CHARPTER II

REVIEW OF RELATED LITERATURE AND RESEARCH

Methamphetamine

Methamphetamine (METH) is known as N-methylamphetamine, methylamphetamine, desoxyephedrine. It is called in different names that depend on country and characteristics such as speed, crank, go, meth, crystal meth, okie coke, crackle, pop, ice, tik, bato and ice drug, and YABA (Morris and Parry, 2006; Qi, et al., 2007; Hayashi, et al., 2011). The most common are in form of tablet, powder and solution (Office of Narcotics Control Division, 2011).

Methamphetamine, an N-methyl homolog of amphetamine (Cadet, et al., 1998), is an abuse psychostimulant drug of phenethylamine and amphetamine class. It has a structure similar to amphetamine, (Figure 1) (Dutta, et al., 2006; Ministry of Public Health, 2011). METH has more potent than amphetamine because METH has a methyl group ($-CH_3$), is attached to the amphetamine molecule. A methyl functional group of METH can make METH through the brain better than amphetamine via blood brain barrier. METH has a half-life of 12 hours. METH has effects similar to those of cocaine, a type of psychostimulant drugs but it has a half-life longer than cocaine 10-30 hours depending on the drug, dosage, urine pH and routes of drug (Winslow, et al., 2007).

METH can be ingested by oral, vapor inhalation, smoking or intraperitoneal, intravenous and subcutaneous injections but most commonly smoke (Mandyam, et al., 2007; Kuczenski, et al., 2007; Mandyam, et al., 2008). The route of drug ingest has effect on duration for drug action; by vapor inhalation and smoking, immediate action to 5 sec; injection to intravenous, 15-30 sec and orally, 30 min that the effects of drug remain 8-24 hours (Office of Narcotics Control Division, 2011). METH is metabolized by the liver (Winslow, et al., 2007) and excreted by urine (Kumihashi, et al., 2007).

Early in the 1970s, METH was initially produced for medical treatment such as narcolepsy, attention-deficit hyperactivity disorder (ADHD), depression and obesity

(Biederman, et al., 2000). METH usually uses pervert together with diet and exercise in the short-term treatment of obesity or appetite suppressants that cause METH abuse, tolerance, sensitization leading to drug dependence, acute intoxication and withdrawal syndrome.

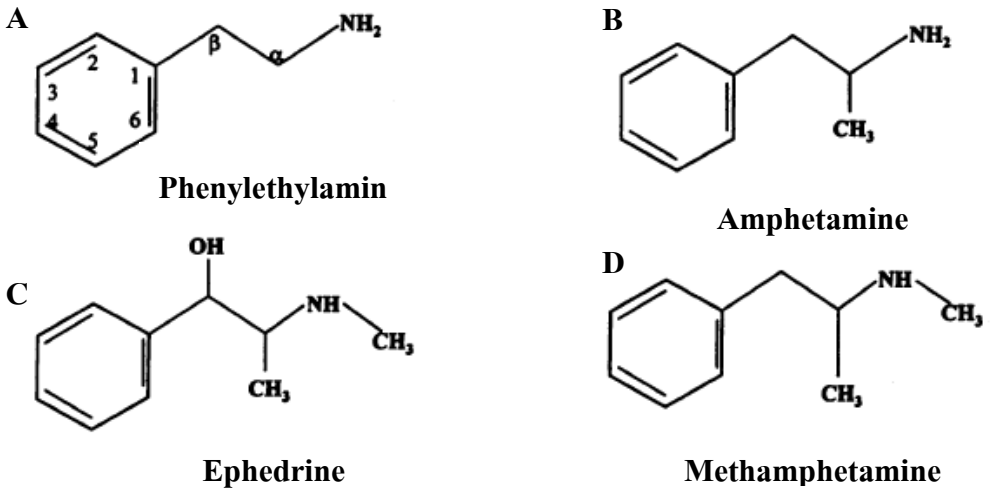

Figure 1 Schematics representation of chemical structures of phenylethylamine (A), amphetamine (B), ephedrine (C) and methamphetamine (D)

Source: Albertson, et al., 1999

Drug dependence

Drug dependence, known as drug addiction, addiction-drug and dependence on drug, is a demand of drug abuser that needs a drug to function normally. It is characterized by behavioral and other responses that always include a compulsion to continue taking the drug to obtain psychic effects, and tends to increase the dose, the effects of the drug on psychic and physical dependence and then detrimental effects on the individual and on society (World Health Organization (WHO), 1957). Determination of drug addictive behavior comprises of factors including unconditioned reward, conditioned reward, sensitization process, reinforcement learning, withdrawal and relapse after periods of abstinence (Miller and Gold, 1995). Drug dependence can be divided into two important

components including physical and psychological dependences. The psychological dependence is a main factor to continuous drug intake for maintaining a sense of well-being that it becomes extremely difficult to abstain. The physical dependence is an alteration of physical of drug abusers to continue administration of the drug to prevent the appearance of a withdrawal syndrome (Fields, 2004). In addition, drug users require increasing large doses to achieve the same high produced previously by a smaller dose of the same drug to maintain an emotional or mental needs as previous used that called tolerance (World Health Organization (WHO), 1957; Field, 2004). The sudden lack of drug, known as drug withdrawal or abstinence syndrome, is a physical symptom resulting from stopping the use of a drug that represents the symptoms and sign opposite of drug effects when drug taking (Fields, 2004). The withdrawal syndrome is composed of psychological and physical symptoms such as hyperactive, euphoria, stereotype, and hypertension and leading to sudden death that based on characteristics of each drug, amount used and length of time over which has been used (Fields, 2004; Meyer and Quenzer, 2005). Experimental data provides evidence about the effects of drug dependence on behavioral changes.

