

# Neuronal Activity-Dependent Regulation of MicroRNAs

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**MicroRNAs are non-coding short (~23 nucleotides) RNAs that mediate post-transcriptional regulation through sequence-specific gene silencing. The role of miRNAs in neuronal development, synapse formation and synaptic plasticity has been highlighted. However, the role of neuronal activity on miRNA regulation has been less focused. Neuronal activity-dependent regulation of miRNA may fine-tune gene expression in response to synaptic plasticity and memory formation. Here, we provide an overview of miRNA regulation by neuronal activity including high-throughput screening studies. We also discuss the possible molecular mechanisms of activity-dependent induction and turnover of miRNAs.**

## INTRODUCTION

Neuronal activity induces various cellular and molecular changes, which results in the alteration of synaptic strength. In particular, at the synapse level, each synapse shows dynamic responses to specific neuronal activity within a few minutes, which implies that fast and precise molecular machineries are indispensable (Lee et al., 2009; Matsuzaki et al., 2004; Padamsey and Empage, 2011).

Recent studies revealed a novel post-transcriptional regulatory system using small non-coding RNAs, so-called microRNAs (miRNA), which inhibit protein synthesis by imperfect complementary binding to 3' untranslated region (3'UTR) of target mRNAs. Transcription of miRNAs produces long primary miRNAs (pri-miRNAs), and then these are processed by Drosha to precursor miRNAs (pre-miRNAs) which form a single hairpin structure. These pre-miRNAs are exported to the cytoplasm by Exportin 5 and further processed by Dicer to ~23-nucleotide-long mature miRNAs. Mature miRNAs are loaded into the RNA-induced silencing complex (RISC) and bind to 3'UTR of

target mRNAs, which results in translational repression and/or mRNA destabilization (Bartel, 2004; Im and Kenny, 2012; Xiong et al., 2013). Translational repression of mRNA driven by miRNAs is an attractive regulatory system for explaining rapid local protein synthesis in response to neuronal activity (Huber et al., 2000; Martin et al., 1997; Sutton and Schuman, 2006). The evidence from many studies showing some miRNAs are specifically enriched in dendrites and synaptosomes also implies the role of miRNAs in neuronal activity (Kye et al., 2007; Lugli et al., 2008; Schrott et al., 2006; Siegel et al., 2009).

In this review, we summarize recent studies reporting activity-dependent regulation of miRNAs and discuss how miRNAs are regulated by various types of neuronal activity.

## REGULATION OF miRNAs BY NEURONAL ACTIVITY

Numerous studies have shown that miRNAs are critically regulated by neuronal activity. We summarized a decade of research showing direct regulation of miRNAs in response to various types of neuronal activity (Table 1).

### miR-132

The first and most studied miRNA induced by neuronal activity is miR-132. Many studies have shown a consistent increase of miR-132 after various types of neuronal activity such as brain-derived neurotrophic factor (BDNF), KCl (membrane depolarization) and bicuculline (GABAR Receptor inhibition) in cultured neurons (Chai et al., 2013; Klein et al., 2007; Vo et al., 2005; Wayman et al., 2008) and seizure, contextual fear conditioning, odorant stimulus, light, cocaine intake and visual stimulus in particular brain regions of living animals (Cheng et al., 2007; Im et al., 2010; Nudelman et al., 2010; Tognini et al., 2011). Moreover, reduced neuronal activity such as monocular deprivation in visual cortex decreases both pre- and mature miR-132, strengthening the evidence for neuronal activity-dependent miR-132 induction (Mellios et al., 2011; Tognini et al., 2011). The induction of miR-132 is regulated by cAMP response element binding protein (CREB) which is a crucial stimulus-induced transcription factor regulating many fast-response genes and playing a key role in dendritic development and synaptic plasticity. Studies using pharmacological inhibitors showed that the induction of miR-132 requires activation of NMDA receptor, CaM kinase and MEK-ERK pathways (Cheng et al., 2007; Wayman et al., 2008).

