J Chin Med 27(1): 2701003, 6 pages, 2016
DOI: 10.3966/241139642016062701003
E-ISSN: 24113964
http://www.nricm.edu.tw/jcm/

中醫藥雜誌
Journal of Chinese Medicine

Yin-Yang in Traditional Medicine and Its Relation to Parasympathetic (NO-cGMP) and Sympathetic (CO-cAMP) Balance

Wan-Chung Hu*

Division of Clinical Chinese Medicine, National Research Institute of Chinese Medicine, Ministry of Health and Welfare, Taipei, Taiwan

Yin-Yang is a key concept in traditional Chinese medicine. In this paper I explain the relationship of Yin-Yang and the parasympathetic and sympathetic system. Our body uses both the sympathetic and the parasympathetic system to balance our body. Yin is related to the parasympathetic system, and Yang is related to the sympathetic system. In addition, there are also secondary messenger systems which match Yin-Yang. The parasympathetic system is mediated by NO-cGMP, and the sympathetic system is mediated by CO-cAMP. NO & CO are hydrophobic secondary messengers, and cGMP & cAMP are hydrophilic secondary messengers.

Key words: Sympathetic, parasympathetic, CO, NO, cAMP, cGMP

Received 5 March 2015,
Accepted 2 December 2015,
Available online 1 June 2016

***Correspondence**: Wan-Chung Hu, Division of Clinical Chinese Medicine, National Research Institute of Chinese Medicine, Ministry of Health and Welfare, Taipei, Taiwan, No. 155-1, Sec. 2, Linong St., Beitou District, Taipei 11221, Taiwan, Tel: +886-2-28201999 ext. 3551, E-mail: wanchung@nricm.edu.tw

The concept of Yin-Yang is very important in traditional medicine. Yin-Yang is the leading rule of eight principal syndromes which are Yin-Yang, Hypofunction-Hyperfunction, Cold-Heat, and Exterior-Interior. The fine antagonism and balance of Yin-Yang in our body can prevent us from contracting diseases. The concept of Yin and Yang is also used in traditional medicine for medication treatment. However, what is Yin? What is Yang? The important concept is not matched to current modern western medicine. Thus, the concept of Yin-Yang is not easily accepted by western people for disease treatment. There are many aspects of Yin-Yang in medicine. Here, I will propose my hypothesis of Yin and Yang to relate to the parasympathetic-sympathetic system in modern medicine.

Yin is related to the parasympathetic system, and Yang is related to the sympathetic system. In the parasympathetic system, the key intracellular molecules are cGMP & NO (Nitrogen monoxide)as the secondary messengers. In the sympathetic system, the key intracellular molecules are cAMP & CO (Carbon monoxide) as the secondary messengers. There is, therefore, a balance between the parasympathetic nerve system and the sympathetic nerve system. cGMP-NO and cAMP-CO, which antagonize each other, allow the parasympathetic system and the sympathetic system to antagonize each other. Thus, the result is a fine balance for our body. Because of the fine balance, our body can avoid contracting diseases. If the parasympathetic system is much stronger than the sympathetic system, this condition is called Yn syndrome. If sympathetic system is much stronger than the parasympathetic system, this condition is called Yang syndrome. As a result, an individual can contract a disease.

In the characteristics eight principal syndromes, the Yang syndrome has the following : excited-maniac, a flushed face, hatred of heat, a loud voice, a dry stool, dark urine, thirst, a cold drink lover, a red tongue, and a strong pulse. The Yin syndrome has the following characteristics: a depression, a pale face, cold extremities, a low voice, a watery stool, clear urine, no thirst, a hot drink lover, a pale tongue, and a weak pulse. This can match the function of the sympathetic system and the parasympathetic system. The sympathetic system, which has a fight-and-run response, will cause alertness and anxiety. Thus, it will causes excite and anger. Blushing is an emotional anxiety. The facial veins have alpha-adrenoreceptors and beta-adrenoreceptors. The facial veins have alpha-adrenoreceptors and beta-adrenoreceptors. At the anxiety sympathetic signal will activate the adrenoreceptors on the facial veins, blushing often happens. That is the reason why not say Yang syndrome is a flushed face [1]. In addition, sympathetic innervations can also cause sweating. That may be the reason for the hatred of heat. The sympathetic branch of the superior laryngeal nerve can decide both the pitch and the loudness of your voice. When you are excited and speak with an up-regulated sympathetic tone, you will have a loud voice. The parasympathetic nerve cause lower GI motility and the sympathetic nerve is the opposite. If the lower GI moves very slowly, the water content will be excessively absorbed by the large intestine. Thus, the up-regulated sympathetic tone will cause a dry stool. Sympathetic nerve activation causes water and sodium retention. Because the water retention, the patient will void dark urine. Thirst is an effect of anti-cholinergic medication. Thus, the patients with similar over-activated sympathetic tone will be thirsty, cold drink loving individual with a red tongue. Finally, the sympathetic nerve will increase an individual's heart rate and pulse rate as well as cardiac contractility. Thus, the heart will be a strong pulse.