Mechanisms of drug dependence

The mechanism of drug dependence has been referred to as the meso-corticolimbic system that interacts between dopamine and glutamate transmissions in several brain regions. In drug-free state or a normal period, the glutamatergic projection from corticolimbic regions consists of prefrontal cortex, amygdala, and hippocampus into the nucleus accumbens (NAS) directly or via the ventral tegmental area (VTA) that facilitates dopamine transmission into nucleus accumbens and return to corticolimbic regions. Initiation of drug taking period, an abnormal high level of dopamine from the ventral tegmental area facilitated greater concentration of dopamine neurotransmission into nucleus accumbens, plays an important role in rewarding effects or reinforcement behaviors that can lead to drug dependence or addiction (Miller, et al., 1987). Repeated drug administration may cause an alteration between dopamine and glutamate interaction and leading to compulsive drug taking behavior. During period of withdrawal and drug-free period, the dopaminergic and glutamatergic activities return to normal levels but these remain

in hypersensitive state. After withdrawal period, exposure to drug may induce overactive glutamatergic systems leading to a trigger relapse (Miller, et al., 1987; Tzschentke and Schmidt, 2003). The mechanisms of drug dependence are shown in Figure 2. The mechanism of drug dependence is associated with abnormalities of dopaminergic transmission. Moreover, the mechanisms of drug dependence have also be relevant as well as other neurotransmitters such as glutamatergic transmission.

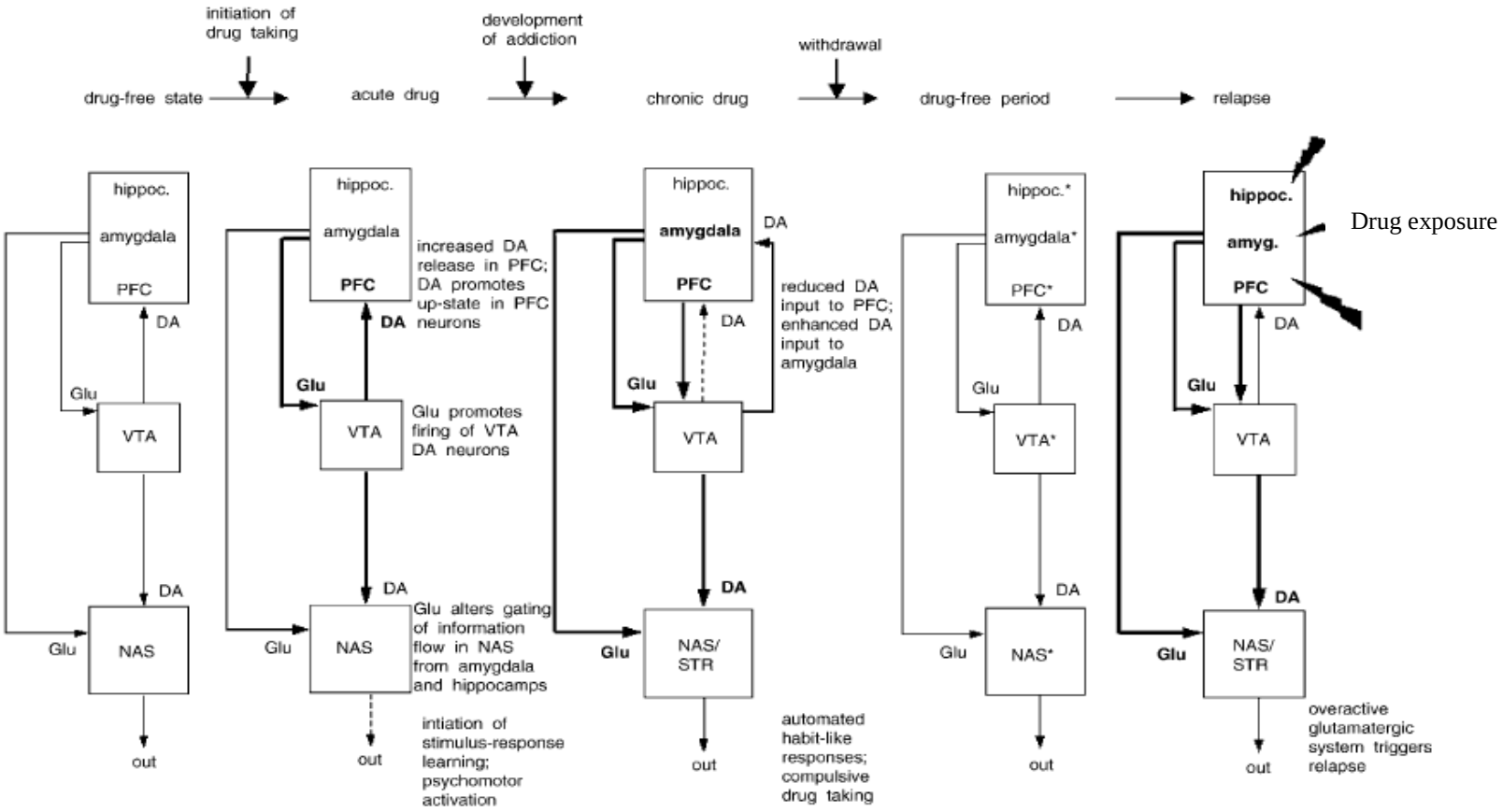

Figure 2 Diagrammatic representations of mechanisms of drug dependence

Source: Tzschentke and Schmidt, 2003

Effects of methamphetamine

The effects of METH can be divided into range from mild to severe toxicity, classified by using behavioral observation. At low dose or an acute use of METH usually begin 20-60 min or 24 hours after METH administration (Office of Narcotics Control Division, 2011). It can produce many effects such as vomiting, nausea and weight loss (O'Mara, et al., 2009), increases blood pressure, heart rate, chest pain, hyperactivity, hyperalertness, irritability, hypertension, and induces cardiac arrhythmia (Kono, et al., 2001). The effects of METH on respiratory system are bronchitis, pleuritic chest pain and pulmonary hypertension (Rogers, et al., 2006). METH may enhance sexuality behavior, increase libido (Winslow, et al., 2007) and cause parenterally transmitted infection disease such as human immunodeficiency virus, viral hepatitis and endocarditis. METH can induce long term behavioral changes including behavioral sensitization (Suzuki, et al., 2004), tolerance (Winslow, et al., 2007; Kuczenski, et al., 2007) and drug dependence (Mandyam, et al., 2007). Moreover, METH and amphetamine are a group of powerful and highly addictive substances that dramatically affect on nervous system especially on central nervous system. Amphetamine and its derivative can induce euphoria, hallucinations, palpitation and tremor, increased alertness and decreased appetite (Dutta, et al., 2006; Bankole, et al., 2007).

