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Review Article

CeA-RVMM serotonergic circuits and sudden unexpected death in epilepsy

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Abstract: Consensus exists on the importance of neural circuit in affecting the clinical outcome after sudden unexpected death in epilepsy (SUDEP). There is growing evidence that the serotonergic neuronal networks have a well-established role in SUDEP. Much progress has been made in our understanding of SUDEP since the seminal experiments of neural circuits. Future studies are that CeM-RVMM serotonergic circuits are poised to integrate multiple synaptic inputs from various sources thought to influence sudden unexpected death in epilepsy by melanocortinergic signaling.

Keywords: Serotonergic circuits, sudden unexpected death,melanocortinergic signaling

Introduction

Knowledge on the neural circuit bases of refractory epilepsy can help us to explain many mechanisms associated with the epileptic seizure phenomena, e.g., sudden unexpected death in epilepsy (SUDEP), representing the main cause of death in patients with drug/treatment-refractory epilepsy. For more than two decades, the epilepsy community had puzzled over what we now call SUDEP, and these researches-seemed to have been lively productive, given that a PubMed search using the sudden unexpected death in epilepsy keywords returns 597 results (as of May 5, 2015) with a steadily increasing number of papers. One result of these interesting discoveries is animportant discussion that the main pathophysiology of SUDEP may be directly or indirectly involved in neural circuit which has to be looked for in the autonomic nervous system.These contemplations have witnessed an explosion in the scientific recognition of serotonergic circuitry involved in SUDEP [1, 2].

SUDEP and serotonergic circuitry

There is growing evidence that the serotonergic neuronal networks have a well-established role in SUDEP [3-6]. The serotonin system modulates key behaviors related to locomotory circuit in vertebrates, for instance, sensory-mediated locomotory behaviors [7]. It has been well established that 5-HT is released during seizures and postictal depression [8]. Many reports have indicated that the serotonergic dysfunction involves in the control of breathing [9-12]. In the study of Massey et al, there exist a consistent idea between a role for 5-HT dysfunction in SUDEP and the known critical role of 5-HT in control of breathing [13].

Animal studies support the notion that functional impairment of serotonergic neurons seems to be important in the pathophysiology of SUDEP [1]. Translational research in animal models has identified that the serotonergic neuronal network of the brainstem may share a common final pathway of SUDEP and sudden infant death syndrome (SIDS) [6, 14]. DBA/2 mice are well known to propose as a SUDEP model exhibiting audiogenic seizures-induced respiratory arrest which implicated in human SUDEP. A study of Tupal et al evaluated the effects of serotonin antagonist cyproheptadineand a selective serotonin reuptake inhibitor (SSRI) fluoxetine on respiratory arrest incidence in DBA/2 mice, and indicated that fluoxetine

decreased respiratory arrestand did not eliminate seizure severity, supportingthe use of serotonin antagonists for SUDEP prevention [6]. 5-HT2C receptors widely expressed throughout the CNS have been believed to mediate numerous actions of serotoninin brain and spinal cord. Tecott et al reported that 5-HT2C receptor-deficient mice are prone to seizures-induced spontaneous death, suggesting that 5-HT2C receptors regulate tonic inhibition of serotonergic signaling excitability [14]. Faingold et al reported differential effects of serotonergic drugs on seizure-induced respiratory arrest in DBA/1 mice, and indicated that certain drugs that enhance the activation of 5-HT receptors, e.g. a selective 5-HT reuptake inhibitor (SSRI) fluvoxamine, are able to prevent seizure-induced respiratory arrest [4]. Otherwise, considering that KCNQ (Kv7) channels are downstream effectors of serotonergic modulation for breathing, and dysfunctions of KCNQ (Kv7) channels may be one cause for epilepsy and respiratory problems associated with SUDEP, Mulkey et al proposed that KCNQ (Kv7) channels represent useful therapeutic targets for the treatment of respiratory control disorders [15]. These data are important towards delineating the role of the serotonergic circuitry in modulation of SUDEP.

