzamine and metyrosine showed a better performance than using phenoxybenzamine alone. The

combined medication seemed to be able to better control blood pressure, reduce blood loss and reduce the need for intraoperative fluid replacement (33).

Another retrospective study investigated patients undergoing initial pheochromocytoma resection. One group was treated using metyrosine and phenoxybenzamine while the other using phenoxybenzamine only. It turned out that preoperative metyrosine improved the hemodynamic stability during operation and decreased the cardiovascular-specific complications rates in patients for pheochromocytoma resection. This report showed that the addition of metyrosine preoperatively may improve surgical outcomes (130).

In the study of Steinsapir *et al.*, the combined use of a metyrosine and  $\alpha$ -blocker showed a good result in better controlling blood pressure as well as reducing the need for antihypertensive drugs or pressor intraoperatively thus reducing the mortality of surgery. Using both medications would make patients with pheochromocytoma receive satisfactory hypertension treatment before operation (131).

From the data presented by Engelman *et al.*, it was clear that metyrosine was useful in inhibiting catecholamine synthesis in human. What's more, a wide range of catecholamine synthesis reduction lead to a remarkable improvement in pheochromocytoma patients' clinical conditions. In some notable cases, metyrosine showed a better performance than other drugs, and seemed more desirable and simpler (132).

There was also a case report showing metyrosine effect on tumor progression. After long-term metyrosine treatment in a malignant pheochromocytoma patient, the size of the functional metastasis in lung shrunk (133). Because pheochromocytoma can also form spontaneous necrosis (142,143) metyrosine treatment may be accidental. However, because of no evidence to prove this phenomenon in pulmonary nodules, the conclusion was drawn that reducing the size of lung metastasis nodule may be due to the action of tyrosine (133).

Though with preferable usage, there are also some limitations reported in metyrosine. First of all, metyrosine is pretty expensive which limits its use in some countries. The cost has increased dramatically which makes the access and availability to this medication limited. Secondly, the main side effects usually include symptoms in the central or peripheral nervous systems, because metyrosine can cross the blood-brain barrier and inhibit catecholamine synthesis. Other side effects usually include anxiety, sedation, fatigue, depression, lethargy, crystalluria and gastrointestinal

manifestations like diarrhea (144-146).

### ***The treatment of pheochromocytoma with calcium channel blockers***

Catecholamine secretion is caused by an increase in intracellular  $\text{Ca}^{2+}$  concentration, which is a result of increased cell membrane permeability to extracellular  $\text{Ca}^{2+}$ . A variety of factors influence the  $\text{Ca}^{2+}$ -mediated catecholamine release process (147-150).

In chromaffin tissues, chromaffin cells release catecholamines through a  $\text{Ca}^{2+}$ -dependent extracellular mechanism (90). Acetylcholine releases in synapse of visceral chromaffin cells, causing cell depolarization and opening voltage-dependent  $\text{Ca}^{2+}$  channels (91-93). After that, extracellular  $\text{Ca}^{2+}$  enters through these channels, triggers the fusion of secretory vesicles with the plasma membrane and releases catecholamines (94).

Under pressure conflict, normal cells show a highly controlled secretory response, while tumor cells begin to secrete in an unsynchronized and uncontrolled manner, producing a large amount of catecholamines into the circulation, resulting in the typical symptoms suffered by pheochromocytoma patients. In these cases, using calcium channel blockers, which include amlodipine, nifedipine, verapamil and nifedipine is an effective method (147).

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. They also prevent catecholamine-related coronary artery spasm and help improve cardiac function (151) without causing orthostatic hypotension (152-154). Due to the pharmacological action of the calcium antagonist, its use alone does not improve all the hemodynamic changes brought by pheochromocytoma, and only in the following three conditions, calcium channel blockers can be used combining with or replacing the  $\alpha$ -blocker (155,156), (I) when single use of  $\alpha$ -blocker, blood pressure control is not satisfactory, calcium channel blockers can be used in combination to improve efficacy. Besides, the dose of  $\alpha$ -blocker can be reduced; (II) when patients cannot tolerate  $\alpha$ -blockers having serious side effects, it can be replaced by calcium channel blockers; (III) when blood pressure is normal or only intermittently elevated, calcium channel blockers can replace  $\alpha$ -blocker to prevent

hypotension or orthostatic hypotension.

### ***Use of magnesium sulfate during the perioperative period of pheochromocytoma***

Magnesium sulfate is mainly used for perioperative hypertension or anesthesia. The mechanism of magnesium sulfate to lower blood pressure is mainly: (I) relaxation of vascular smooth muscle and expansion of vascular wall, (II) inhibition of adrenal medulla and adrenergic nerve endings to secrete catecholamine, and (III) direct inhibition of catecholamine receptors (157).

### ***Reducing tyrosine-rich food intake***

Tyrosine is one of the raw materials for the synthesis of catecholamines. Preoperative reduction of tyrosine-rich food intake may be important in reducing the increase of blood pressure caused by intraoperative catecholamine secretion. Tyrosine-rich foods include pickled fish, milk, lactic acid drinks, cheese, animal liver, beef, fermented food, broad beans, as well as beer.

## **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  $\alpha$ -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  $\alpha$ -blockers. In our review, we summarized the articles that tried the therapies using metyrosine or combining  $\alpha$ -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  $\text{Ca}^{2+}$  by different causes, the intracellular  $\text{Ca}^{2+}$  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  $\alpha$ -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.

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