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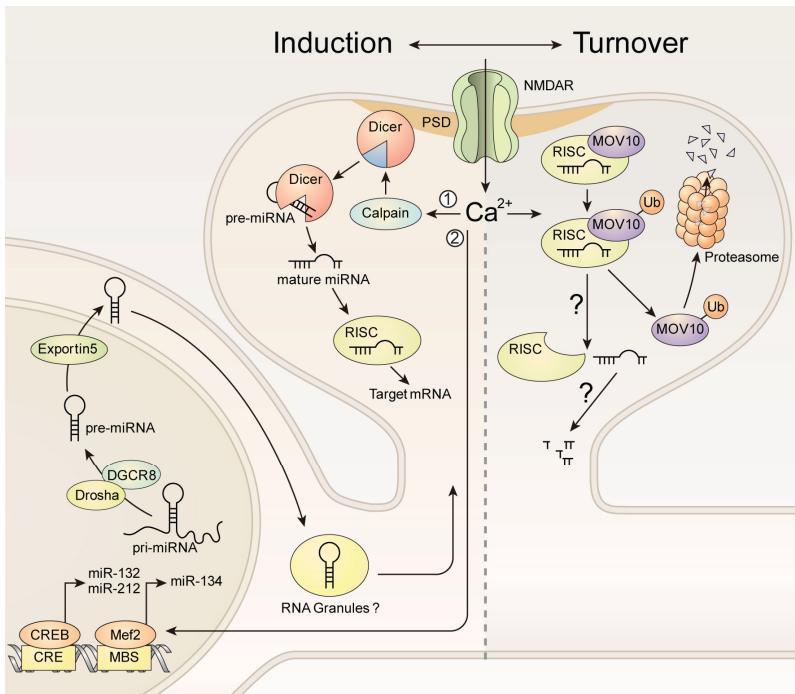
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**Table 1.** Neuronal activity-dependent regulation of microRNAs

miRNA	Neuronal sources	Stimuli to induce neuronal activity	Regulation of miRNAs			References
			Primary	Precursor	Mature	
let-7d	Ventral tegmental area				↓	Chandrasekar and Dreyer (2009)
	Hippocampus	Cocaine			↓	
	Prefrontal cortex				↓	
miR-96	Retina	Dark adaptation	↓	↓	↓	Krol et al. (2010)
miR-124	Aplysia neurons	Serotonin			↓	Rajasethupathy et al. (2009)
	Caudate putamen			↓	↓	
	Ventral tegmental area	Cocaine			↓	
miR-128b	Hippocampus				↓	Chandrasekar and Dreyer (2009)
	Infralimbic prefrontal cortex	Fear extinction learning			↑	
	Cortical neuron culture	BDNF	↑	↑	↑	Lin et al. (2011)
miR-132	Cortical neuron culture	Forskolin	↑	↑	↑	Vo et al. (2005)
	Suprachiasmatic nuclei	Light	↑	↑	↑	Klein et al. (2007)
	Hippocampal neuron culture	Bicuculline	↑	↑	↑	Cheng et al. (2007)
		KCl	↑	↑	↑	Wayman et al. (2008)
	Hippocampus	Seizure -muscarinic receptor agonist	↑			Nudelman et al. (2010)
miR-132		Cocaine	↑			
		Contextual fear conditioning	↑			
	Olfactory bulb	Odorant exposure	↑			
	Dorsal striatum	Cocaine			↑	Im et al. (2010)
	Primary visual cortex	Dark rearing or monocular deprivation	↓		↓	Mellios et al. (2011)
miR-134	Visual cortex	Visual stimulus	↑	↑	↑	Tognini et al. (2011)
		Monocular deprivation	↓		↓	
	Cortical neuron culture	BDNF	↑			Chai et al. (2013)
	Cortical neuron culture	BDNF			Inactivating miR-134-associated silencing complex	Schratt et al. (2006)
	Cortical neuron culture	KCl	↑			Fiore et al. (2009)
miR-134	Infralimbic prefrontal cortex	Auditory fear conditioning	↑			Lin et al. (2011)
		Fear extinction learning	↑			
	Cortical neuron culture	Bicuculline			Increase in mature miR-134 in some interneurons	Chai et al. (2013)
miR-146a-5p	Hippocampal neuron culture	DHPG			↓	Chen and Shen (2013)
miR-181a	Nucleus accumbens	Cocaine			↑	Chandrasekar and Dreyer (2009)
miR-182	Hippocampus					
	Retina	Dark adaptation	↓	↓	↓	Krol et al. (2010)
miR-183	Lateral amygdala	Auditory fear conditioning	↓	↓	↓	Griggs et al. (2013)
	Retina	Dark adaptation	↓	↓	↓	Krol et al. (2010)
miR-184	Aplysia neurons	Serotonin			↓	Rajasethupathy et al. (2009)
miR-188	Hippocampus	Chemical LTP			↑	Lee et al. (2012)
miR-204	Retina	Dark adaptation	↓	↓	↓	Krol et al. (2010)
miR-206	Medial prefrontal cortex	Prolonged alcohol exposure			↑	Tapocik et al. (2014)
miR-211	Retina	Dark adaptation	↓	↓	↓	Krol et al. (2010)
miR-212	Dorsal striatum	Cocaine			↑	Hollander et al. (2010)
miR-219	Prefrontal cortex	Acute injection of dizocilpine, NMDAR antagonist			↓	Kocerha et al. (2009)
	Suprachiasmatic nuclei	Circadian rhythm, subjective day			↑	Cheng et al. (2007)
miR-485	Hippocampal neuron culture	Bicuculline 4-aminopyridine (4-AP)			↑	Cohen et al. (2011)