Serotonergic microcircuits in the amygdala

Pharmaco behavioral studies in experimental animals support the notion that the amygdala is a core component of neural circuits that mediate processing ofrefractory epilepsy. Since Munkenbeck et al reported a suppressive role of serotonergic mechanisms in the development of amygdaloid-kindled seizures in 1982 [16], consensus existed on the serotonergic microcircuits in the amygdala. It has become increasingly clear that the amygdala is a heterogeneous structure which plays a key role in the processing of epilepsy [17, 18]. 5-HT has been rendered to neural plasticity in adulthood implicated in sudden infant death syndrome [19, 20]. Morphological and functional studies have yielded strong evidence that different subregions of the amygdala subserve certain functions. First, lateral amygdala (LA) is believed to be gatekeeper receiving external sensory input, and different information arising from LA and hippocampus further transferto the basolateral nucleus of amygdala (BLA) [21]. Second, neurons from LA and BLA send highly processed projection to the central nucleus of amygdala (CeA), which is a major endocrine and autonomous output station of the amygdala to send axons to the hypothalamus and brainstem [22]. Findings in experimental animals rendered that the serotonin receptors 1A (5-HT1A), 2C (5-HT2C) and 3 (5-HT3) were observed in the LA and BLA [23, 24]. A study of Smith et al indicated that the dorsal raphe nucleus sent dense serotonergic projections to neurons in LA and BLA for the regulation of adequate autonomous, emotional and behavioral reactions [25, 26]. Petrov et al observed that 5-HT release in the CeA was been positively correlated with the dorsal raphe nucleuswhich providesserotonergic innervation to the CeA [27]. Akmaev et al reported thatCeA received serotonergic information via LA and BLA from wide range of cortical and subcortical structures [28]. Asan et al reported that serotonergic alterations in amygdala responsivity, focusing particularly on the extensively studied neural circuits which are involved in LA and BLA, were found in neuropsychiatric disorders [29]. Mo et al reported that serotonergic activity in CeA was mediated by corticotropin-releasing factor involved in initiating stress responses [30]. Therefore, there exist LA-BLA-CeA serotonergic microcircuits in the amygdala complex. These findings indicated interactionsof the serotonergic signaling with amygdaloid microcircuits of significant interest implicated in various functions in the CNS.

Our research data about serotonergic and melanocortinergic signaling in pons and medulla

Though without the complete elucidation of the complex neurocircuitry underlying the serotonergic control of MC4R functions, findings in experimental animals indicate that serotonergic pathway is tightly linked to melanocortinergic signaling [31-33]. Recently, our previous studies suggested that the CeA may involve in SUDEP by melanocortinergic signaling [34-36]. In this context, our lab contributed to reveal and elucidate different distribution of serotonergic and melanocortinergic signaling in pons and medullain particular reporting co-localization in the autonomic nervous system by using retrograde transsynaptic tracer PRV-614 [37-44]. Since there is no evidence that the motor

