1. Introduction

Preface: Memory taxonomy in human

Studies on "memory" were inspired by the case of H. M. He had suffered epilepsy after the traffic accident when he was 7 years old. At the age of 27, the brain region thought to be responsible for his epilepsy was removed by Dr. Scoville in 1953. H. M.'s memory impairment is typically characterized as anterograde amnesia with serious loss of episodic component. He is an 'instant' person who could hardly remember events that had occurred a few minutes ago. These symptoms have not been altered for more than 40 years since the date of his surgery. The removed part included the hippocampus, amygdala and their surrounding regions. He did not suffer epilepsy after the surgery, but at the same time, he could no longer remember daily events that occurred to him. On March 3, 1953 and at the age of 27 he undertook the surgery. He answers "It is March 3, 1953." to a question "What is the date today?" He regards himself as a 27-year-old person. He cannot remember any events that happened after the surgery that he would be a 27-year-old man for the rest of his life. His memory functions are closely described by Ogden & Corkin (1991). The spared functions of H. M. were short-term memory, retrograde memory, and implicit memory. In contrast, long-term memory, anterograde memory, and explicit memory were severely impaired. Furthermore, his memory loss after the surgery ranged from non-verbal to verbal, and semantic to episodic memory. The significant feature of H. M.'s memory loss is that he is almost incapable of new learning. He demonstrates an

inability to learn stories, verbal and nonverbal paired associates, block patterns, songs and drawings, new vocabulary words, visual and tactual stylus mazes, digit strings, object names, and object locations.

On the other hand, H. M. is said to be capable of skillful activities such as imitating the movement of himself seen through a mirror (mirror tracing skill). Other examples that H. M. shows almost intact ability are demonstrated in experiments employing the technique of priming. He can complete a word that is imperfectly written on a sheet of paper as 'H□R□'. The answer may be plural such as 'HERE' or 'HERO'. When H. M. is previously presented the word 'HERO', he usually responds with previously experienced 'HERO', not 'HERE' or 'HARD'. It is noteworthy that he cannot recall aloud the previously presented word when requested. He is also capable of drawing a figure by tracing nine dots when previously asked and experienced to trace the same nine dots. Here again, he cannot recognize the drawing he has completed when presented several drawings in front of him and requested to choose the one he has drawn.

According to the case that H. M.'s memory impairment is not a total loss of his memory function, it is naturally supposed that human beings are likely to keep plural memory functions that can be classified depending on their nature.

Ogden & Corkin (1991) discussed that H. M. highlights the importance of the hippocampus and amygdala for encoding and storage of new explicit information, as episodic or semantic it is, whereas these brain regions are not responsible for implicit learning involving motor, perceptual, and cognitive skills.

Fig. 1 is a memory taxonomy advocated by Squire (1986) who classified memory into two major categories, which are 'declarative' and 'non-declarative' memory. Declarative memory can be consciously retrieved through verbal or visual images, while non-declarative memory is a type of memory that are unconsciously stored and retrieved almost automatically depending on the situations where organisms are. Typical example of the former is a memory of 'when', 'where', and 'who' and this kind of memory can be oriented on the time axis (episodic memory). Another example of the former can be represented as 'What is "memory"?', which is a memory for the meaning or knowledge of every existing thing (semantic memory). Lesion of the hippocampus typically impairs declarative memory, and especially episodic memory. In contrast, typical examples of non-declarative memory are skillful movements such as throwing a ball, driving a car, riding a bike, typing, writing, drawing, and so on. These skills are almost automatic that we are unconsciously using them in our daily lives. However, they are considerably essential with regard to our survival that we can never continue to exist in this world without them. Skills are not acquired instantly and it requires repetitive procedure to be retrieved automatically. Once it is acquired, however, it does not vanish easily. Basal forebrain including the striatum and the cerebellum are likely to play a critical role in this type of memory.

Declarative memory can be reset by every coming event and non-declarative memory cannot be re-written easily and clings on in the brain for a long time. In the case of survival for wild animals, both memory functions are necessary in the sense that animals have to escape rapidly

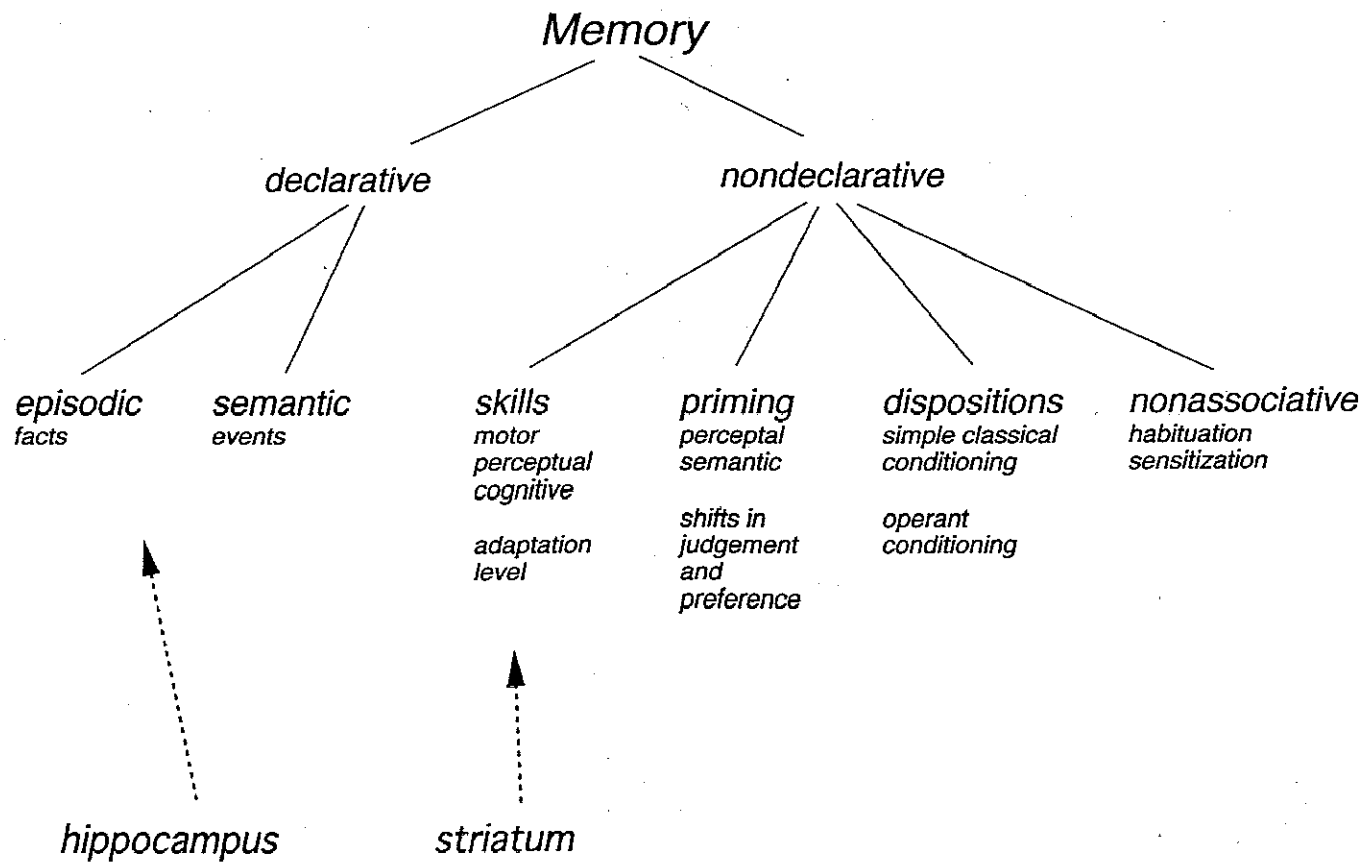


Fig. 1. A memory taxonomy (by Squire, 1987), and the striatal and hippocampal involvements.

in front of a predator (hard to be re-written) and at the same time they have to remember where they have come across the predator so coming back there involves a life threatening risk (re-writeable). Thus, animals need to keep functions that are re-writeable and are not re-writeable.

