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Original Article

Cross interaction of melanocortinergic and dopaminergic systems in neural modulation

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Abstract: Melanocortinergic and dopaminergic systems are widely distributed in the CNS and have been established as a crucial regulatory component in diverse physiological functions. The pharmacology of both melanocortinergic and dopaminergic systems including their individual receptors, signaling mechanisms, agonists and antagonists has been extensively studied. Several lines of evidence showed that there existed a cross interaction between the receptors of melanocortinergic and dopaminergic systems. The data available at present had expanded our understanding of melanocortinergic and dopaminergic system interaction in neural modulation, which will be main discussed in this paper.

Keywords: Melanocortinergic system, dopaminergic system, receptor, dopamine

Introduction

Over the last 20 years, basic and clinical studying of the melanocortinergic system has made several progress in neural modulation. The central melanocortinergic system regulates body energy homeostasis and multiple processes including food intake, reward behaviors, and autonomic function [1, 2]. The dopaminergic system, sometimes called dopaminergic pathway, involves in modulation of a variety of physiological functions including motor control, motivation, arousal, cognition, and reward. It is well known that dopamine (DA), a key neurotransmitter modulating reward (natural and drug rewards), is implicated in the rewarding effects of food [3, 4]. Thereby, the melanocortinergic and dopaminergic system pathways are intricately linked. However, the pathway involved is complex and has not yet been clearly defined.

Whereas melanocortinergic and dopaminergic system normally interacts with their individual receptors, there is compelling evidence indicating that they could cross interact with the receptors of each other in some important brain regions. This paper highlighted relevant functional interactions, and discussed the evidence regarding their links of the neural modulation.

Neuroanatomical substrates of melanocortinergic and dopaminergic systems

Dopaminergic pathways, sometimes called dopaminergic projections, are neural pathways in the brain [5]. Many lines of evidence show that the ventral tegmental area (VTA) and its dopaminergic projections are key components of a reward circuit [4, 6]. Luo et al reported that the dorsal hippocampus CA3-caudodorsal lateral septum (cd-LS)-VTA circuit in context-induced reinstatement of cocaine-seeking and a proposed diagram of the circuit's mechanisms [7], suggesting that a circuit from area CA3 of dorsal hippocampus to ventral tegmental area (VTA) that uses lateral septum (LS) as a relay. Several studies have shown that tyrosine hydroxylase (TH), the rate limiting enzyme for the biosynthesis of dopamine and norepinephrine [8-10], is the marker of dopamine neurons in the VTA [11-15]. We systemically investigated the expression of TH-positive neurons in the several CNS nuclei by using fluorescence immunohistochemistry, and found that TH-positive neurons were located in VTA, nucleus accum-

bens (NAc), the prefrontal cortex, the substantia nigra, the dorsal striatum (caudate and putamen), limbic regions (hippocampus and amygdala), the lateral hypothalamus and the rostral ventromedial medulla (RVM) [16, 17]. Therefore, there exists specific neuroanatomical distribution of dopaminergic systems in the brain.

The melanocortins, derived from proopiomelanocortin in the arcuate nucleus of the hypothalamus [18-21], involve in a variety of physiological functions including the regulation of food intake and weight control [22]. The effects of melanocortin peptides are mediated by G protein-coupled receptors, including the MC3R and MC4R, which are distributed in several CNS nuclei [20]. In contrast, MC1R, MC2R, and MC5R are expressed at very low or undetectable levels in these brain regions [23]. Rodent studies and clinical observations support a linkage of the melanocortin peptides to regulation of food intake, leptin, weight control, and now blood pressure [22, 24]. It is known that neuroanatomic studies of the MC4R are limited by the lack of high-affinity antibodies. In combination of a transgenic mouse line that expressing green fluorescent protein (GFP) under MC4R promoter and immunohistochemistry, Liu et al found that GFP-positive neurons were mainly located in the cerebral cortex layer 5, lateral septal nucleus, VTA, NAc, the central amygdaloid nucleus (CeA), bed nucleus of the stria terminalis (BST), the tuberal hypothalamus, the lateral hypothalamic area (LHA), and the perifornical area (PFA) [25]. A study of Alvaro et al also reported the expression of MC4-R mRNA in the striatum and nucleus accumbens [23]. Gelez et al also reported that MC4R-positive cells were especially abundant in the hypothalamus, including the lateral septal nucleus, arcuate nucleus, and lateral hypothalamic area whereas a moderate number of MC4R-positive neurons were found in the piriform cortex, bed nucleus of the stria terminalis, amygdala, periaqueductal gray and raphe nucleus [26]. To sum up, between melanocortinergic and dopaminergic pathways share several important nuclei in the brain.