**Fig. 1.** Possible mechanisms for neuronal activity-dependent miRNA regulation. There are two possible mechanisms for miRNA induction. First, the influx of  $\text{Ca}^{2+}$  via NMDAR activates a calcium-dependent enzyme, calpain. Activated calpain is known to release Dicer from PSD and to stimulate Dicer RNase III activity, which facilitates the process of pre-miRNAs into mature miRNAs. Second, increased intracellular  $\text{Ca}^{2+}$  level triggers downstream signaling pathways and induces *de novo* miRNA transcription. However, little is known about the mechanism of miRNA turnover. One possible mechanism is the activity-dependent degradation of RISC. MOV10, RISC factor, is degraded by proteasome in activity-dependent manner, but is still not clear whether this degradation of MOV10 induces the disassembly of RISC and the turnover of miRNA.

### miR-212

miR-212 is another CREB-dependent miRNA. The locus of miR-212 is located only 200 bases upstream from that of miR-132 and the promoter regions of both miR-132 and miR-212 have CRE sequences (Magill et al., 2010; Remenyi et al., 2013; Vo et al., 2005). There are fewer studies about miR-212 compared to miR-132. Kenny and colleagues have studied the role of miR-212 in cocaine addiction related to CREB signaling in dorsal striatum (Hollander et al., 2010; Im et al., 2010). Authors showed that miR-212 is specifically induced by extended but not restricted cocaine access and amplifying CREB signaling via a novel molecular feed-forward circuit.

### miR-134

The regulation of miR-134 is more complicated than other miRNAs. Schratt et al. (2006) showed that synaptodendritically localized miR-134 negatively regulates dendritic spine size by repressing the translation of target Lim-domain-containing protein kinase 1 (LimK1) mRNA. After BDNF treatment, the translation of LimK1 is increased by the relief of miR-134 inhibition, which suggests miR-134-associated silencing complex is inactivated or diminished at the synaptodendritic compartment. On the other hand, Fiore et al. showed that BDNF stimulation increases the level of pre-miR-134 via *de novo* miR-134 transcription. In their paper, the authors showed that the miR-134 gene is included in a large cluster of miRNAs (more than 50 miRNAs) and polycistrionically transcribed by the activity-regulated transcription factor, myocyte enhancing factor 2 (Mef2) (Fiore et al., 2009). The results of these two studies imply that miR-134 might be regulated differently in the local synaptodendritic compartment compared to the global transcription level. Moreover, a recent paper suggested a new possibility. It showed activity-dependent response of miR-134 is only restricted to certain types of cortical interneurons, Somatostatin (SST) and Calretinin positive interneurons (Chai et al.,