Tulving and Shacter (1990) classified these memory components from an evolutionary point of view. According to the view, the memory that human acquired first was a memory of skill, and other memory components emerged as follows: priming effect, short term memory, semantic memory, and episodic memory. Therefore, skill is a memory component that is relatively more primitive than episodic memory in the evolutionary point of view. In addition, human babies show similar process in acquiring the series of memory components. In the aspect of extinction, however, the order becomes the opposite. Skill is said to be the most long-lasting component. It makes sense that more essential for one's survival, more long-lasting the memory component would be.

1.1. Learning deficits following physical tissue lesion of the striatum and hippocampus

1.1.1. Striatal lesion

There have been a number of arguments on the structural definition of the striatum due to its homogeneous cytological similarity with the nucleus accumbens, the olfactory tubercle, and the basal forebrain. Here, the striatum technically refers to an inclusive structure of the caudate nucleus and the putamen. The striatum receives direct or indirect inputs

from the prefrontal cortex, the amygdala, the hippocampus, the thalamus, the substantia nigra, and the neo-cortex. On the other hand, major outputs from the striatum project to the globus pallidus and the substantia nigra. Studies in comparative anatomy have reported impairments in motor activity resulting from the striatal lesion, whereas studies on the striatal function in learning and memory have been a major interest since 1960's. The striatal lesion causes various learning deficits. A rough list of learning deficits followed by striatal lesion is shown in the left panel of Table 1.

In 1960's, roles of the striatum were quite controversial in studies of memory as a neural substrate which subserves a type of memory dissociated with the hippocampal function. Early studies mainly focused on the effect of striatal lesion using tasks as the spatial alternation, visual discrimination, and reversal learning. Chorover & Gross (1963) first reported the impairment in learning caused by striatal lesion. Spatial alternation task employed here was a chamber with two levers inside, which were supposed to be pushed alternatively. In this task, animals with striatal lesion showed serious impairment both in the acquisition and retention processes. The striatal lesion does not impair Hebb-Williams maze task, so the deficit may not be due to motivational components or 'general' learning abilities. Mikulus (1966) also employed spatial alternation task using T maze in which animals were required to choose one arm out of two arms in an alternative order, or to choose only one arm which was spatially identical throughout the trials from a randomly assigned start arm. In both procedures, two conditions were employed. In one condi-

Table 1. Learning deficits following striatal and hippocampal lesion in rats.

Lesion of the striatum	*Lesion of the hippocampus*
Spatial alternation (Chorover & Gross, 1963)	Two-way active avoidance facilitation (Jarrard, 1976)
Spatial discrimination reversal (Thompson & Yang, 1982)	Operant avoidance facilitation (Duncan & Duncan, 1971)
Brightness discrimination reversal (Kirkby, 1969)	Passive avoidance (Isaacson & Wickelgren, 1962)
Active and passive avoidance (Kirkby & Kimble, 1968)	Operant conditioning (DRL) (Jackson & Gergen, 1970)
Reference memory (Packard & White, 1990)	Visual discrimination (Woodruff & Isaacson, 1972)
Radial arm maze behavior (Masuda & Iwasaki, 1984)	Radial arm maze behavior (O'Keefe & Nadel, 1978)
Egocentric localization (EL) (Potegal, 1969)	Working memory (Olton, 1978)
Delayed response & alternation (Divac et al., 1967; Oberg & Divac, 1979)	Morris water maze behavior (Morris et al, 1982)
Return from a passive transport (Abraham et al., 1983)	

tion, a correct arm was associated with a lit lamp given above the arm entrance and a lamp was not lit in the other condition. Consequently, the striatal lesioned animals took more trials to acquire the task in both procedures regardless of lit or non-lit condition. There are more empirical supports showing the impairments in spatial alternation following striatal lesion (Thompson & Yang, 1982). Spatial alternation requires animals to choose a lever or arm alternatively avoiding previously chosen lever or arm. Therefore, the impairment in this learning is likely to be due to a loss of short-term memory or response inhibition.

Striatal lesion also impairs discrimination reversal. Kirkby (1969) employed the discrimination reversal procedure with Y maze in which animals first had to choose one arm which was lit by a 40 W lamp above the arm entrance so that they could avoid an electric shock and then they were given a shock in a lit arm (reversal learning). The striatal lesioned animals could acquire the initial task but they spent more trials in the reversal learning compared to the control animals. Winocur & Mills (1969) investigated the effect of striatal lesion on active and passive avoidance learning using a shuttle box. In active avoidance, a conditioned stimulus (light or tone) was given to animals 5 sec after they had put in a start box. Then they were given an electric shock if they did not escape into the adjacent box within 5 sec. In passive avoidance, in contrast, animals were given the electric shock if they escaped into the adjacent box. The striatal lesioned animals did not show impairment in the active avoidance learning, while they took more trials to acquire the passive avoidance learning compared to the control animals. These animals with the striatal lesion

could eventually acquire the passive avoidance task, so the impairment may be due to the interference effect by the learning procedure given to animals prior to the passive avoidance learning (the active avoidance learning), or deficit of response inhibition.

Early studies on the role of the striatum focused on spatial alternation (Chorover & Gross, 1963; Mikulus & Isaacson, 1965; Mikulus, 1966; Butters & Rosvold, 1968; Gross, Chorover, & Cohen, 1965; Hannon & Bader, 1974; Thompson & Yang, 1982) and discrimination reversal (Winocur & Mills, 1969; Winocur, 1974). In addition, in discrimination learning, there are findings in which striatal lesion did not impair the learning when a light was associated with a reward (Mikulus, 1966; Kirkby, 1969), or the impairment manifested depending on the brightness (Schwartzbaum & Donovick, 1968) of the conditioned stimuli or the frequency of flash lights given to animals (Reading, Dunnett, & Robbins, 1991). The similar type of impairment was also shown with monkeys (Divac, Rosvold, & Szwarcbart, 1967), so the critical role of the striatum in spatial alternation, discrimination reversal, and avoidance learning may be common in all mammalian animals.