Cross interaction of two systems in reward regulation

The mesolimbic dopamine pathway and the melanocortin system are important components of the central circuitry controlling reward-related aspects of feeding. There is evidence that the melanocortins can act on mesolimbic dopamine pathways to regulate feeding [27, 28]. Roseberry et al reported that injection of the melanocortin receptor agonist MTII into the VTA inhibited feeding for up to 24 h whereas injection of the melanocortin receptor antagonist SHU9119 into the VTA stimulated feeding for up to 24 h, and chronic blockade of melanocortin receptors through repeated daily injections of SHU9119 into the VTA increased feeding, body weight, and caloric efficiency [28]. These results suggest that endogenous melanocortin peptides may control feeding through the mesolimbic dopamine pathways. A study of Yen et al also added to the growing body of evidence showing that the melanocortin receptor agonist MTII can interact with the mesolimbic dopamine pathways to regulate multiple reward-related behaviors [27]. It is well known that retrograde tracing techniques of transgenic recombinants of pseudorabies virus (PRV) were widely used to characterize neuroanatomic circuits. Our observation found that injection of a PRV-Bartha derivative PRV-614 expressing red fluorescence protein (RFP) into the gastrocnemius muscle resulted in retrograde transfection of the ipsilateral intermediolateral nucleus (IML) of spinal segments, VTA, nucleus accumbens and the prefrontal cortex neurons in spinally transected transgenic MC4R-GFP mice. PRV-614/MC4R-GFP neurons were detected in the VTA, nucleus accumbens and the prefrontal cortex (**Figure 1**), suggesting that the VTA, nucleus accumbens and the prefrontal cortex may play an important role in the sympathetic pathway by the melanocortinergic signaling.

As an important part of the reward pathway, the major dopaminergic pathways are involved in the VTA, NAc and the prefrontal cortex [4, 6, 29-31]. A study of Alvaro et al also indicated that expression of MC4R mRNA was found to be enriched in the periaqueductal gray, striatum and NAc [23]. Several recent studies have found that the activity of the dopamine D1-type receptor (D1R) is tightly interconnected for procedural memory learning via central MC4R [32-34]. Cui et al demonstrated that MC4R is co-located with the D1R-positive cells in the striatum, and found that restoration of MC4R-mediated signaling in D1R-positive neurons normalized procedural learning and procedural