As for the parasympathetic "Yin", the situations are the opposite. Since the sympathetic tone is a fear-and-fight response and the parasympathetic is for restful tone, the Yin syndrome will appear depressive. Although the pale face in a parasympathetic tone is compared to flushing in the sympathetic tone, a sympathetic fear-and-fight reaction can also cause pale face. Chillness and extremity coldness is now considered as autonomic dysfunction. Because the sympathetic branch is related to both the loudness and the high pitch of voice, parasympathetic overactivity will result in a low voice. Parasympathetic innervations will increase bowel motility and then reduce water absorption. Watery diarrhea is usually related to the overactivity of the parasympathetic system. Thus, high parasympathetic is related to watery stools. During micturition, parasympathetic stimulation causes the detrusor muscle to contract and the internal urethral sphincter to relax. Thus, at the parasympathetic nerve is related to urine/water expelling, it is related to urine. Because anti-cholinergics cause thirst, the up-regulated parasympathetic activity will cause non-thirst, a desire for hot drink and a

pale tongue with whitish and slippery coating. Finally, at the parasympathetic nerve will decrease both an individual's heart rate, pulse rate and cardiac contractility, it is related to person's weak pulse.

Macroscopelly, parasympathetic/sympathetic is associated with Yin/Yang. Dose microscopelly have a machinery of antagonism and balance in a cell? I think it is in the cGMP/cAMP secondary messenger system. Dr. Goldberg in 1975 first proposed the cGMP-cAMP Yin-Yang hypothesis, and here I would like to extend his hypothesis to a boarder view [2]. cGMP is made of guanine (G), a kind of purine. cAMP is made of adenine (A), also a kind of purine. However, the $^{-}$NH2 group of A and G is appears as almost in the opposite direction in chemical composition. Thus, the two kinds of purines can be used in a cell as the balancing to machinery corresponding to the parasympathetic system and the sympathetic system. cAMP should be related to sympathetic nerve activation, and cGMP should be related to parasympathetic nerve activation [3]. I will describe the opposite function of cAMP and cGMP below.

As for cAMP, it has multiple functions in different cells or organs. It works via activating protein kinase A. PKA phosphorylates proteins that have the motif Arginine-Arginine-X-Serine exposed, in turn (de)activating the proteins. In adipocyte, epinephrine binds to the beta adrenergic receptor to activate a second messenger cAMP. The final result is lipase stimulation and lipolysis. In skeletal myocytes, epinephrine also binds to a beta adrenergic receptor to activate a second messenger cAMP. The final results are glycogenolysis and glycolysis stimulation as well as glycogenesis inhibition. In cardiac myocyte, norepinephrine binds to a beta adrenergic receptor to activate a second messenger cAMP. The final result is a calcium sequestering and a myocyte contraction [4]. In hepatocyte, epinephrine binds to a beta adrenergic receptor to activate a second messenger cAMP. The final result is a production of glucose via stimulating glycogenolysis, inhibiting glycogenesis, stimulating gluconeogenesis, and inhibiting glycolysis. In a cardiovascular smooth muscle cell, epinephrine also binds to a beta2 adrenergic receptor to activate a second messenger cAMP. The net result is vasoconstriction or vasodilation. In a kidney juxtaglomeruler cell, a sympathetic agonist binds to either a beta or an alpha2 adrenergic receptor to activate a second messenger cAMP. The net result is a rennin secretion [5].

As for cGMP in many cells or organs, it has many contrasting functions compared to cAMP. It works via activating the protein kinase G. The substrate amino acid sequence consensus motif for PKG appears to require more multiple basic residues than PKA does (consensus -R/K2-3-X-S/T-N). N is a neutral amino acid. In contrast to PKA whose target motif is R-R/K-X-S/T-B, in the beginning PKA's motif has less basic amino acids and there should be a hydrophobic amino acid (B) after the Ser or Thr [6]. In adipocyte, acetylcholine binds to muscarinic [3] receptor to activate a second messenger cGMP [7,8]. The net result is lipogenesis. This is opposite to the action of a cAMP sympathetic system. In a skeletal myocyte, cGMP can enhance glucose oxidation. In a cardiac myocyte, cGMP can reduce contractility [4]. In a vascular smooth muscle with intact endothelium, cGMP can cause vasodilation. cGMP also acts on skeletal muscle [9]. These all are opposite to cAMP's actions [10].