Recently, studies on the striatal functions are carried out using the radial arm maze and the Morris water maze. One of the onsets of these series of studies was Potegal's study (1969) on "egocentric localization (EL)" (for a detail illustration of EL, see the following chapter, 'Functional dissociation of striatal and hippocampal systems'). Masuda & Iwasaki (1984) found that the performance of the striatal lesioned animals were poor in the radial maze learning. Lavoie & Mizumori (1994) found neu-

rons that selectively respond to specific spatial positions. These studies suggested that the striatum also plays a critical role in spatial behavior, but its functional difference with the hippocampus remained to be clarified. At the same time, there is a finding that the striatal lesion did not impair the radial arm maze behavior (Becker, Walker, & Olton, 1980). The contradiction may be explained by the idea of egocentric localization (EL), which is described later in the chapter 'Functional dissociation of striatal and hippocampal systems'.

Packard & White (1990) reported the impairment in reference memory using 8-arm radial maze. "Reference memory", the ability to store information such as extramaze cues and task-solving strategies throughout trials, makes a contrast to working memory. In the radial maze, fixed four out of eight arms were baited throughout trials. The striatal lesioned rats were unable to avoid entering arms with no food throughout trials. These animals could avoid entering previously visited arms in which animals had already consumed the food within a trial, so the working memory component was considered to be spared. Colombo, Davis, & Volpe (1989) used 12-arm radial maze and employed a procedure in which animals were required to choose 7 baited arms fixed throughout trials. The striatal lesioned animals showed the same level of working memory errors as the control animals, while the level of reference memory errors of the animals were higher compared to the control animals. These findings suggest that the striatum plays a critical role in reference memory but not in working memory.

The mechanism of the impairment following striatal lesion is yet to

be summarized. It is presumable that the various transmitter systems within the striatum such as cholinergic, dopaminergic, glutamatergic, GABAergic, or serotonergic systems, may contribute to different types of learning. Each transmitter system's function within the striatum remains to be addressed.

1.1.2. Hippocampal lesion

The hippocampus belongs to the cerebral cortex and includes the dentate gyrus and Ammon's horn. The Ammon's horn is further substructured as CA1, CA2, and CA3. CA1 and CA2 show systematic layer pattern and have molecular layer, stratum lacunosum, stratum radiatum, pyramidal cell layer, stratum orience, and alveus in order. The dentate gyrus consists of granular cell layer and polymorphic layer (Seki & Zyo, 1992). Hippocampal formation usually refers to the region including the Ammon's horn, dentate gyrus, subiculum, and entorhinal cortex.

Lesions of the hippocampus cause various impairments. A rough list of learning deficits followed by hippocampal lesion is shown in the right panel of Table 1.

Jarrard (1976) reported that the fimbria-fornix lesion facilitated 2-way active avoidance learning. Myhrer (1975) found the same facilitation when the fimbria was completely destroyed. These facilitative effects of the hippocampal lesion were also found in the operant avoidance learning (Duncan & Duncan, 1971).

On the other hand, passive avoidance learning is impaired by the hippocampal lesion (Isaacson & Wickelgren, 1962). It is suggested that

the ventral part of the hippocampus, including entorhinal cortex, primarily contributes to passive avoidance learning (Nadel, 1968). The impairment in passive avoidance learning following hippocampal lesion has been reported in studies employing other mammalian animals (Nonneman & Isaacson, 1973; Papsdorf & Woodruff, 1970). On the other hand, Cogan & Reeves (1979) reported that the impairment in avoidance learning following hippocampal lesion was suppressed by manipulating the CSs' parameters. They showed that animals could acquire the avoidance learning by manipulating the frequency and intensity of shocks given to animals. When inter-trial interval was 60 min, animals could learn the task with the high intensity of electric shock. Whereas animals showed impairment in the avoidance learning when inter-trial interval was reduced to 60 sec. It was suggested that hippocampal lesion altered a certain mechanism in attention process that the passive avoidance learning was impaired. In addition, presumably the most responsible area lies in the subiculum and entorhinal cortex in avoidance learning, (Kimura, 1958; Nadel, 1968).

Ackil, Mellgren, Halgren, & Frommer (1969) employed the two-way active avoidance learning task to show that the hippocampal lesion produces a deficit in latent inhibition. Latent inhibition is a phenomenon in which the effect of surrounding stimuli on animals in the training session is attenuated if they were previously exposed to the same stimuli prior to the training. They used an auditory stimulus (tone) as a conditioned stimulus. Thirty times of presentation of the tone prior to the training session prolonged the learning in the normal animals. Besides, the acquired learn-

ing extinguished faster than that of animals presented no auditory stimulus prior to the training. In contrast, the hippocampal lesioned animals acquired the task immediately and resistance to extinction was higher than the normal animals. Thus, the presentation of the tone did not affect the performance of the hippocampal lesioned animals. The deficit in latent inhibition has been shown in studies with other mammalian animals (Solomon & Moore, 1975). The results show that the hippocampus in mammalian animals plays a critical role in latent inhibition. Thus, early studies on the role of the hippocampus focused on its inhibitory aspects. However, it was indicated by Olton (1973) that the series of avoidance learning would be impaired if animals could not have been capable of using spatial information. If spatial cues are not available for animals in avoidance learning, the spatial information when they are given a shock is also unavailable. In this regard, all kinds of associative learning in terms of associating shocks with spatial cues are presumably impaired. Thus, the impairment in avoidance learning is controversial whether inhibitory or spatial component is primarily involved in the learning.

The hippocampal lesion impairs the operant conditioning in differential reinforcement of low rate (DRL) schedule (Jackson & Gergen, 1970). The impairment of DRL following hippocampal lesion has been shown with several primates excluding human (Jackson & Gergen, 1970). The hippocampal lesioned animals are impaired even on DRL-2 (two-sec delay) schedule (Jarrard & Becker, 1977). The DRL impairment is typically characterized as a deficit when animals are trained in a certain reinforcement schedule, and then shifted to a different schedule. In DRL, any cues

to show the end of a delay are not usually given. Animals are required to use inner cues for a delay interval. The hippocampal lesioned animals are not seriously impaired in DRL if explicit cues for the end of a delay are given (Pellegrino & Clapp, 1971). Isaacson (1982) discussed that the impairment in DRL following hippocampal lesion may be due to an intense increase of motivational factors.

Woodruff & Isaacson (1972) found a serious impairment in the visual discrimination learning following the hippocampal lesion. They employed the operant paradigm in the discrimination task. In the operant chamber, animals were trained to push a lever above which a light was lit. Ten to 20 days of training failed to complete the visual discrimination learning.

O'Keefe & Nadel (1978) suggested that the hippocampus plays a critical role in processing a "cognitive map", the internal map which contributes to an efficient spatial behavior in finding food or hiding from predators. Some neurons in the hippocampus activate when animals are staying around a specific place (O'Keefe, 1976). Ranck (1973) found neurons that were responsive to animals' behavior on the maze and presence of reward. Cognitive map theory of the hippocampus is strongly supported by the finding that the hippocampal lesioned animals were incapable of avoiding previously visited arms in which a reward had already been consumed in the radial arm maze (Olton, 1978). However, in order to explain the impairment in the radial maze, Olton and co-workers proposed the idea "working memory" (Olton & Samuelson, 1976; Olton & Papas, 1979), which could be explained, in experimental conditions, as a

comparably shorter memory valid within a trial.