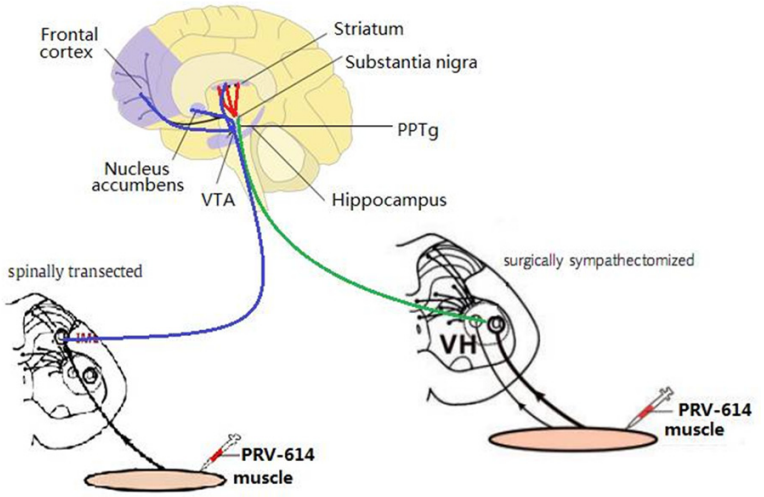

Figure 1. Summary diagram showed that the sympathetic and motor pathway between the several CNS nuclei and skeletal muscle. Left (blue line): As an important part of the reward pathway, the major dopaminergic pathways are involved in the VTA, NAc and the prefrontal cortex. Injection of recombinant PRV-614 expressing red fluorescence protein (RFP) into the gastrocnemius muscle resulted in retrograde infection of the ipsilateral intermediolateral nucleus (IML) of spinal segments, VTA, nucleus accumbens and the prefrontal cortex neurons in spinally transected transgenic MC4R-GFP mice; PRV-614/MC4R-GFP neurons were detected in the VTA, nucleus accumbens and the prefrontal cortex, suggesting that the VTA, nucleus accumbens and the prefrontal cortex may play an important role in the sympathetic pathway by the melanocortinergic signaling. Right (green line): Dopaminergic motor functions are linked to a separate pathway, and the major dopaminergic motor pathways are involved in the substantia nigra and the striatum. PRV-614 was injected into the gastrocnemius muscle of surgically sympathectomized transgenic MC4R-GFP mice as a specific transsynaptic retrograde tracer. After 3, 4, 5 or 6 days, spinal cord and brain were collected for immunofluorescence staining. The temporal order of PRV-614 labeled neurons was found in the ventral horn (VH) motor neurons of spinal segments on day 3; pedunculopontine tegmental nucleus (PPTg) and substantia nigra on day 4-5; and the dorsal striatum (caudate and putamen) on day 5-6. We found that PRV-614/MC4R-GFP double-labeled neurons in the VH, PPTg, substantia nigra and the dorsal striatum, suggesting that the PPTg, substantia nigra and the dorsal striatum may play a major role in the initiation of skeletal muscle tone by the melanocortinergic and catecholaminergic pathway. Some drawings were taken from Qing-Xiong Hong (Epilepsy & Behavior 2014) and Hong-Bing Xiang (Brain 2013).

memory learning in the cued water maze also required MC4R-mediated signaling in D1R-positive neurons, suggesting that MC4R-mediated signaling in distinct regions of the striatum is critical for learning various aspects of procedural memory learning and food reward [32]. Though these data indicated anatomical intertwinement of two pathways, further research is needed to delineate their regulatory functions.

Otherwise, some reports indicated that the VTA is one of the highest sites of MC3R expression. Lippert et al characterized the neurochemical identity of the MC3R neurons in the VTA and determined the effects of global MC3R deletion on VTA DA homeostasis by using a MC3R-GFP transgenic mouse and a MC3R knockout mouse strain, and found that the MC3R was expressed in up to a third of dopaminergic neurons of the VTA and Global deletion of the MC3R increased total dopamine by 42% in the VTA and decreases sucrose intake and preference in female but not male mice, suggesting the function of MC3R in regulation of the mesolimbic dopaminergic system and reward [10]. Further work on elucidating the difference of MC3R and MC4R in the VTA will contribute to understand the important mechanisms of reward regulation.

Cross interaction of two systems in motion regulation

As a part of the regulation of motor functions, dopaminergic projections are linked to a separate pathway. The major dopaminergic motor pathways are involved in the substantia nigra (SN) and the striatum. In this pathway, dopaminergic cell bodies locate within the SN and manufacture and release dopamine into the striatum. Zhou et al reported that between tyrosine hydroxylase mRNA expression in the rat SN and the levels of striatal dopamine were significantly decreased in Parkinson's disease rat models induced by 6-hydroxy-dopamine injection into SN [35], suggesting that the dopaminergic activities of SN and striatum involved in the regulation of movement. Mena-Segovia et al reported that a substantial projection from the pedunculopontine tegmental nucleus (PPTg) innervates dopaminergic neurons of the SN pars compacta (SNc), which in turn modulate

striatonigral and striatopallidal pathways [36], suggesting there are interconnections between the basal ganglia and the PPTg.