2013). The authors of this paper compared the induction of miR-134 and miR-132 by BDNF-stimulation in hippocampal culture, and found a relatively small increase of miR-134 compared to that of miR-132. Therefore, they measured cell type-specific responses using a fluorescent miRNA sensor (Magill et al., 2010) and found an activity-dependent response restricted to SST and Calretinin positive interneurons. There are two studies supporting this cell type-specific regulation of miR-134. First, similar results were observed in the study of Bramham and colleagues. When the levels of miR-132, miR-212 and miR-134 were measured 2 h after *in vivo* long-term potentiation (LTP) in the dentate gyrus (DG) of the hippocampus, two CREB-regulated miRNAs, miR-132 and miR-212, showed a significant increase but the level of miR-134 was unchanged (Wibrand et al., 2010). More evidence can be found in a fabulous study by Huang and colleagues. Using conditional GFP-myc-Ago2 transgenic mice and various Cre recombinase mice, the authors revealed cell type-specific expression profiles of miRNAs. In their results, the expression of miR-134 is more enriched in parvalbumin (PV), SST and glutamate decarboxylase 2 (GAD2) positive GABAergic interneurons than Calcium/Calmmodulin-dependent protein kinase II alpha (CaMKIIα) positive glutamatergic pyramidal neuron, whereas miR-132 and miR-212 are predominantly expressed in CaMKIIα positive neurons (He et al., 2012). More research is required to clarify the exact activity-dependent regulation of miR-134.

### miR-124

The brain-enriched and highly conserved miRNA, miR-124, has been studied largely for its role in neuronal development (Cao et al., 2007; Cheng et al., 2009; Landgraf et al., 2007; Makeyev et al., 2007; Yu et al., 2008). Kandel and colleagues first demonstrated the activity-dependent regulation of miR-124 in *Aplysia californica*. miR-124 showed restricted expression in the sensory neuron compared to the motor neuron. The treatment

**Table 2.** Screening studies for activity-regulated miRNAs

References	Sources	Stimulus	Protocol	miRNA detection methods
Park and Tang (2009)	Hippocampal slices	Chemical LTP mGluR-LTD	TEA (25 mM), no Mg <sup>2+</sup> , high Ca <sup>2+</sup> , 15 min DHPG (100 uM), 15 min	Microarray
Wibrand et al. (2010)	Hippocampal DG	<i>In vivo</i> LTP	Single session: 8 pulses at 400 Hz, repeated four times, 10 s interval Apply 3 sessions with 5 min interval	
Eacker et al. (2011)	Hippocampus	Electroconvulsive shock (synchronous depolarization)	1 s, 100 Hz, 22 mA current	Deep sequencing Taqman low-density array
Kye et al. (2011)	Hippocampal CA1 DIV15 hippocampal culture	Contextual conditioning Chemical stimulation	2 s, 0.75 mA, 3 footshock NMDA (60 uM), 5 min Bicuculline (20 uM), 1 h	qRT-PCR
Mellios et al. (2011)	Primary visual cortex	Visual deprivation Dark rearing	Reared with eyelid sutured from P24-28 Reared in darkness from birth	Microarray qRT-PCR
van Spronse et al. (2013)	DIV21 hippocampal culture	Chemical LTP Chemical LTD Prolonged decrease of synaptic activity Prolonged increase of synaptic activity	Glycine (200 uM), 5 min NMDA (50 uM), 5 min TTX (2 uM), 4 h or 48 h Bicuculline (40 uM), 4 h or 48 h	Microarray
Pai et al. (2014)	Hippocampal DG	<i>In vivo</i> LTP	Single Session: 8 pulses at 400 Hz, repeated four times, 10 s interval Apply 3 sessions with 5 min interval	Ago2 immunoprecipitation Microarray

of five spaced pulses of 5-hydroxytryptamine (5-HT) which induces long-term facilitation (LTF) at the sensory-to-motor synapse decreased the level of mature miR-124, whereas the treatment of one pulse of 5-HT did not show any change. The decrease of miR-124 is dependent on the MAPK signaling pathway but not on PKA, PKC and the proteasome pathways (Rajaselvupathy et al., 2009). The decrease of miR-124 by neuronal activity was also observed in the mammalian nervous system. Chronic cocaine administration induced a significant decrease of precursor miR-124 in the caudate putamen and decrease of mature miR-124 in the hippocampus, in the nucleus accumbens and in the caudate putamen. The significant up-regulation of repressor element 1 silencing transcription factor (REST), a transcriptional repressor which inhibits the expression of miR-124 (Conaco et al., 2006), in the nucleus accumbens and in the caudate putamen suggests the decrease of miR-124 is mediated by the regulation of REST (Chandrasekar and Dreyer, 2009).