Thus, there have been a considerable number of arguments on the role of the hippocampus in spatial behavior, yet it is undoubtedly clear that the hippocampal lesioned animals are severely impaired in spatial behavior such as the radial arm maze and Morris water maze behavior.

1.1.3. Functional dissociation of striatal and hippocampal systems

A number of studies have indicated that memory process is an integration of information mediated in several brain systems which can be dissociated in types of memory. Recently, the idea that several brain systems function simultaneously for an efficient problem solution has drawn attention. An ideal solution of a given problem appears to be due to a parallel and efficient use of plural information. Behavioral evidence suggests that the striatum and hippocampus of rats mediate different types of information simultaneously on tasks using the Morris water maze (McDonald & White, 1994) and 8-arm radial maze (McDonald & White, 1995).

Packard, Hirsh, & White (1989) first focused on the dissociation of the striatum and hippocampus in learning and memory processes using rats. Though studies on the role of the striatum day back to 1960's as described previously, studies from the view of functional dissociation between the striatum and hippocampus and the view that both neural systems contribute to an efficient performance in a certain learning situation were quite original. Here, animals were trained either in the standard radial maze task (win-shift task) or in the newly devised win-stay task. In

the win-stay task, each arm entrance had a 6-W light above, and four baited arms were lit during the trial session. Animals were required to choose the same arm twice within a trial. The correct arms were lit until animals had entered the arm twice and consumed a reward twice. A typical conventional win-stay procedure using the radial maze was to choose fixed four arms throughout trials. The major differences between the conventional and new one are presence of lights, that correct arms are not fixed in the new one, and that correct arms were required to be chosen twice within a trial. The striatal lesioned animals were not impaired in the win-shift task, while they showed serious impairment in the win-stay task. On the other hand, the hippocampal lesion seriously impaired the win-shift performance, whereas the hippocampal lesion had facilitative effect on the win-stay behavior, in which tendency of the hippocampal lesioned animals to choose lit arms was even higher compared to the control animals. Packard & McGaugh (1992) used the Morris water maze with an escapable hidden platform attached to a visual stimulus (pattern on a ball). Two tasks were prepared. One condition was with a spatially fixed hidden platform with different visual stimulus (pattern on a ball), the other was with a spatially random hidden platform with an identical visual stimulus. In both conditions, facing quadrant included inescapable platform attached to a certain visual stimulus (pattern on a ball), so animals were required to learn which cue (out of spatial position and visual stimulus) was associated with an escapable platform. Consequently, the striatal lesioned animals were selectively impaired in the condition where an escapable platform was associated with a specific visual stimu-

lus. In contrast, the hippocampal lesioned animals were selectively impaired in the condition where an escapable platform was given at a spatially fixed position. McDonald & White (1994) trained animals with the standard Morris water maze task in which animals were required to search for a visible escapable platform spatially fixed throughout trials. Then animals were tested in a probe trial in which position of the visible escapable platform was moved into a different quadrant. The striatal lesioned animals swam toward the visible platform moved into a different quadrant, whereas the hippocampal lesioned animals swam toward the quadrant in which a visual platform was originally located. Furthermore, the sham lesioned animals showed both behavioral tendencies as described above in a probe trial. According to the series of studies, they suggested that the striatum is involved in reinforcement of approaching response to a visual stimulus, whereas the hippocampus is involved in spatial learning. It should be noted again that their studies are quite original in the sense that the striatum and hippocampus both function simultaneously for an efficient performance in spatial learning tasks such as the radial arm maze and Morris water maze tasks.

Some studies that focused on the striatal function in spatial localization involves the idea of egocentric localization (EL) described previously. Some lines of evidence suggest that the striatum is involved in spatial localization with regard to EL function (Cook & Kesner, 1988). It is proposed that five salient attributes characterize mnemonic information for animal memory, i.e., labeled space, time, affect, sensory perception, and response (Kesner and DiMattia, 1987). EL was first labeled as the interac-

tion between these spatial and response attributes (Potegal, 1982). Recently, EL has been generally regarded as an ability to encode and store responses with reference to the organism's body position. Potegal (1969) first reported that the striatal lesion impairs EL behavior using the radial maze. The striatal lesioned animals could not acquire the task in which an arm with the fixed direction from a start arm was baited. The striatal animals also showed the impairment in the task with an octagon field surrounded by rectangle walls where animals were required to obtain a reward given at the place with the fixed distance and direction from animals' body position. The task is called the return from a passive transport task, in which animals are required to find the goal spout on the basis of vestibular feedback (Abraham, Potegal, & Miller, 1983). Thompson, Guilford, & Hicks (1980) trained animals in a T maze in which spatially fixed arm was baited throughout trials and then did a probe test with rotated T maze by 180° . Animals with striatal lesion tended to choose an arm based on spatial cues and did not make the same turn as in the training session. Animals with cortex lesion showed the opposite behavioral tendency that they tried to make the same turn as in the training session. Here again, animals of the control group showed both tendencies seen in animals with striatal and cortex lesion, so these two functions may be essential for spatially organized behavior. Mitchell & Hall (1988) also reported the effect of striatal lesion using a Y maze to show that animals with striatal lesion showed more errors in EL behavior. The involvement of the striatum in EL was discussed with regard to the impairment in the delayed response and delayed alternation that were described previously

(Divac, Rosvold, & Szwarcbart, 1967; Oberg and Divac, 1979; Sanberg, Lehmann, & Fibiger, 1978). Cook & Kesner (1988) discussed that the ability of EL is suggested to be required in these tasks. Studies on EL highlighted the striatal function in spatial localization that can be dissociated with the hippocampal function. From 1980's, the striatal function was extensively studied with regard to its function in spatial localization.

Brain lesion studies have shown that rats with striatal lesion are found deficient in the radial maze task (Masuda & Iwasaki, 1984; Winocur, 1980). Lavoie & Mizumori (1994) recorded neural activities in the striatum when animals were trained in the radial maze. Consequently, the neurons selectively responded to a certain spatial position, a specific time of acquiring rewards, and a certain specific movement. These findings strongly suggest the involvement of the striatum in the spatially organized behavior. Yet, its functional difference with the hippocampus cannot be clarified by the findings above. Furthermore, there are contradictory findings that animals with striatal lesions are not impaired in the standard radial maze task (Becker, Walker, & Olton, 1980; Cook & Kesner, 1988; Packard, Hirsh, & White, 1989; Packard & White, 1990).

The discrepancy of the behavioral evidence above may be explained by a possible involvement of EL in the radial maze behavior. The radial maze learning undoubtedly involves allocentric localization (AL), which is an ability to localize oneself regardless of organism's body position, which may be involved in the idea of cognitive mapping. Yet, the idea that an efficient use of both EL and AL simultaneously contributes to the spatially organized behavior would be the key to understand the discrep-

ancy.

Masuda & Iwasaki (1984) discussed that rats were impaired in the radial maze learning because the task's feature of reduced visual cues required animals to use kinesthetic and/or vestibular (egocentric) cues rather than extramaze cues. It is likely that efficient performance on the radial maze learning results from a parallel information processing of both egocentric and allocentric cues since there is no boundary between salient and poor conditions in terms of available cues (Fig. 2). It should also be noted that the hippocampal lesioned animals are not found deficient in these tasks (Abraham et al., 1983).