By using a mouse line expressing GFP under MC4R gene promoter, we systemically investigated MC4R signaling in the motor neuronal circuitry between the skeletal muscle and the several CNS nuclei in surgically sympathectomized transgenic MC4R-GFP mice by combining double immunohistochemistry and retrograde tracing techniques (**Figure 1**). Recombinant PRV-614 expressing red fluorescence protein (RFP) was injected into the gastrocnemius muscle of mice as a specific trans-synaptic retrograde tracer [37-42]. After 3, 4, 5 or 6 days, spinal cord and brain were collected for immunofluorescence staining. The temporal order of PRV-614 labeled neurons was found in the ventral horn (VH) motor neurons of spinal segments on day 3; PPTg and SN on day 4-5; and the dorsal striatum (caudate and putamen) on day 5-6. We found that PRV-614/MC4R-GFP double-labeled neurons in the VH, PPTg, SN and the dorsal striatum (**Figure 1**). Otherwise, TH/MC4R-GFP double-labeled neurons in the PPTg [43], SN and the dorsal striatum. These data indicated that the PPTg, SN and the dorsal striatum may play a major role in the initiation of skeletal muscle tone by the melanocortinergic and catecholaminergic pathway.

Conclusion

The data available at present have expanded our understanding to cross interaction of melanocortinergic and dopaminergic system in neural modulation. It is obvious that the melanocortinergic and dopaminergic system are more intimately connected than traditionally believed from the knowledge accumulated during the past two decades. Further investigations are clearly needed to to understand the impact of cross interaction of the melanocortinergic and dopaminergic system by specific pharmacological interventions in neural modulation.

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Disclosure of conflict of interest

None.

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References

[1] Cui H, Sohn JW, Gautron L, Funahashi H, Williams KW, Elmquist JK and Lutter M. Neuroanatomy of melanocortin-4 receptor pathway in the lateral hypothalamic area. J Comp Neurol 2012; 520: 4168-4183.

[2] Boswell T and Takeuchi S. Recent developments in our understanding of the avian melanocortin system: its involvement in the regulation of pigmentation and energy homeostasis. Peptides 2005; 26: 1733-1743.

[3] Wise RA. Role of brain dopamine in food reward and reinforcement. Philos Trans R Soc Lond B Biol Sci 2006; 361: 1149-1158.

[4] Volkow ND, Wang GJ and Baler RD. Reward, dopamine and the control of food intake: implications for obesity. Trends Cogn Sci 2011; 15: 37-46.

[5] Doyon WM, Thomas AM, Ostroumov A, Dong Y and Dani JA. Potential substrates for nicotine and alcohol interactions: a focus on the mesocorticolimbic dopamine system. Biochem Pharmacol 2013; 86: 1181-1193.

[6] Thomas MJ and Malenka RC. Synaptic plasticity in the mesolimbic dopamine system. Philos Trans R Soc Lond B Biol Sci 2003; 358: 815-819.

[7] Luo AH, Tahsili-Fahadan P, Wise RA, Lupica CR and Aston-Jones G. Linking context with reward: a functional circuit from hippocampal CA3 to ventral tegmental area. Science 2011; 333: 353-357.

[8] Masi A, Narducci R, Resta F, Carbone C, Kobayashi K and Mannaioni G. Differential contribution of Ih to the integration of excitatory synaptic inputs in Substantia Nigra pars compacta and Ventral Tegmental Area dopaminergic neurons. Eur J Neurosci 2015; 42: 2699-706.

[9] Margolis EB, Coker AR, Driscoll JR, Lemaitre AI and Fields HL. Reliability in the identification of midbrain dopamine neurons. PLoS One 2010; 5: e15222.