A high dose or chronic use of METH can induce many symptoms to METH abusers such as cardiomyopathy and myocardial infarction (Yu, et al., 2003). Moreover, METH induced aging effects, abscesses and skin lesion has been reported (Winslow, et al., 2007). Recent studies have reported that METH can induce neurologic symptoms such as cerebral hemorrhage (Rogers, et al., 2006), verbal learning impairment and memory loss (O'Dell, et al., 2011; Winslow, et al., 2007). Moreover, high dose and prolong METH use can cause addiction (Ago, et al., 2008) and psychosis (Rogers, et al., 2006; Ago, et al., 2008) that similar to paranoid type schizophrenia disorder (Dutta, et al., 2006; Ago, et al., 2008) such as depression, psychosis, suicidal ideation (Arielle, et al., 2005; Dutta, et al., 2006), paranoia, auditory and visual hallucinations and panic (Dutta, et al., 2006), psychosis, anxiety, seizures and death (Winslow, et al., 2007).

The effects of methamphetamine on neurotransmitter system

Although, the effects of METH on the neurotransmitter system have been focused on the dopaminergic system, the glutamatergic system has been recently studied. The abnormalities of neurotransmitter system after METH exposure are described below.

The effects of methamphetamine on dopaminergic system

The dopaminergic system plays a major role in the process of psychostimulant addiction (Shuto, et al., 2005; Urbina and Jones, 2011). The normal regulation of dopamine functions are involved in reinforcement behavior, reward and cognition. It has been reported that amphetamine and METH are indirect dopamine agonists which bind to dopamine receptors and directly affect on dopaminergic system (Fasciano, et al., 1997; Maeda, et al., 1985). The dopamine neurotransmitters at out of the synapse are re-uptaken into presynaptic neurons by dopamine transporters which play a crucial role in the behavioral pharmacology of psychostimulants. Amphetamine and METH have been reported a direct effect to elevate the levels of dopamine release in extracellular space by interfere with the dopamine transporter function. Firstly, blocking of dopamine transporter, inhibiting re-uptake of dopamine transporters protein into presynaptic nerve terminal lead to an increase dopamine levels in extracellular space (Rothman and Baumann, 2003). Secondly, the dopamine in synaptic cleft can bind to transporter proteins which are subsequently transported into the cytoplasm of nerve terminals. Finally, these drugs also increase cytoplasmic levels of dopamine neurotransmitter by disrupting storage of transmitters in vesicles and consequently diminish of dopamine levels from vesicles to cytosol and extracellular spaces (Rudnick and Clark, 1993; Rudnick, 1996). Dopamine transporter function is shown in Figure 3.

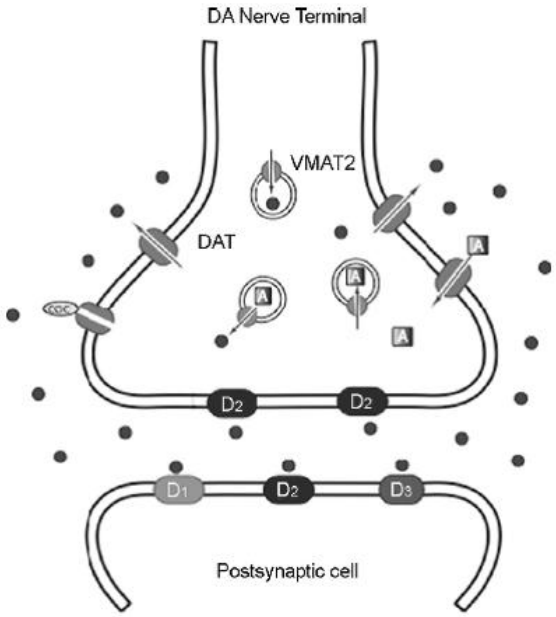

Figure 3 Schematic representation dopaminergic transporter functions, amphetamine also blocks the dopamine transporter and inhibits dopamine uptake, but also acts to release dopamine from intracellular vesicles. A = amphetamine; DAT = dopamine transporter; VMAT2 = vesicular monoamine transporter 2 and D1, D2, D3 = dopamine receptors type 1, 2, 3, respectively

Source: Howell and Kimmel, 2008

The effects of methamphetamine on glutamatergic transmission

METH is an indirect dopamine agonist that directly affects on dopaminergic system (Fasciano, et al., 1997; Maeda, et al., 1985). It has been reported about the abnormalities of interaction between dopaminergic and glutamatergic systems leading to drug addiction (Tzschentke and Schmidt, 2003; Kalivas, et al., 2009). The abnormal levels of glutamate that project from corticolimbic region to the nucleus accumbens being important in the expression of addictive behaviors, such as drug-seeking or behavioral sensitization (Pierce and Kalivas, 1997; Tzschentke and Schmidt, 2003; Kalivas, 2004). The effects of METH cause elevated levels of glutamate in several brain regions such as prefrontal

cortex (Stephans and Yamamoto, 1996), nucleus accumbens (Ohmori, et al., 1996), striatum (Ohmori, et al., 1996; Stephans and Yamamoto, 1996; Mark, et al., 2004), amygdala (Tzschentke and Schmidt, 2003) and hippocampus (Raudensky and Yamamoto, 2007).

Glutamatergic system

Glutamate is a non-essential amino acid neurotransmitter that plays a primary role in excitatory neurotransmitter in the central nervous system (Gos, et al., 2002; Rogers, et al., 2006; Kalivas, et al., 2009) and a mediator of the normal synaptic transmission, synaptic plasticity which involves in cognitive functions especially learning and memory (Nakanishi, 1994). Moreover, glutamate is synthesized in presynaptic neurons and stored in synaptic vesicles, when nerve impulses are triggered and glutamate is then released from the presynaptic neurons via exocytosis. The glutamate in synaptic cleft is removed from extracellular fluid by diffusion or uptake to presynaptic or postsynaptic neurons and glia cells by driving force of electrochemical gradients across the plasma membrane of glutamate transporters (Niels, 2001). The glutamate is released from presynaptic nerve terminal that acts on glutamate receptors and leads to function on synaptic plasticity (Debanne, et al., 2003).