At the same time, hippocampal lesions also result in serious impairment in spatial learning such as standard 8-arm radial maze behavior (O'Keefe & Nadel, 1978; Olton & Wertz, 1978; Walker & Olton, 1984; Winocur, 1980) and Morris water maze behavior (Morris, Garrud, Rawlins, & O'Keefe, 1982). It is assumed that tasks called 'spatial task' (i.e. 8-arm radial maze task, Morris water maze task) primarily require the ability to localize on the basis of visual cues external to the organism (Zoladek & Roberts, 1978), so the hippocampus is likely to represent the neural substrate that mediates AL (Cook & Kesner, 1988). It should be noted that animals with striatal lesions are not found deficient in these tasks (Becker, Walker, & Olton, 1980; Cook & Kesner, 1988; Packard, Hirsh, & White, 1989; Packard & White, 1990). Thus, the striatum and hippocampus may function simultaneously for an efficient performance in spatial localization.

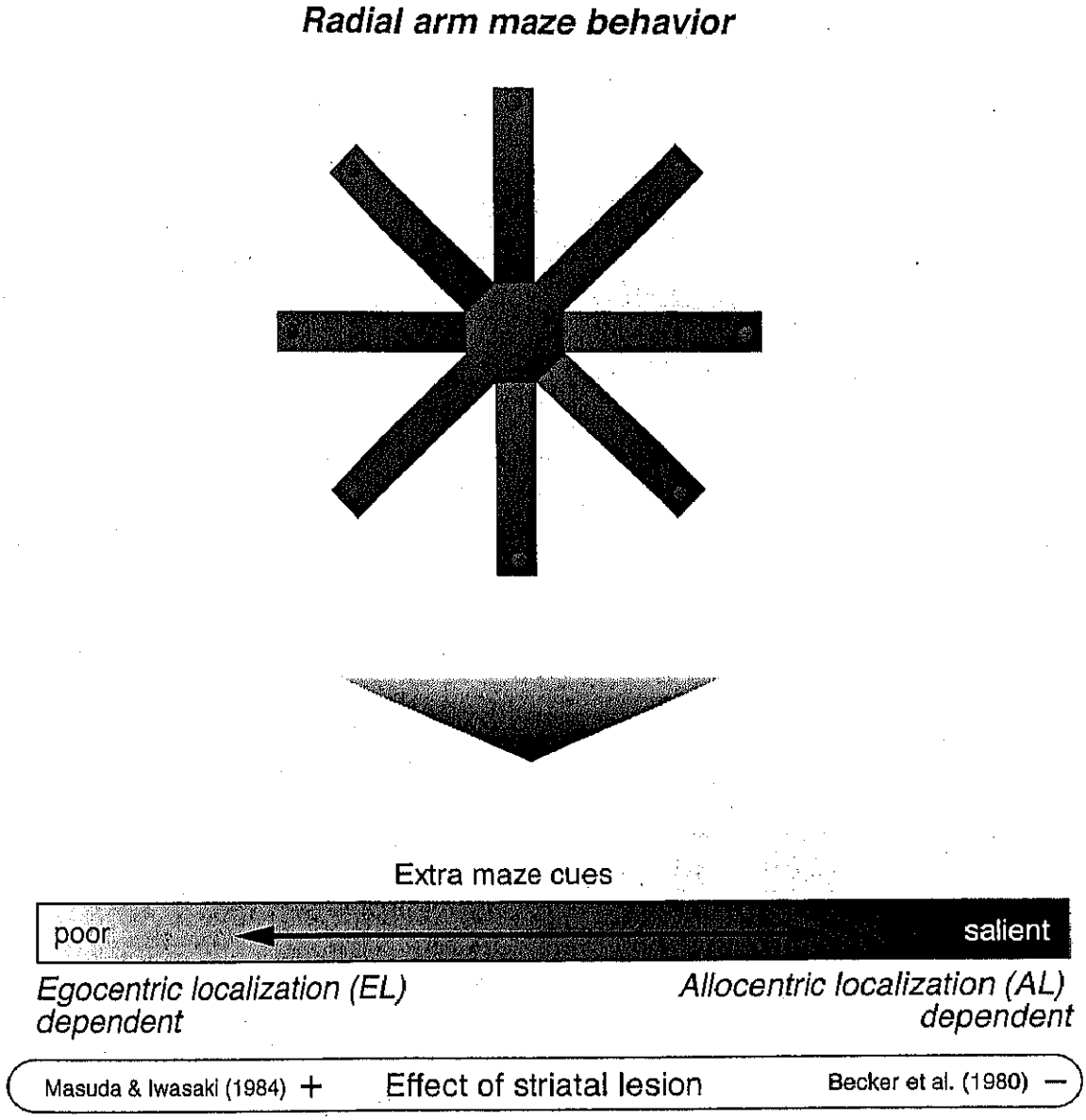


Fig. 2. A schematic illustration of the radial arm maze behavior. The radial maze is hypothesized to require animals to use both EL and AL cues depending on the given visual cue conditions. When extramaze cues are rich or salient, animals tend to depend mainly on extramaze visual cues, while animals may depend on internal cues such as a body position and direction with regard to intramaze cues when extramaze cues are poor or not salient.

1.2. Deficits following lesion of brain cholinergic systems

Acetylcholine (ACh) is a first chemical substance to be identified as a neurotransmitter. It functions as a neurotransmitter in the myoneural junction, parasympathetic ganglia, and central nervous system. It is synthesized within cytoplasms from its antecedents, choline and acetyl CoA, and stored in synaptic vesicles in the size of 30 to 40 nm numerous of which are in the nerve terminals. In neuronal activation, a few thousands of ACh are released from terminals as a quantum that serves as a minimum unit for the chemical transmission. Cholinergic neurotransmission is illustrated in Fig. 3. ACh released from terminals binds to postsynaptic receptors. ACh also binds to presynaptic receptors, process of which functions as part of a negative feedback circuit for ACh release. Acetylcholinesterase (AChE) decomposes ACh into choline and acetic acid. Choline is taken into terminals and re-used as ACh's antecedent.

The anatomy of the cholinergic systems is summarized by Dekker, Connor, & Thal (1991). Schematic representation of the cholinergic system in the rat brain is illustrated in Fig. 4. Mammalian cholinergic neurons in the prosencephalon (forebrain) are generally classified into following three groups: the projection from the medial septal nucleus and the nucleus of the vertical limb (diagonal band of Broca) to the hippocampus via the fimbria fornix; the projection from the nucleus basalis of Meynert (It accounts for 70-80% of the cholinergic innervation to the cortex. Other input to the cortex comes from neurons in the midbrain reticular system and the dorsolateral pontine tegmentum) (Vincent, Satoh, Armstrong, & Fibiger, 1983); and the interneurons in the striatum.