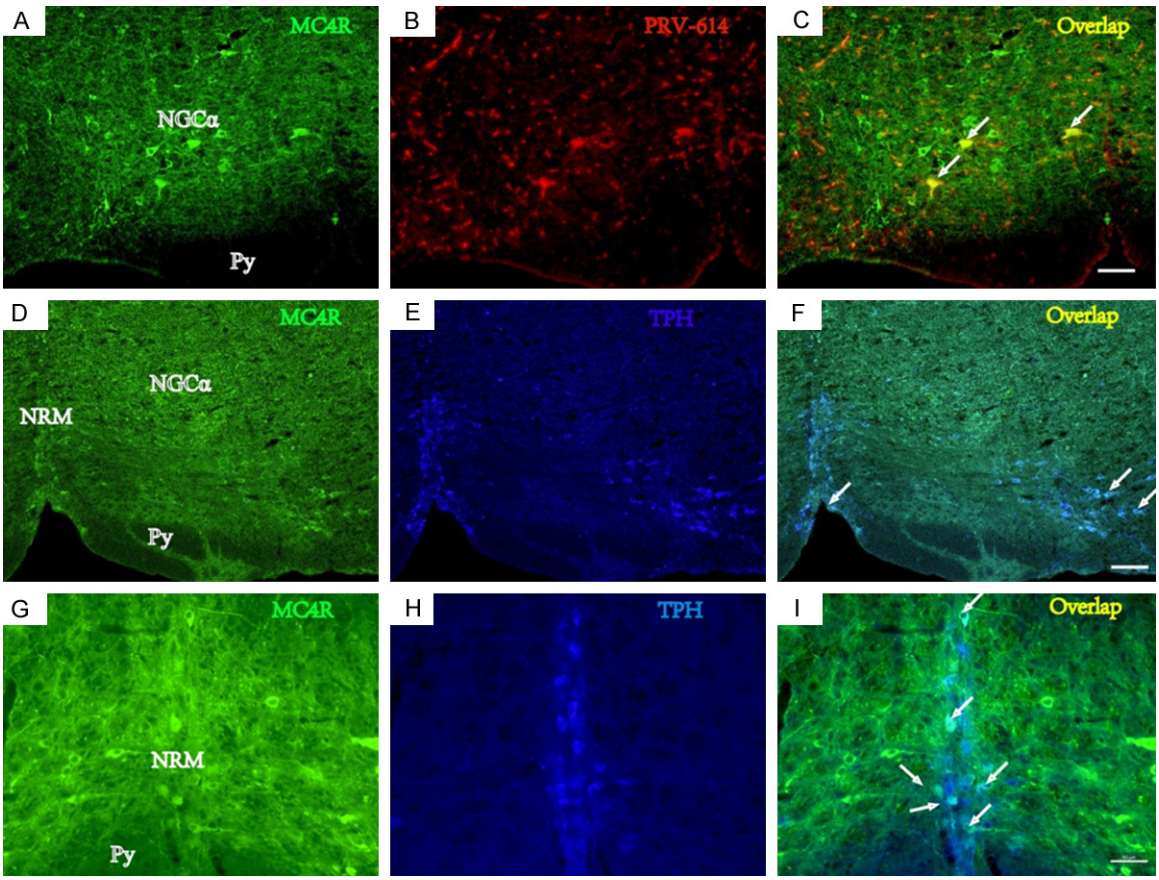

Figure 1. Co-localization of TPH in subsets of MC4R-GFP positive neurons within RVMM areas. A, D and G: MC4R-GFP positive neurons (green); B: PRV-614positive neurons (red); E and H: TPH-positive neuron (blue); C: Overlaid images of A plus B, arrows indicate double-labeled neurons (yellow). F and I: Overlaid images of D plus E, and G plus H, arrows indicate double-labeled neurons (cyan). MC4R-GFP was mostly colocalized with TPH positive neurons. Scale bar: 50 μm for A-C, G-I; 25 μm for D-F. NGCα, gigantocellular reticular nucleus α part; NRM, nucleus raphe magnus; Py, pyramidal tract. Some drawings were taken from Hong-Bing Xiang [31].

and parasympathetic nerve provide any innervations ofthe kidney, it has become a model system in which to study sympathetic pathway. Thus, neurons in pons and medulla were infected with PRV-614 injection into the kidney via the sympathetic nerve.Neuronal tryptophan hydroxylase (TPH) is the rate-limiting enzyme in the synthesis of 5-HT in the CNS, and has been used as a marker of serotoninergic neuron [45, 46]. Our research data included several facts as follows: First, we demonstrated that the presence of PRV-614/5-HT, PRV-614/TPH, PRV-614/MC4R-GFP dual-labeled neurons in the rostral ventral medulla (RVMM) including gigantocellular reticular nucleus α part (NGCα) and nucleus raphe magnus (NRM) after PRV-614 injection into the kidney, suggesting these 5-HT-, PRV-614-positive cells and TPH-expressing neurons can project directly or indirectly to the kidney via sympathetic pathway. Second, we found that 5-HT/MC4R-GFP, TPH/MC4R-GFP dual-labeled neurons were detected in the RVMM (**Figure 1**) by using fluorescence immunohistochemistry, suggesting that there exists melanocortinergic-serotonergic signaling in the RVMM microcircuits [47].

Distribution of serotonergic signaling in pons and medulla

It has been known that there exists the caudal serotonergic (5-HT) circuit, animportant component of a medullary “homeostatic network”, which modulates energy metabolic responses and potentially integrates autonomic function according to the physiological level [48-50]. In vitro and in vivo evidences have supported the idea that medullary 5-HT neurons are central “sensors” of CO_2/pH [51-53]. A study of