Glutamate receptors

The glutamate receptors are located primarily on membrane of presynaptic or postsynaptic neuronal and glia cells. These receptors are categorized into two major types including ionotropic glutamate receptors (iGlu receptors) and metabotropic glutamate receptors (mGlu receptors). The metabotropic glutamate receptors are coupled to intracellular signal transduction via G-proteins. They are divided into three groups based on their sequence homology, second messenger coupling, and pharmacological characteristics: group I (mGlu1 and mGlu5), group II (mGlu2, mGlu3) and group III (mGlu4, mGlu6, mGlu7 and mGlu8) (Riedel, et al., 2003; Chaffey and Chazot, 2008). In contrast, ionotropic glutamate receptors are the ligan-gate non-selective cation-specific ion channels which facilitate fast synaptic transmission and act as postsynaptic receptors to mediate the extensive majority of excitatory neurotransmission in the brain. They are also classified into three groups

based on their physiological and pharmacological properties: the *N*-methyl-D-aspartate (NMDA) receptors, the α-amino-3-hydroxy-5-methyl-isoxazole-4-propionate (AMPA) receptors and kainate receptors (Riedel, et al., 2003; Chaffey and Chazot, 2008). The ionotropic glutamate receptors are tetra- or pentameric ion channels which consist of specific class subunits. Each subunit has a large extracellular N-terminus and shorter intracellular C-terminus. It has four hydrophobic domains (MI-MIV) within the central portion of the sequence; MI, MII and MIV form membrane-spanning domains while MII domain forms a loop within the membrane and form the channel pore.

The *N*-methyl-D-aspartate receptor (NMDARs) plays a central role at excitatory synapses that relate in multiple functions associated with synaptic plasticity especially learning and memory (Debanne, et al., 2003; Riedel, et al., 2003). NMDA receptors, a subtype of ionotropic glutamate receptors, are heteromeric integral membrane protein complex that form ligan-gate ion channels. NMDA receptors consist of different subunit including NMDAR1, NMDAR2A-D or NMDAR2A-B subunits. Each subunit has specific binding sites that locate on corresponding regions of different subunits of NMDA receptor (Chaffey and Chazot, 2008). The NMDAR1 subunits have a specific glycine binding site which binds with specific co-agonist glycine. Moreover, and NMDAR2 and NMDAR3 subunits are bound with glutamate neurotransmitter on specific glutamate binding sites (Riedel, et al., 2003). The NMDA receptors are composed of at least one of NMDAR1 subunit and various amounts of NMDAR2 subunits (Fan and Raymond, 2007; Chaffey and Chazot, 2008). NMDA receptor and their binding sites are shown in Figure 4.

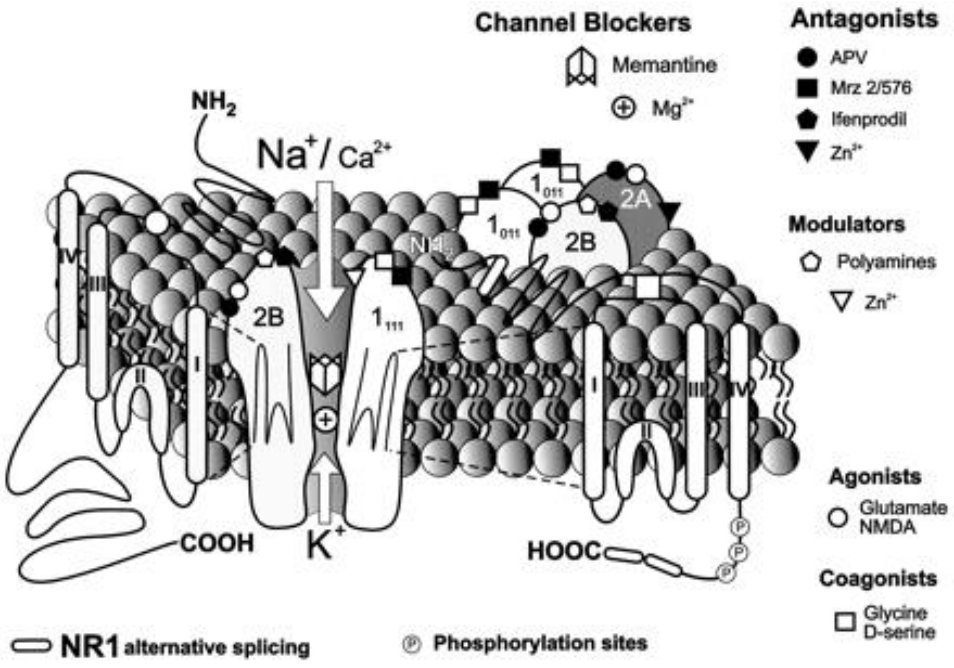

Figure 4 Schematic representation of NMDA receptor and their binding sites

Source: Danysz and Parsons, 1998

The NMDA channel is highly permeable to calcium ion (Ca^{2+}) and sensitive to modulation by several cation, including Na^{+}, K^{+}, Zn^{2+}, H^{+} and Mg^{2+}ions that pass into the cell. At resting state, NMDA receptor is inactivated by blocking of extracellular Mg^{2+} ion that located in channel pore. NMDA function requires glutamate release from presynaptic neurons and depolarization of the postsynaptic membrane to relieve the voltage-dependent blockade by Mg^{2+} ion from the channel pore and lead to open the channel of the receptors. Thereafter, high Ca^{2+} and Na^{+} are flowed into the neuronal cell and K^{+} out of the neuronal cell. The calcium ion entries into the cell through NMDA receptor and plays a primary role in synaptic plasticity, a cellular mechanism for learning and memory (Riedel, et al., 2003; Fan and Raymond, 2007; Chaffey and Chazot, 2008).

Learning and memory

Learning and memory are related synaptic plasticity which is an ability of synapse between the neurons that cause changes the strength of transmission at excitatory synapse. The long-term potentiation (LTP) and long-term depression (LTD) are most common uses as models of cellular mechanism that form synaptic plasticity. LTP and LTD have been reported in the long-term changes of synaptic plasticity that cause in learning and memory formation. The mechanism of LTP and LTD is related with an activation of the glutamate receptor (especially NMDA and AMPA receptors) due to influx of ion to the neuronal cell. The high levels of cellular depolarization of postsynaptic cell that leads to the removal of the Mg^{2+} block from channel pore. Follow by, induce calcium ion to enter into the cell through the channel of NMDA receptor which is stimulate LTP and LTD pathways. In addition, an elevation of calcium levels in the cell can stimulate the LTP and LTD synaptic strength via intracellular secondary messenger mechanism. These mechanisms of LTD are in contrast with LTP, it requires a smaller number of calcium ion flow into the neuron than LTP. A decrease of calcium level can activate the phosphorylation of protein kinases that lead to removal of phosphate group from AMPA receptors and dismissal their receptor from synapse. These mechanisms cause a decrease of synaptic strength (Riedel, et al., 2003; Lynch, 2004; Malenka and Bear, 2004).