#### Retinal miRNAs

The study of Krol et al. (2010) provides clear evidence of dynamic regulation of miRNAs by a stimulus. Several retinal miRNAs, miR-183/96/182 cluster, miR-204 and miR-211, were dynamically up- and down-regulated by light. The levels of these miRNAs were remarkably decreased by dark adaptation and rapidly recover to their maximum levels within 30 min after return to light.

#### HIGH-THROUGHPUT SCREENING STUDIES

There are several screening studies looking for global changes

of miRNAs after neuronal activities (Table 2).

#### Chemical stimulation in hippocampal slices

The study of Park and Tang examined a time-dependent change in miRNAs after chemical LTP (c-LTP) or metabotropic glutamate receptor-dependent long-term depression (mGluR-LTD) in hippocampal slices. Among 237 miRNAs tested by microarray, 50 miRNAs and 59 miRNAs were increased more than 8 folds after c-LTP and mGluR-LTD stimulation, respectively. Interestingly, most of the miRNAs were increased within 15 min after c-LTP and 30 min after mGluR-LTD (Park and Tang, 2009).

#### *In vivo* electrical stimulation

The rapid induction of miRNAs was also observed in living animals. Electroconvulsive shock was given to induce massive and synchronous depolarization of hippocampal neurons. Expression levels of miRNAs measured by Taqman low-density array showed that most miRNAs were increased rapidly within 1 h (Eacker et al., 2011).

Bramham and colleagues performed microarray analysis using the high frequency stimulus (HFS) paradigm for *in vivo* LTP in DG of urethane-anesthetized rats. Tested time points were 10 min and 2 h after HFS, and only 2 h after-HFS showed significant miRNA expression changes. The expression levels of 10 miRNAs were increased and 11 miRNAs were decreased among 237 tested miRNAs (Wibrand et al., 2010). Compared to a previous study (Park and Tang, 2009), fewer miRNAs were induced at the delayed time point and even some miRNAs were decreased. We believe these milder changes were caused by different stimulus protocols. The HFS stimulation

used in this paper is considered closer to physiological conditions compared to the chemical stimulus used in the previous study.

#### Chemical stimulation in neuron cultures

The study of van Spronsen et al. (2013) examined the activity-dependent change in miRNA using mature primary hippocampal neuron cultures. The authors investigated the change in 264 miRNAs after NMDA receptor-mediated synaptic plasticity or homeostatic synaptic plasticity using microarray analysis. A chemical LTP or a chemical long-term depression (LTD) protocol was used for NMDA receptor-mediated synaptic plasticity, which induced a change in expression of 51 miRNAs. For homeostatic synaptic plasticity, either voltage-gated sodium channel blocker tetrodotoxin (TTX, suppress action potential) or GABA<sub>A</sub> receptor antagonist bicuculline (increase synaptic activity) was treated for 4 h or 48 h. Prolonged change of synaptic activity in neuron culture altered the expression of 31 miRNAs.

#### Behavioral stimulation and pathogenic condition

Specific experiences may induce the changes in miRNA expression. Kye et al. (2011) studied the change in miRNAs in the hippocampus after contextual fear conditioning. The expression of 187 miRNAs in the hippocampal CA1 region was measured by quantitative real time PCR (qRT-PCR) at three different time points after training (1 h, 3 h, and 24 h). Astonishingly, a single training session significantly changed the expression level of almost half of measured miRNAs (90 miRNAs). Sur and colleagues screened miRNAs in the primary visual cortex (V1) responding to visual deprivation via microarray analysis. Among the top 100 most highly expressed miRNAs in V1, the expression level of 21 miRNAs was altered by visual deprivation. The authors verified the altered 21 miRNAs using qRT-PCR, and confirmed that the expression of 9 miRNAs was changed (Mellios et al., 2011).