[10] Lippert RN, Ellacott KL and Cone RD. Gender-specific roles for the melanocortin-3 receptor in the regulation of the mesolimbic dopamine system in mice. Endocrinology 2014; 155: 1718-1727.

[11] Luquin MR, Montoro RJ, Guillen J, Saldise L, Insausti R, Del Rio J and Lopez-Barneo J. Recovery of chronic parkinsonian monkeys by autotransplants of carotid body cell aggregates into putamen. Neuron 1999; 22: 743-750.
[12] Morales M and Root DH. Glutamate neurons within the midbrain dopamine regions. Neuroscience 2014; 282C: 60-68.
[13] Ford CP, Mark GP and Williams JT. Properties and opioid inhibition of mesolimbic dopamine neurons vary according to target location. J Neurosci 2006; 26: 2788-2797.
[14] Karachi C, Grabli D, Bernard FA, Tande D, Wattiez N, Belaid H, Bardinet E, Prigent A, Nothacker HP, Hunot S, Hartmann A, Lehericy S, Hirsch EC and Francois C. Cholinergic mesencephalic neurons are involved in gait and postural disorders in Parkinson disease. J Clin Invest 2010; 120: 2745-2754.
[15] Bachmann LC, Matis A, Lindau NT, Felder P, Gullo M and Schwab ME. Deep brain stimulation of the midbrain locomotor region improves paretic hindlimb function after spinal cord injury in rats. Sci Transl Med 2013; 5: 208ra146.
[16] Pan XC, Song YT, Liu C, Xiang HB and Lu CJ. Melanocortin-4 receptor expression in the rostral ventromedial medulla involved in modulation of nociception in transgenic mice. J Huazhong Univ Sci Technolog Med Sci 2013; 33: 195-198.
[17] Xiang HB, Liu C, Guo QQ, Li RC and Ye DW. Deep brain stimulation of the pedunculopontine tegmental nucleus may influence renal function. Med Hypotheses 2011; 77: 1135-1138.
[18] Huo L, Grill HJ and Bjorbaek C. Divergent regulation of proopiomelanocortin neurons by leptin in the nucleus of the solitary tract and in the arcuate hypothalamic nucleus. Diabetes 2006; 55: 567-573.
[19] Chaki S and Okuyama S. Involvement of melanocortin-4 receptor in anxiety and depression. Peptides 2005; 26: 1952-1964.
[20] Starowicz K and Przewlocka B. The role of melanocortins and their receptors in inflammatory processes, nerve regeneration and nociception. Life Sci 2003; 73: 823-847.
[21] Schwartz MW, Seeley RJ, Woods SC, Weigle DS, Campfield LA, Burn P and Baskin DG. Leptin increases hypothalamic pro-opiomelanocortin mRNA expression in the rostral arcuate nucleus. Diabetes 1997; 46: 2119-2123.
[22] Carlson SH and Wyss JM. Mechanisms underlying hypertension and obesity: a melanocortin linkage in the brain. Hypertension 2011; 57: 375-376.
[23] Alvaro JD, Tatro JB, Quillan JM, Fogliano M, Eisenhard M, Lerner MR, Nestler EJ and Duman RS. Morphine down-regulates melanocortin-4 receptor expression in brain regions that mediate opiate addiction. Mol Pharmacol 1996; 50: 583-591.
[24] Millington GW. The role of proopiomelanocortin (POMC) neurones in feeding behaviour. Nutr Metab (Lond) 2007; 4: 18.
[25] Liu H, Kishi T, Roseberry AG, Cai X, Lee CE, Montez JM, Friedman JM and Elmquist JK. Transgenic mice expressing green fluorescent protein under the control of the melanocortin-4 receptor promoter. J Neurosci 2003; 23: 7143-7154.
[26] Gelez H, Poirier S, Facchinetti P, Allers KA, Wayman C, Bernabe J, Alexandre L and Giuliano F. Neuroanatomical distribution of the melanocortin-4 receptors in male and female rodent brain. J Chem Neuroanat 2010; 40: 310-324.
[27] Yen HH and Roseberry AG. Decreased consumption of rewarding sucrose solutions after injection of melanocortins into the ventral tegmental area of rats. Psychopharmacology (Berl) 2015; 232: 285-294.
[28] Roseberry AG. Altered feeding and body weight following melanocortin administration to the ventral tegmental area in adult rats. Psychopharmacology (Berl) 2013; 226: 25-34.
[29] Lim BK, Huang KW, Grueter BA, Rothwell PE and Malenka RC. Anhedonia requires MC4R-mediated synaptic adaptations in nucleus accumbens. Nature 2012; 487: 183-189.
[30] Kelley AE and Berridge KC. The neuroscience of natural rewards: relevance to addictive drugs. J Neurosci 2002; 22: 3306-3311.
[31] Norgren R, Hajnal A and Mungarndee SS. Gustatory reward and the nucleus accumbens. Physiol Behav 2006; 89: 531-535.
[32] Cui H, Mason BL, Lee C, Nishi A, Elmquist JK and Lutter M. Melanocortin 4 receptor signaling in dopamine 1 receptor neurons is required for procedural memory learning. Physiol Behav 2012; 106: 201-210.
[33] Cui H and Lutter M. The expression of MC4Rs in D1R neurons regulates food intake and locomotor sensitization to cocaine. Genes Brain Behav 2013; 12: 658-665.
[34] Oude Ophuis RJ, Boender AJ, van Rozen AJ and Adan RA. Cannabinoid, melanocortin and opioid receptor expression on DRD1 and DRD2 subpopulations in rat striatum. Front Neuroanat 2014; 8: 14.
[35] Zhou Q, Chen J, Yi S, Lou Y, Tang W, Liu Y and Zhang P. Zhichan powder regulates nigrostriatal dopamine synthesis and metabolism in Parkinson's disease rats. Neural Regen Res 2012; 7: 2107-2114.
[36] Mena-Segovia J, Bolam JP and Magill PJ. Pedunculopontine nucleus and basal ganglia: distant relatives or part of the same family? Trends Neurosci 2004; 27: 585-588.