Learning means mechanisms received new or modifies existing knowledge, behavior or skill that may relate with synthesizing different types of information. It has been categorized in many ways that Bloom's taxonomy can divide learning into three domains including cognitive, a mental skill that involves knowledge and development to intelligence skills; affective, feelings or emotional areas or known as attitude; and psychomotor, a change or development in behavior and skill. In addition, it has been reported that learning is a cause of long-term potentiation in hippocampus that plays a major role in memory functions in both human and rats (Lynch, 2004; Whitlock, et al., 2006).

Memory is the ability or mechanism to encode, retain and recall information or experiences. There are three main stages of information processing and retrieval of memory; the first stage is memory encoding, known as registration or process of interest to be changed into a construct that can be stored and recalled later from

short-term memory or long-term memory. Memory encoding can be divided into four types including acoustic encoding, a process of encoding of sound, word, and all other auditory input; visual encoding, a process of encoding of image and visual sensory information; tactile encoding, how something feels, normally through touch and semantic encoding, a process of sensory input that has specific meaning. The second stage of memory is storage, more or less process of retention information later encoding memory. Encoding memory can be divided into three types including sensory memory, short-term memory and long-term memory. Sensory memory recognized is consistent with approximately to the initial 200–500 milliseconds after an item is recognition. Short-term memory is a potential to remember and hold temporary a small amount of information for a short period of several seconds to a minute without rehearsal. In addition, it is available only in a certain period and can not to retain indefinitely. In contrast with short-term memory, long-term memory is related with a storage permanent caused from sensory memory and short-term memory. Long-term memory depends on a strictly limited capacity and duration. Short-term memory can be different into long-term memory by process of transferring of information that related encoding or consolidation of information. The final stage of memory is memory retrieval or recall which is referred to the information from the past encoded and stored in the brain previously. Memory retrieval consists of three types including free recall which is a process of test of volunteer after received list of item to remember. The model of memory is shown in Figure 5.

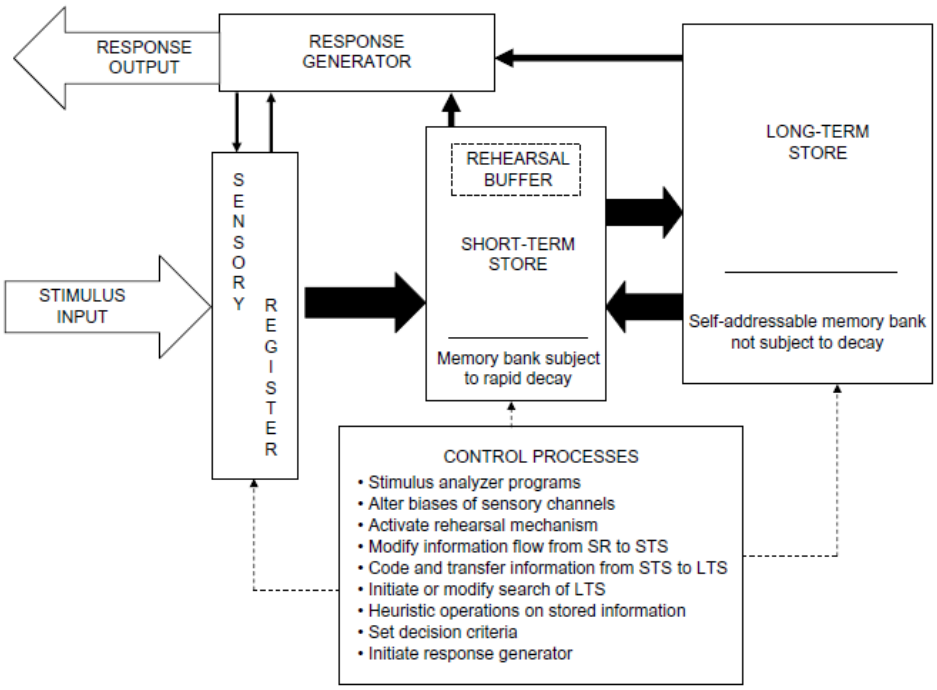

Figure 5 Diagrammatic representations of a model of memory

Source: Atkinson and Shiffrin, 1969

It has been reported that memory is involved related with several brain regions such as hippocampus, subiculum, perirhinal and parahippocampus, temporal cortex, posterior parietal cortex, amygdala and prefrontal cortex (Phelps, et al., 2004; Runyan, et al., 2004; Rogers, et al., 2006; O'Mara, et al., 2009). In addition, the integrity of brain regions depending on learning and memory has been reported (Lynch, 2004). However, many factors to implicate with memory impairment such as age (Tong, et al., 2007), disease (Gildas, et al., 1998; Joubert, et al., 2010), injury (Perbal, et al., 2003; Newsome, et al., 2007), stress (Schwabe, et al., 2010), depression (Kizilbash, et al., 2002; Barry, et al., 2006), and drug abuse (Barbier, et al., 2008; Reske, et al., 2010; Roussotte, et al., 2011). Experimental data have provided evidence that METH dependence can cause cognitive functions impairment especially learning and memory (Bisagno, et al., 2002; Simões, et al., 2007; Lee, et al., 2010). There are various experiments to test learning and memory depending on types of learning and memory such as spatial learning and memory; Morris water maze and radial arm

maze, non-spatial working memory; object recognition, non-spatial learning and memory; olfactory discrimination and memory, spatial reference memory; Barnes maze.

Novel object recognition (NOR) Test

Novel object recognition test is a non-spatial memory which is related with hippocampus and prefrontal cortex. This test is a model for investigate the neurobiological mechanism of learning and memory especially recognition memory that animals have potential to discriminate between familiar and new or novel object in an otherwise familiar environment (Winters, et al., 2008). Moreover, novel object recognition does not involve primary reinforcement such as food. The systems of novel object recognition test consist of open field square empty chamber with frontal glass wall. The floor of open field chamber is divided into 12 equal rectangular by black line. In addition, the model of object recognition is very important including color, dept, button, square, form and surface of objects which can affect to obtain reliable results (Figure 6).