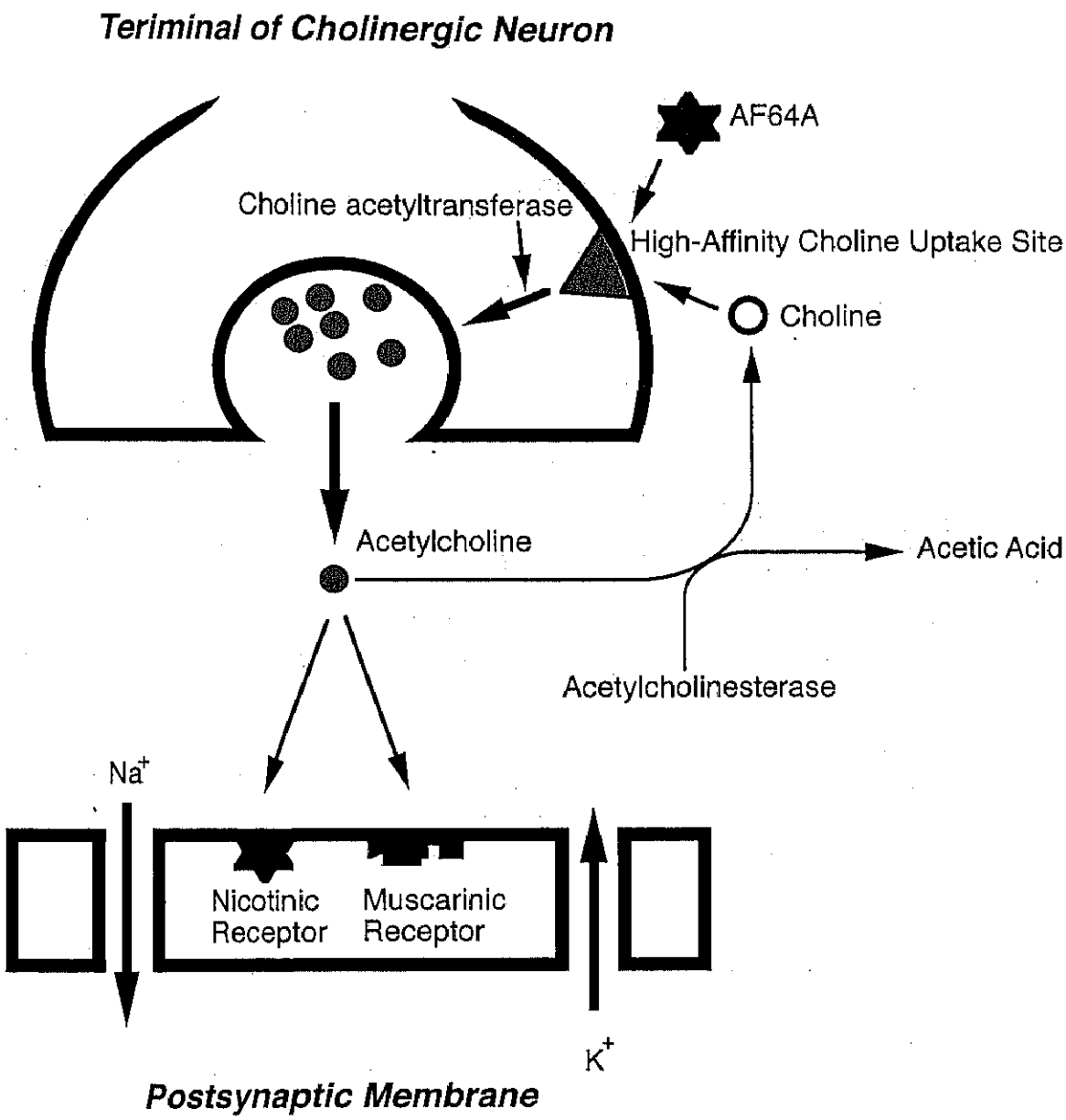


Fig. 3. Schematic illustration of the synaptic site of cholinergic neuron system.

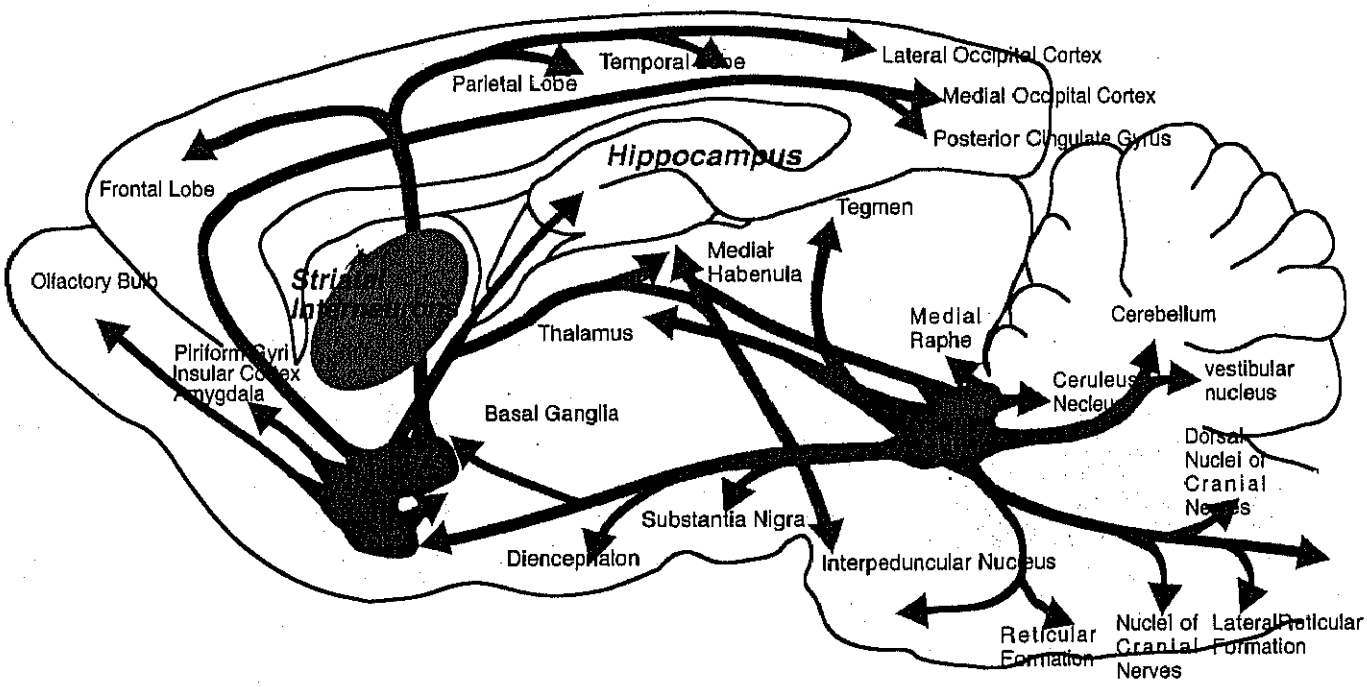


Fig. 4. Schematic representation of the major cholinergic system in the rat brain. Depiction is modified from Cooper, Bloom, & Roth (1996). Abbreviations: BAS, basal nucleus of Meynert; DLTN: dorso-lateral tegmental nuclei; MS: medial septal nucleus; POMA: magnocellular preoptic field; SI: substantia innominata; TD: diagonal band of Broca; TPP: pedunculopontine tengmental nuclei.