If we compare the consensus motif of target protein for PKA and PKG, we can see they are basically the same. Here, I propose that PKA phosphorylate is not nor the target but PKG dephosphorylate is the target since the two enzymes antagonize each other. We know at the enzymes are bi-directional both will depend on their reactants concentrations. In the situations, the ATP concentration for PKA or PKG reaction is important. If the ATP is excessive in a cell, then the protein phosphorylation will tend to occur when using one molecule of ATP. Thus, ATP should be excessive in a PKA reaction. In sympathetic-cAMP signaling, glucose production is driven by using excessive ATPs. Thus, gluconegenesis stimulation, glycolysis inhibition, glucogenolysis stimulation, and glucogenogenesis inhibition tend to occur when excessive ATPs and activated corresponding enzymes. On the other hand, ATPs are locking when there is at present parasympathetic-cGMP signaling. Thus, PKG will tend to dephosphorylate the target protein to release ATP. Another reaction which generates ATP will also tend to occur. This condition is the Yin-Yang modification for cellular physiology [11,12].

Besides cGMP and cAMP, NO and CO molecules are used as secondary messengers in our body. The reason why gaseous molecules are used is that they are hydrophobic and can easily transmit through the membrane structure of or

in the cell (cellular membrane and organelles). cGMP and cAMP are hydrophilic, so they can be only used as cytosolic messenger transmitters. It is worth noting that Nitrogen has 5 electrons in the outer layer of its' atom and Carbon has 4 electrons in the outer layer of its' atom. NO is a free radical with one unpaired electron. It is like a nucleophile. On the contrary, CO is an electrophile which usually accepts other massive electron atoms. Thus, we can conclude that the functions of both CO and NO are opposite to each other.

As for CO & NO, CO administration can cause bronchodilation, vasoconstriction with intact endothelium, and increased heart rate [13–15]. Chronic CO intoxication can cause poor adipocyte formation to reduce obesity. These are all similar to the sympathetic system effect. cAMP can activate heme oxygenase which is responsible for CO synthesis in our body. In turns, CO can activate adenylyl cyclase to generate more cAMP [16]. This is a positive feedback route. On the other hand, cGMP can up-regulate nitric oxide synthase to generate NO. In turn, NO can activates guanylyl cyclase to generate more cGMP. This is also a positive feedback route. NO administration can cause bronchoconstriction, vasodilation with intact endothelium, and decreased heart rate with a reducing preload [9,17]. Thus, NO-cGMP is responsible for the parasympathetic system.

Sympathetic-parasympathetic balance or antagonism is just a case of Yin-Yang in our body. Yin-Yang is not simply equal to parasympathetic-sympathetic. There are also lots of examples of Yin-Yang in our body. For example, androgen and estrogen are for male and for female, respectively. RNAi is to suppress expression of gene and protein is to show expression of gene. However, sympathetic-parasympathetic balance and antagonism is important to physiology. For example, sympathetic nerve will increase our heart rate, but parasympathetic nerve will reduce our heart rate. The balance will let our heart rate in the normal range. During the fear-and-fight situation, sympathetic system will be activated to enhance heart beat to face the stressful environment. During sleep or rest, parasympathetic system will be activated to let us calm down. Thus, this kind of antagonism or balance is very important. It is also important to have RNAi and protein balance. Generally, protein can execute DNA function, and RNAi can shot down DNA function. Thus, by means of this antagonism, our cell can turn on or off a gene to face different environment. Yin-Yang is very important for maintaining our body.

Conclusion

The concept of Yin-Yang of traditional Chinese medicine can be related to the balance of the sympathetic and the parasympathetic systems. The sympathetic system is mediated by secondary messengers: hydrophobic CO and hydrophilic cAMP. The parasympathetic system is mediated by second messengers: hydrophobic NO and hydrophilic cGMP. The antagonism or balance of the two systems can well explained the physiological functions of our body.

Acknowledgement

I am very thankful for Professor Moulton Belcher's suggestion in grammar modification in this article. I am very grateful for Professors Yuh-Chiang Shen and Wen-Fei Chiou's kind help and guidance during my work.

References

1. Koeda T, Sato J, Kumazawa T, Tsujii Y, Mizumura K. Effects of adrenoceptor antagonists on the cutaneous blood flow increase response to sympathetic nerve stimulation in rats with persistent inflammation. *Jpn. J. Physiol.*, 52:521–530, 2002.
2. Goldberg ND, Haddox MK, Nicol SE, Glass DB, Sanford CH, Kuehl FA Jr., *et al*. Biologic regulation through opposing influences of cyclic GMP and cyclic AMP: the Yin Yang hypothesis. *Adv. Cyclic Nucleotide Res.*, 5: 307–330, 1975.
3. George WJ, Polson JB, O'Toole AG, Goldberg ND. Elevation of guanosine 3',5'-cyclic phosphate in rat heart after perfusion with acetylcholine. *Proc. Natl. Acad. Sci. USA*, 66:398–403, 1970.
4. Dunham EW, Haddox MK, Goldberg ND. Alteration of vein cyclic 3':5' nucleotide concentrations during changes in contractility. *Proc. Natl. Acad. Sci. USA*, 71: 815–819, 1974.
5. Tresguerres M, Levin LR, Buck J. Intracellular cAMP signaling by soluble adenylyl cyclase. *Kidney Int.*, 79:1277–1288, 2011.
6. Kennelly PJ, Krebs EG. Consensus sequences as substrate specificity determinants for protein kinases and protein phosphatases. *J. Biol. Chem.*, 266:15555–15558, 1991.
7. Mitschke MM, Hoffmann LS, Gnad T, Scholz