Interestingly, there is a report showing that miRNA dysregulation is linked to the pathogenesis of neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS) (Campos-Melo et al., 2013). This study analyzed the expression profile of 664 miRNAs in the sporadic ALS spinal cord tissues. The results showed that there is a specific group of dysregulated miRNAs and that specific miRNA dysregulation might be related to the selective suppression of neurofilament miRNA observed in sporadic ALS.

### MECHANISM OF ACTIVITY-DEPENDENT miRNA REGULATION

#### Mechanism for induction

There are two possible mechanisms for the induction of miRNA (Fig. 1). The first mechanism is suggested by the finding which showed neuronal activity induces the cleavage of Dicer and increases its RNase III activity. This study showed that enzymatically inactive Dicer is enriched at postsynaptic densities (PSD), and is released and activated by calcium-dependent calpain activation (Lugli et al., 2005). Because Dicer is a key enzyme to produce mature miRNAs, the release of active Dicer might process most of the pre-miRNAs located in dendritic spine all at once. This mechanism may explain the results of previous studies reporting fast induction of many miRNAs after stimulation (Eacker et al., 2011; Park and Tang, 2009). The second miRNA induction mechanism is *de novo* transcription of miRNAs by activity-regulated transcription factors such as CREB and Mef2. As mentioned above, many studies have

shown CREB-dependent induction of miR-132 and miR-212 (Nudelman et al., 2010; Remenyi et al., 2013; Vo et al., 2005; Wayman et al., 2008) and one study proved Mef2 binds upstream of the miR-379-410 cluster, which includes the miR-134 gene, and transcribes the gene in an activity-dependent manner (Fiore et al., 2009). There is still another mechanism for regulating miR-134 transcription. Tsai and colleagues found that the mammalian Sir2 homolog, SIRT1, forms a repressor complex with transcription factor, Yin Yang 1 (YY1), and binds upstream of miR-134 to inhibit its expression (Gao et al., 2010). Even though this paper did not demonstrate a direct induction of miR-134 after neural activation, other evidence clearly suggests transcriptional regulation of miR-134 via SIRT1 and YY1.

#### Mechanism for turnover

Compared to induction of miRNA, little is known of the activity-dependent neuronal miRNA turnover. This lack of attention might be related to previous studies which have shown that miRNAs are highly stable and have slow turnover rates (Bhattacharyya et al., 2006; Gantier et al., 2011; van Rooij et al., 2007). Meanwhile, Krol et al. (2010) provide a new insight into the nature of miRNA turnover, reporting that miRNAs in neuron have rapid turnover rates that are dependent on neuronal activity. The level of miRNAs in mouse retina was rapidly, within a few hours, decreased after transcriptional shut-down via transcription inhibitors. This fast turnover of neuronal miRNA was also observed in non-retinal neurons, such as organotypic hippocampal slices, hippocampal and cortical culture neurons and even neurons derived from mouse embryonic stem cells. Furthermore, the authors showed that the treatment of TTX blocks rapid turnover of miRNAs, which implies that the high turnover rate of neuronal miRNAs is dependent on neuronal activity.

Until now, almost nothing is known about the mechanism for neuronal activity-dependent miRNA turnover. One possible mechanism is the degradation of RISC by neuronal activity (Fig. 1). In *Drosophila*, Armitage, one of the RISC factors, is rapidly degraded after neuronal activity (Ashraf et al., 2006). Kosik and colleagues also observed the activity-dependent degradation of MOV10, a mammalian ortholog of Armitage (Banerjee et al., 2009). Both Armitage and MOV10 are degraded by the proteasome.

### CONCLUSION

Synaptic activity across neurons is the most fundamental feature of neurons. We focused here on how neuronal activity regulates the level of miRNAs. From a decade of efforts, a good body of evidence has elucidated the mechanism of miRNA regulation. Particularly, high-throughput studies provide new insights for understanding global changes in miRNAs.

In the future, more studies about cell type-specific or neuronal circuit-specific miRNA regulation are demanded to understand the diversity and complexity of brain function.

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