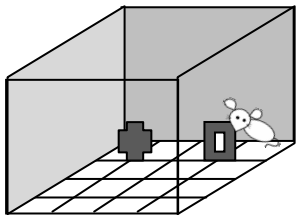

Figure 6 Schematic representation of open field chamber of novel object recognition

Novel object recognition can test both short-term memory and long-term memory. It can be divided into three sessions including habituate (1 day before experimental begin), training (24 h after habituation) and test sessions (a few hours and 24 h after training session for short-term and long-term memory recognition, respectively) which each session is replaced new object for investigate the potential of learning and memory of each animal. Previous studies have employed novel object recognition test to investigate the effects of drug dependence such as caffeine, cocaine,

alcohol especially METH on learning and memory which drug dependence has reported to induce learning and memory impairments (Ryabinin, et al., 2002; Kamei, et al., 2006; Sambeth, et al., 2007; Costa, et al., 2008; Bortolato, et al., 2010). As described above, METH induced neurotoxicity can cause learning and memory disabilities. Of cause, METH can induce behavioral changes.

Behavioral Tests

Behavioral tests are experiments to evaluate behavioral changes that cause the effects of drug dependence such as locomotor and behavioral tests. The locomotor test is the most common test to evaluate the behavioral effects of drug treatment that refer to movement from place to place, a high score of locomotor activity is indicated to hyperactivity and alertness. Previous studies have been investigated behaviors after drug dependence and they found that drug dependence can cause hyperlocomotion (Shimosato and Ohkuma, 2000; Good and Radcliffea, 2011). In addition, it has been reported about an increase of behavioral rating scale score after METH administration (Davidson, et al., 2005; Fujii, et al., 2007). However, METH has not only shown the effects on behaviors, neurotransmitter and learning and memory but the effects of neuronal abnormalities have also been reported.

The effects of methamphetamine on neuronal abnormalities

Experimental data have provided evidence that METH has neurotoxic effects (Cappon, et al., 2000; Riddle, et al., 2005) on induce dysfunctions of neuronal cells or neurodegeneration in several brain regions such as parietal cortex, frontal cortex and hippocampus (Guilarte, et al., 2003; Krasnova and cadet, 2009). Moreover, neurotoxic effects of METH has been reported to induce neuronal cells death (Deng, et al., 2007; Zhu, et al., 2006; Chen, et al., 2007; Kitamura, et al., 2010) in nucleus accumbens (Krasnova and cadet, 2009), prefrontal cortex (Fujii, et al., 2007), olfactory bulb (Atianjoh, et al., 2008) and hippocampus (Krasnova and cadet, 2009). In addition, neurotoxic effects of METH can induce diminish process of generating new neuronal cells (Mandyam, et al., 2008; Schaefers, et al., 2009) in striatum (Zhu, et al., 2006), medial prefrontal cortex (Kadota and Kadota, 2004; Mandyam, et al., 2008) and hippocampus (Mandyam, et al., 2008; Schaefers, et al., 2009).

Neurogenesis

Neurogenesis is a process of generating new neuronal cells (neuronal stem cells). Neuronal stem cells are a type of stem cells that has potential to self-renewal and produce numerous cycle of cell divisions but still maintaining the undifferentiated cells (Shi, et al., 2008), proliferation and differentiation into neurons or glia cells (Bauer, et al., 2006). Neurogenesis occur in vivo in brain and spinal cord, during development (Hastings, et al., 2001; Grandel, et al., 2006; Bonfanti and Ponti, 2008; Whitman and Greer, 2009) that most active during prenatal and early postnatal development (Jacobs, 2002; Balu and Lucki, 2008). Moreover, neurogenesis has been reported to occur during development (Grandel, et al., 2006; Christina, et al., 2007; Bonfanti and Ponti, 2008; Whitman and Greer, 2009).

Process of neurogenesis

The process of neurogenesis has begun with neuronal stem cell divided into new neuronal stem cells and progenitor cells. The neuronal stem cells and progenitor cells express proliferating cell nuclear antigen or PCNA when their cells proliferate. Mitosis of progenitor cells can give rise to new progenitor cells, neuronal and glial progenitor cells. Then, neuronal progenitor cells are differentiated into two daughter neurons that express microtubule-associated protein 2 (MAP2). Glial progenitor cells can be divided to progenitor cells (themselves) and astrocytes (Jacobs, 2002) that specific protein of astrocyte is glia fibrillary acid protein (GFAP). In addition, glia progenitor cells can be differentiated to oligodendrocytes that the myelin basic protein (MBP) is a protein which important in the process of myelination of nerve in central nervous system and specific for oligodendrocytes. The process of neurogenesis is shown in Figure 7.