D, Kruithoff K, Mayer P, *et al*. Increased cGMP promotes healthy expansion and browning of white adipose tissue. *Faseb. J.*, 27:1621–1630, 2013.

8. Turovsky EA, Turovskaya MV, Dolgacheva LP, Zinchenko VP, Dynnik VV. Acetylcholine promotes Ca^{2+} and NO-oscillations in adipocytes implicating Ca^{2+}-->NO-->cGMP-->cADP-ribose-->Ca^{2+} positive feedback loop--modulatory effects of norepinephrine and atrial natriuretic peptide. *PLoS One*, 8: e63483, 2013.
9. Stamler JS, Meissner G. Physiology of nitric oxide in skeletal muscle. *Physiol. Rev.*, 81:209–237, 2001.
10. Francis SH, Busch JL, Corbin JD, Sibley D. cGMP-dependent protein kinases and cGMP phosphodiesterases in nitric oxide and cGMP action. *Pharmacol. Rev.*, 62:525–563, 2010.
11. Taylor SS, Zhang P, Steichen JM, Keshwani MM, Kornev AP. PKA: lessons learned after twenty years. *Biochim. Biophys. Acta*, 1834: 1271–1278, 2013.
12. Hofmann F, Feil R, Kleppisch T, Schlossmann J. Function of cGMP-dependent protein kinases as revealed by gene deletion. *Physiol. Rev.*, 86:1–23, 2006.
13. Cardell LO, Ueki IF, Stjarne P, Agusti C, Takeyama K, Linden A, *et al*. Bronchodilatation in vivo by carbon monoxide, a cyclic GMP related messenger. *Br. J. Pharmacol.*, 124:1065–1068, 1998.
14. Volti GL, Vanella L, Gazzolo D, Galvano F. Carbon monoxide: vasoconstrictor or vasodilator? That's the question. *Am. J. Physiol. Renal Physiol.*, 295:F901–F903, 2008.
15. Johnson RA, Kozma F, Colombari E. Carbon monoxide: from toxin to endogenous modulator of cardiovascular functions. *Braz. J. Med. Biol. Res.*, 32:1–14, 1999.
16. Middelhaufe S, Leipelt M, Levin LR, Buck J, Steegborn C. Identification of a haem domain in human soluble adenylate cyclase. *Biosci. Rep.*, 32:491–499, 2012.
17. Durante W, Christodoulides N, Cheng K, Peyton KJ, Sunahara RK, Schafer AI. cAMP induces heme oxygenase-1 gene expression and carbon monoxide production in vascular smooth muscle. *Am. J. Physiol.*, 273:H317–H323, 1997.

J Chin Med 27(1): 2701003, 6 pages, 2016
DOI: 10.3966/241139642016062701003
E-ISSN: 24113964
http://www.nricm.edu.tw/jcm/

中醫藥雜誌
Journal of Chinese Medicine

傳統醫學陰陽與副交感（一氧化氮 - 環鳥苷酸）以及交感（一氧化碳 - 環腺苷酸）平衡

胡萬炯 *

中醫藥臨床研究組，衛生福利部國家中醫藥研究所，台北，台灣

陰陽為傳統中國醫學之要素。在此論文，我解釋陰陽的概念與副交感和交感神經系統之關係。我們的身體用交感和副交感系統來做平衡。陰與副交感神經有關而陽與交感神經有關。此外，存在有二級傳導物質與陰陽相符合。副交感神經由一氧化氮及 cGMP 來媒介而交感神經則透過一氧化碳及 cAMP 來媒介。一氧化氮和一氧化碳是疏水性二級傳導物質而 cGMP 和 cAMP 是親水性二級傳導物質。

關鍵字：交感、副交感、一氧化碳、一氧化氮、環腺苷酸、環鳥苷酸

104 年 3 月 5 日受理
104 年 12 月 2 日接受刊載
105 年 6 月 1 日線上出版

***聯絡人**：胡萬炯，衛生福利部國家中醫藥研究所中醫藥臨床研究組，11221 台北市北投區立農街二段 155-1 號，電話：02-28201999 分機 3551，電子郵件信箱：wanchung@nricm.edu.tw