Central actions of ACh are mediated by both muscarinic and nicotinic receptors. Muscarinic receptors are prominent compared to the nicotinic in the central nervous system. Muscarinic receptors activation causes both excitatory and inhibitory effects in the central nervous system, yet the former effects are more predominant. Excitatory effects of muscarinic receptor activation are as follows: K-conductances down in postsynaptic neurons of widespread brain regions; GABAergic inhibitions down in presynaptic neurons of the hippocampus; facilitation of NMDA receptors in postsynaptic neurons of the hippocampus; and enhanced ephaptic interactions in the hippocampus. Inhibitory effects of muscarinic receptor activation are, less evident as they are, as follows: K-conductances up in postsynaptic neurons in the brainstem; Glutamatergic EPSPs down in presynaptic neurons of the hippocampus; and Ca-current down in the hippocampus (whether pre- or post-synaptic is unknown yet). On the other hand, effects of nicotinic receptor activation is not well-investigated, yet so far they are presumed as mainly excitatory and supposed as follows: non-selective cationic conductances up in postsynaptic neurons of the spinal cord and brainstem; and glutamatergic EPSPs up in presynaptic neurons of the hippocampus (Krnjevic, 1993).

A possible involvement of brain cholinergic systems in cognitive function has been suggested since memory loss of patients with Alzheimer's disease was found to show cholinergic hypofunction. Patients with Alzheimer's disease show hypofunction in acetylcholinesterase (AChE), choline acetyltransferase (ChAT), and high affinity choline uptake (HACU) (Arendt, Bigl, Tennstedt, & Arendt, 1985; Coyle, Price, & DeLong, 1983).

Since the reports, a substantial body of studies have been carried out with humans to show that the central cholinergic systems play critical roles in selective attention, consciousness, and learning and memory.

It should be noted here that the brain cholinergic systems have been discussed with regard to their role in the process of attention or consciousness as well as learning and memory. The series of studies have been carried out from pathological and psychopharmacological aspect in human. Perry, Walker, Grace, & Perry (1999) reviewed roles of the brain cholinergic systems in consciousness. They suggested that the brain cholinergic systems play a critical role in selective attention, which is an essential component of conscious awareness. Parkinson's diseases include pedunculopontine (PPN) cholinergic activities. Patients with dementia with Lewy bodies also show the same REM deficits resulting from PPN cholinergic hypofunction. In addition, they experience visual hallucinations, and the hypofunction is suggested to be associated with reductions in neocortical ACh-related activity. Alzheimer's disease patients also show explicit memory and REM disorder characterized as decreased REM duration and density and increased REM latency, which may result from the basal forebrain ACh-related neuropathology. These studies were carried out based on the idea that the brain cholinergic systems play a critical role as a neuromodulator.

From the behavioral aspect employing lesion techniques, deficits following lesions of the nucleus basalis of Meynert (the nuclei origins of major cholinergic projections) are habituation, classical conditioning, discrimination (taste aversion), passive and active avoidance, spatial alter-

nation, delayed matching to sample, T-maze alternation, cross maze, stone maze, radial arm maze, hole board food search, Morris water maze, and timed conditioned responding (Dekker et al., 1991). Thus, lesion of the nucleus basalis of Meynert produces various kinds of learning deficits. However, the accumulation of studies described above are based on electrolytic or radiofrequency lesions that its non-selective effects on other neurotransmitter systems are implicated. Thus, most of recent studies focusing of the brain cholinergic systems use neurotoxic excitatory amino acids such as ibotenic and kainic acids or selective neurotoxins such as AF64A and to produce more selective decrease on cholinergic activities. However, these chemical tools also carry danger to produce non-selective effects. Though ibotenic and kainic acids destroy neuronal perikarya around the injection site and do not affect the elements passing through the area, which also means that these drugs show non-selective effects on other neurotransmitter systems around the injection site except for the neurons passing there. Furthermore, higher doses of kainic acid into the ventricle can damage the area surrounding the ventral and medial globus pallidus as well as the cholinergic cells of the nucleus basalis of Meynert (Salamone, Beart, Alpert, & Iversen, 1984). AF64A, which is used in the present study, has been regarded as a strong tool for a selective lesion of cholinergic neural systems. Though there are reports suggesting its non-selective effects with doses which were later assumed by Hanin (1990) to be higher than the very limited rage of dose that could be selective (Fisher, Mantione, Abraham, & Hanin, 1982; Mantione, Zigmond, Fisher, & Hanin, 1983), it can be a selective drug for cholinergic neurons if its dose and

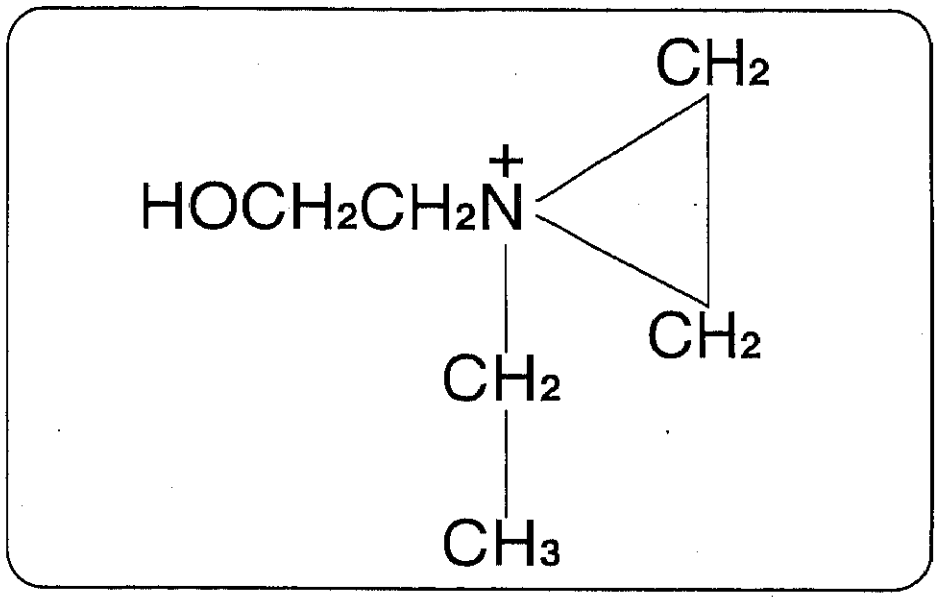
volume are determined carefully (for more detail, see the following section and general discussion).

Thus, studies on brain cholinergic systems should be discussed closely since accumulated studies have employed various kinds of cholinergic lesion techniques that might be non-selective to other neurotransmitter systems. The following is the accumulation of studies on brain cholinergic systems employing the neurotoxin lesion technique, cholinergic ligands, and studies with regard to aging.