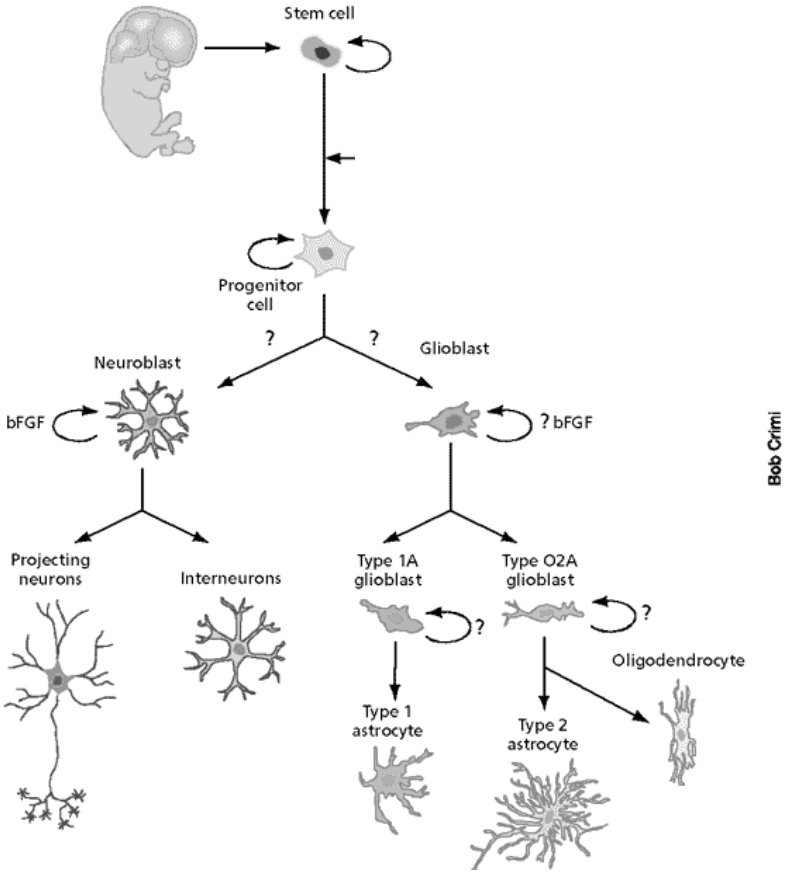

Figure 7 Schematic representation of process of neurogenesis

Source: http://cmbi.bjmu.edu.cn/cmbidata/stem/specific/specific03.htm

The process of neurogenesis is prescribed from growth factors that important to regulate neurogenesis during neuronal stem cells proliferation and differentiation into neurons or glia cells (Schuldiner, et al., 2001; Wilkins, et al., 2009; Kim, et al., 2010). In addition, a decrease of number of neurogenesis is related with aging (Cowen, et al., 2008), stress (Gould and Tanapat, 1999), depression (Sahay, et al., 2007) and drug abuse such as cocaine (Brown, et al., 2010), morphine (Eisch, et al., 2002), alcohol (McClain, et al., 2010) as well as METH (Mandyam, et al., 2008; Schaefers, et al., 2009).

Region of neurogenesis

Neurogenesis can occur in several brain regions such as posterior parietal cortex, (Magavi and Macklis, 2002), temporal cortex (Magavi and Macklis, 2002; Takemura, 2005), olfactory bulb (Yamada, et al., 2004) and hippocampus (Jacobs, 2002; Huang and Herbert, 2006; Verret, et al., 2007). There are predominant regions of neurogenesis such as subgranular zone of hippocampal dentate gyrus (Mandyam, et al., 2007; Mandyam, et al., 2008; Arisi, al., 2011) and subventricular zone (Pencea, et al., 2001; Luca and Paolo, 2007; So, et al., 2008; Lai, et al., 2010). A region of neurogenesis is shown in Figure 8.

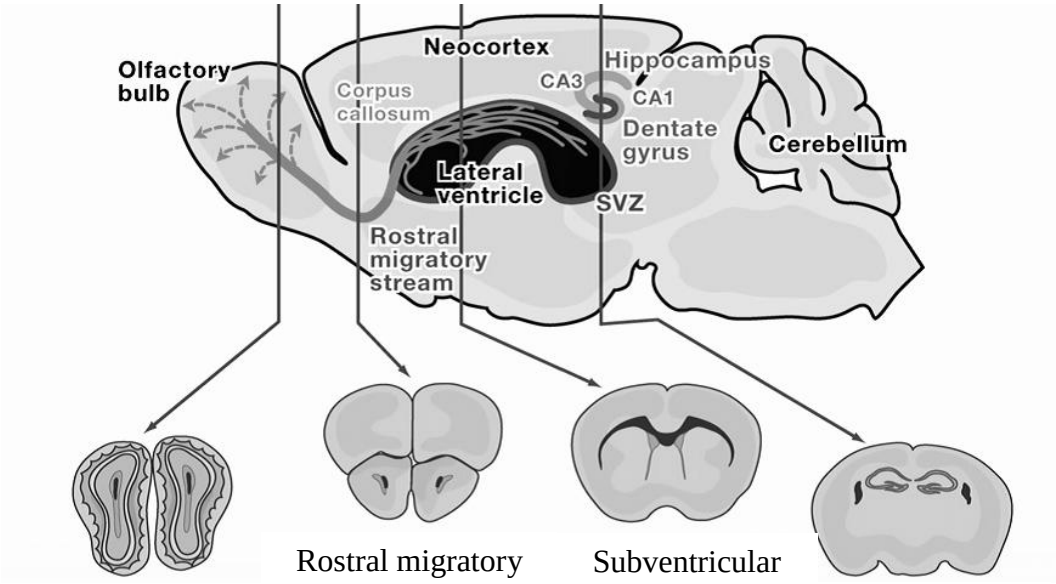

Figure 8 Schematic representation of regions of neurogenesis

Source: Zhao, et al., 2008

Subgranular zone (SGZ)

Subgranular zone is a narrow cells layer that located between granular layer and hilus of hippocampal dentate gyrus. This area is rich source of several cells type in various stage of proliferation, migration; and differentiation of neuronal stem cells (Whitman and Greer, 2009). After neuronal stem cell born which they migrate into the granule cell layer of the hippocampal dentate gyrus and then become dentate granule cells (Zhao, et al., 2008). Subgranular zone has 2 types of neural progenitors which are separate by morphology and expression of marker including; hippocampal progenitor type 1, a radial process spanning enter into the granular layer and ramify in the inner molecular layer, known as radial glia cells. In contrast with hippocampal progenitor type 2, has short process than type 1. Previous study suggested that hippocampal progenitor type 2 may arise from hippocampal progenitor type 1 (Zhao, et al., 2008). Hippocampal progenitor type 1 has been reported that can differentiate into astrocytes, expression glial fibrillary acidic protein (GFAP) (Campbell and Götz, 2002; Zhao, et al., 2008; Fernanda, et al., 2009). After neuronal cells proliferate and migrate into the granular layer, their dendrites were entering to molecular layer of hippocampal dentate gyrus (Bohlen and Halbach, 2011). Moreover, subgranular zone has neuroblasts (Whitman and Greer, 2009) and postmitotic or immature neurons (Llorens-Martín, et al., 2007). Subgranular zone is shown in Figure 9 and Figure 10.