[37] Ye DW, Liu C, Tian XB and Xiang HB. Identification of neuroanatomic circuits from spinal cord to stomach in mouse: retrograde transneuronal viral tracing study. Int J Clin Exp Pathol 2014; 7: 5343-5347.

[38] Ye DW, Liu C, Liu TT, Tian XB and Xiang HB. Motor cortex-periaqueductal gray-spinal cord neuronal circuitry may involve in modulation of nociception: a virally mediated transsynaptic tracing study in spinally transected transgenic mouse model. PLoS One 2014; 9: e89486.

[39] Xiang HB, Liu TT, Tian XB and Zhu WZ. Therapeutic mechanism of subthalamic nucleus stimulation for refractory epilepsy involved in melanocortin-4 receptor signaling. Mol Cell Epilepsy 2014; 1: 13-18.

[40] Xiang HB, Liu C, Liu TT and Xiong J. Central circuits regulating the sympathetic outflow to lumbar muscles in spinally transected mice by retrograde transsynaptic transport. Int J Clin Exp Pathol 2014; 7: 2987-2997.

[41] Qiu Q, Li RC, Ding DF, Liu C, Liu TT, Tian XB, Xiang HB and Cheung CW. Possible mechanism of regulating glucose metabolism with subthalamic nucleus stimulation in parkinson's disease: a virally mediated trans-synaptic tracing study in transgenic mice. Parkinsonism Relat Disord 2014; 20: 468-470.

[42] Hao Y, Tian XB, Liu C and Xiang HB. Retrograde tracing of medial vestibular nuclei connections to the kidney in mice. Int J Clin Exp Pathol 2014; 7: 5348-5354.

[43] Xiang HB, Zhu WZ, Guan XH and Ye DW. The cuneiform nucleus may be involved in the regulation of skeletal muscle tone by motor pathway: a virally mediated trans-synaptic tracing study in surgically sympathectomized mice. Brain 2013; 136: e251.