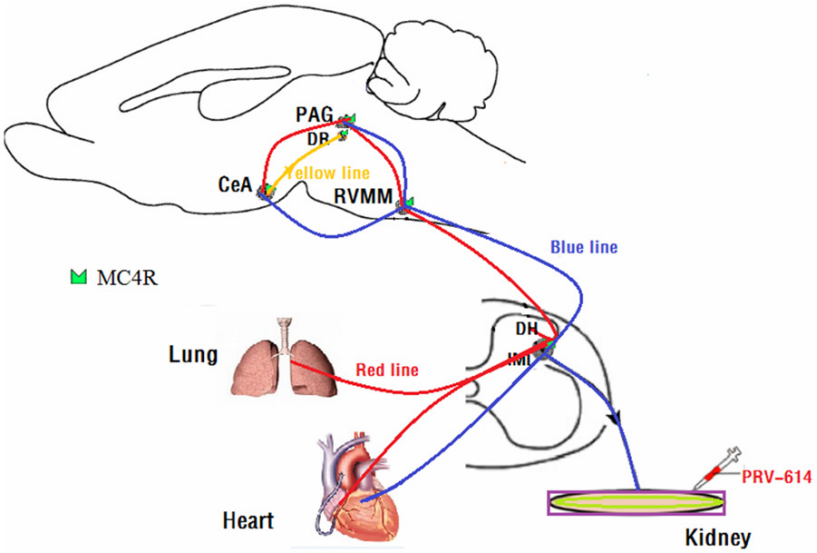

Figure 2. The pattern graph showed that CeA-RVMM serotonergic circuits. This figure has been updated according to that reported in previous studies. Yellow line: the dorsal raphe nucleus (DR) provides 5-HT innervation to the CeA. Red line: CeA-RVMM descending serotonergic circuits are collective structure which contains sympathetic premotor neurons within the RVMM including raphe magnus and gigantocellular reticular nucleus, pars alpha, and it is an important route of PAG projection which involved in facilitatory modulation of lower Cardiovascular respiratory center centers in pons and medulla. Blue line: Injection of PRV-614 into the kidney resulted in retrograde infection of neurons in the IML, atrioventricular node and sinus node, RVMM, PAG and CeA by sympathetic pathway. PRV-614/MC4R-GFP dual-labeled neurons were detected in the IML, RVMM, PAG and CeA; 5-HT/MC4R-GFP, TPH/MC4R-GFP dual-labeled neurons were detected in the RVMM, PAG and CeA. Some drawings were taken from HB Xiang [34, 60, 61].

Richerson et al showed the chemosensitivity of serotonergic neurons in the rostral ventral medulla (RVMM), suggesting that the cellular properties of serotonergic raphe neurons play an important role in the CNS response to hypercapnia [54]. He also reported that serotonergic neurons within the ventrolateral medulla (VLM) localized respiratory chemoreception regions, consistent with a specialized study that abnormalities of serotonergic systems in the ventral medulla neurons were identified in sudden infant death syndrome (SIDS) [54]. Gdovinet al reported the serotonergic modulation of respiratoryrhythmogenic and chemoreceptive circuits, and found that 5-HT1A receptors were involved in neural respiratory rhythmogenesis and central chemoreception in the bullfrog tadpole, supporting the hypothesis that serotonergic abnormality may be an underlying component of SIDS [51].

The medullary 5-HT neurons are interspersed with melanocortinergic, gabaergic and glutamatergic neurons [31, 55-58]. Crawford et al reported the distinct functions of 5-HT neurons in dorsal raphe (DR) subfields providingthat there exist increased 5-HT output in the ventromedial DR (vmDR) regions whereas decreased 5-HT output in the lateral wing DR (lwDR) regions using electrophysiology recordings [57], which were in agreement with a previous study in which raphe serotonin neurons were not homogenous [59]. A study of Pan et al observed a large number of MC4R-GFP-positive neurons in the nucleus raphe magnus and nucleus gigantocellularis pars alpha by fluorescence immunohistochemistry, and revealed that 50%-75% of those neurons coexpressed tryptophan hydroxylase, indicating that they were serotonergic, supporting the hypothesis that MC4R signaling in the rostral ventral medulla may modulate the activity of serotonergic sympathetic signals [31]. Paterson et al reported the identification of chemosensitive 5-HT and glutamatergic neurons in the ventral medulla oblongata region (VMS), suggesting that important functional interactions exist between 5-HT and glutamate in the VMS [55].

Summary

Taken together, consensus exists on the importance of neural circuit in affecting the clinical outcome after sudden unexpected death in epilepsy, nevertheless mechanisms involved have not been recently addressed. Much progress has been made in our understanding of SUDEP since the seminal experiments of neural circuits (**Figure 2**). Future studies are that CeM-RVMM serotonergic circuits are poised to integrate multiple synaptic inputs from various sources thought to influence sudden unexpect-

ed death in epilepsy by melanocortinergic signaling.

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Disclosure of conflict of interest

None.

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