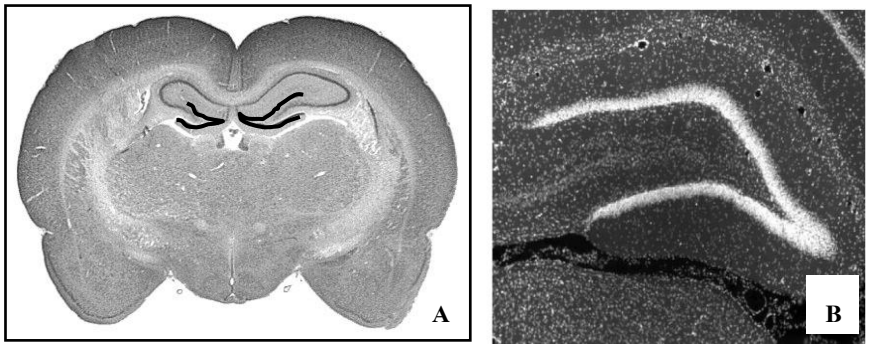

Figure 9 The subgranular zones (SGZ) of rat, black lines (A) and white line (B)

Source: Fiala and Josef, 2001

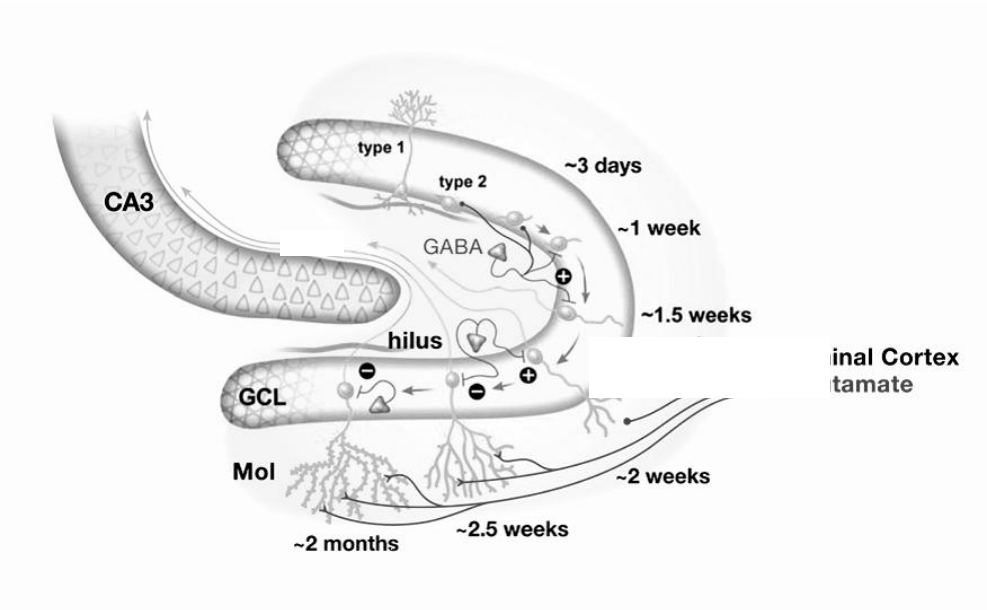

Figure 10 Hippocampal progenitor cell type 1 and type 2 in subgranular zone of hippocampal dentate gyrus

Source: Zhao, et al., 2008

Subventricular zone (SVZ)

Subventricular zone is paired brains structure that lining throughout lateral wall of lateral ventricle, located next to that ependyma (Romanko, et al., 2004; Barami, 2007; Zhao, et al., 2008). This area is another one that rich source of neuronal progenitor cells, has a capacity to generate neurons and migrate along the rostral migratory stream (RMS) and differentiate into the interneurons in the olfactory bulb (Pencea, et al., 2001). Subventricular zone has several cells type such as neuronal progenitor cells (Romanko, et al., 2004; Tonchev and Yamashima, 2006; So, et al., 2008), neuroblasts (Bonfanti and Ponti, 2007) and mature neurons; ependymal cells (produce cerebrospinal fluid) (Romanko, et al., 2004), oligodendrocytes (Romanko, et al., 2004; Tonchev and Yamashima, 2006; Carmen, et al., 2007; Gonzalez and Alvarez, 2011), astrocytes (Romanko, et al., 2004; Bonfanti and Ponti, 2007). Subventricular zone and chain migration are shown in Figure 11 and Figure 12, respectively.

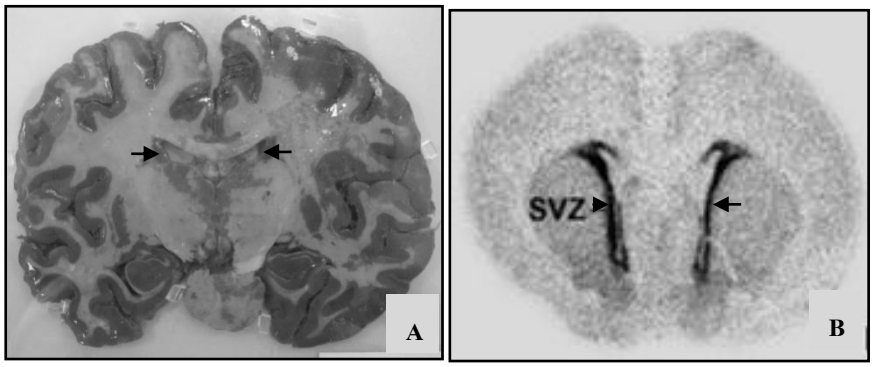

Figure 11 The subventricular zones (SVZ) of human (A) and rat (B), arrows

Source: Popp, et al., 2009

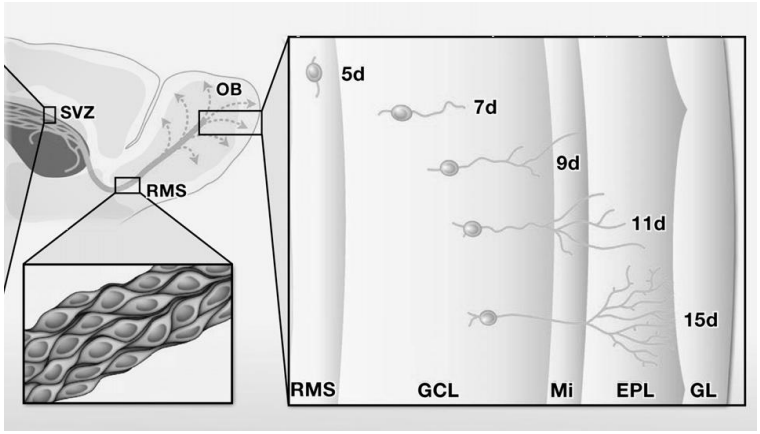

Figure 12 Schematic representation of chain migration in subventricular zone that lining the lateral wall of lateral ventricle. Mi, mitral cell layer; EPL, external plexiform layer; RMS, rostral migratory stream

Source: Zhao, et al., 2008