1.2.1. Neurotoxin administration

Ethylcholine mustard aziridinium ion (AF64A) is a cholinergic neurotoxin that has been used as a strong tool for a selective lesion on cholinergic neurons. AF64A does not pass through blood-brain barrier. Therefore, it is necessary to be injected directly to the central nervous system. AF64A's effects vary depending on its dose, volume, and brain region to be injected so that these factors are determined carefully based on elaborate pilot experiments. AF64A's affinity to choline uptake sites is quite high (Hanin, 1996) due to its chemical structure that it is quite similar to that of choline, antecedent of ACh (Fig. 5). If its dose is high enough to be taken into low affinity choline uptake site that is not involved in the synthesis of ACh, AF64A can be non-selective. Therefore, it is necessary that the drug is administered in an appropriate dose to be taken only from high affinity choline uptake site to make selective lesions on cholinergic neurons. AF64A's toxic effect is alleviated and inhibited by a selective blocker of HACU, hemicholimium-3 (HC-3), which shows that AF64A

AF64A



Choline

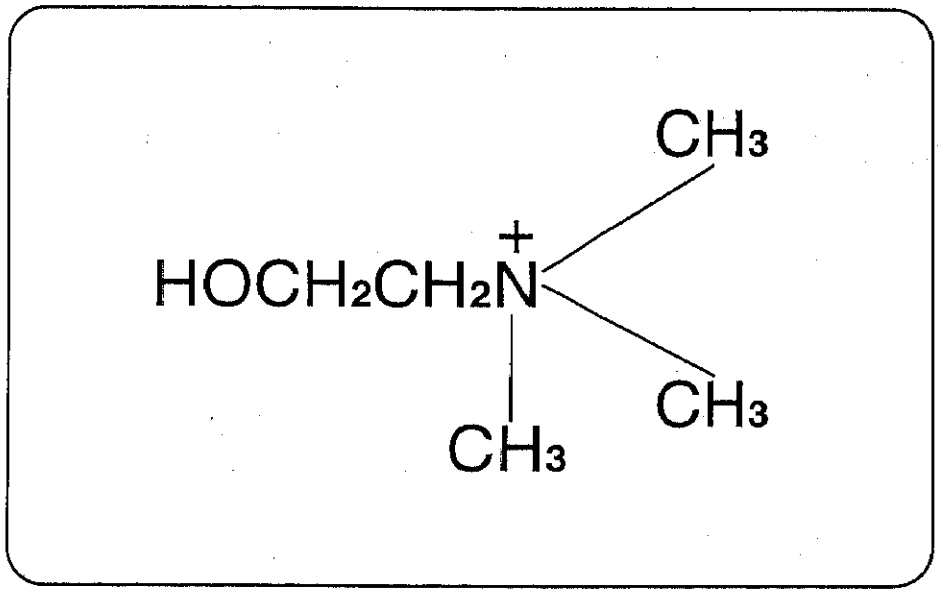


Fig. 5. Chemical structures of ethylcholine mustard aziridinium ion (AF64A) and choline.

shows its effect via HACU. Hanin (1996) reported that AF64A's effect can be observed from 48 hr after treatment. Neurochemical effects of AF64A on cholinergic neurons are more complex. If administered into rat's ventricle, ChAT and AChE activities decreased in the hippocampus, whereas ChAT activity in the septum increased. AChE activity was not altered. As for the mRNA levels, the effect was quite different. Two nmol of AF64A into the rat's ventricle resulted in as 10 times of AChE mRNA level as observed in normal rats 7 days after the treatment but the level of mRNA falls to the normal level in 2 months. In the septum and striatum, in contrast, AChE mRNA level is approximately 80 and 67 % to normal rats 7 days after the treatment, respectively. Besides, the level does not fall even 2 months after the treatment. The difference between ChAT and AChE activities and the ChAT and AChE mRNA levels is explained as follows: Transcription of AChE and ChAT is impaired in the septum that ACh level in the hippocampus decreases as a consequence due to the neural projection of cholinergic neurons from the septum to the hippocampus. Neurons with ACh receptors in the hippocampus temporarily increase local transcription of AChE mRNA. Consequently, feedback circuit of ChAT mRNA-transcription is reinforced and the septal ChAT levels increase (Hanin, 1996).

There have been substantial body of studies using AF64A. AF64A is a sensitive tool in the sense it might destroy brain tissues when its dose and volume are inappropriate, and therefore, AF64A has been injected in the ventricle within which cerebrospinal fluid (CSF) helps diffusion of the drug.

Walsh, Tilson, Dehaven, Mailman, Fisher, & Hanin (1984) investigated the effect of AF64A on the acquisition of the standard radial maze task. Consequently, AF64A injection into the rats' ventricle increased trials to criterion and deteriorated the correct choices compared to the control animals. Jarrard, Kant, Meyerhoff, & Levy (1984) measured working and reference memory components. First, animals were trained in the task in which spatially fixed four arms were baited throughout trials. After acquiring the task, AF64A was injected into the rats' ventricle and then tested on the same task. Animals treated with AF64A showed both working memory errors to enter previously chosen arms and reference memory errors to enter non-reward arms. Chrobak, Hanin, Schmechel, & Walsh (1988) further investigated these working and reference memory components. Animals were given 1 hr delay between fourth and fifth choice in the standard radial maze task. After acquiring the task, AF64A was injected into rats' ventricle and then tested employing the same task. AF64A treated animals could not avoid entering previously chosen arms prior to a delay (working memory error). At the same time, these rats were tested on the non-matching to sample task using the radial maze whose five arms were removed to make a T configuration. AF64A treated animals were not impaired in the task. Thus, intraventricular injection of AF64A caused working memory impairment and did not impair reference memory component which is supposed to be necessary in performance of simple discrimination task (non-matching to sample task).

Opello, Stackman, Ackerman, & Walsh (1993) investigated the effect of intraventricular injection of AF64A on the Morris water maze task. In

the task, the standard procedure in which hidden platform was set in spatially fixed position throughout trials and the cued procedure in which escapable platform was attached to a visual cue are assigned to animals. AF64A treated animals took longer time to find hidden escapable platform in the standard task. In contrast, those animals were not impaired in the cued version of the task. Similar results are reported by Gower, Rousseau, Jamsin, Gobert, Hanin, & Wulfert (1989) that AF64A induced impairment is not limited to the radial maze behavior but general in spatial tasks.

Intraventricular injection of AF64A mainly affects septo-hippocampal cholinergic neurons (Fisher, Mantione, Abraham, & Hanin, 1982). The findings above suggest that septo-hippocampal cholinergic systems play critical role in spatial learning. Yet, since it was injected in the ventricle, it is presumable that AF64A had diffused throughout the whole brain to show the effects above. To a closer examination of cholinergic neurons in each region of the central nervous system, direct administration of AF64A into the highly responsible area for learning and memory such as the hippocampus and striatum is necessary. However, the direct administration technique has not well-established yet with regard to its injection dose and volume, so there are only a few studies adapted the technique. For example, Baily, Overstreet, & Crocker (1986) injected AF64A directly into the hippocampus and found that the drug impaired both acquisition and retention of the passive avoidance learning. As for the striatum, however, most studies with direct administration technique focused on motor or motivational functions (Sandberg, Hanin, Fisher, & Coyle, 1984;

Sandberg, Sandberg, & Coyle, 1984; Stwertka & Olson, 1986; Dawson, Dawson, Filloux, & Wamsley, 1988; Meana, Johansson, Herrera-Marschitz, O'Connor, Goiny, Parkinson, Fredholm, & Ungerstadt, 1992; Zhou, Zhang, Connell, & Weiss, 1993). Therefore, brain regions which contains cholinergic neurons are necessary to be investigated employing the technique of direct AF64A injection. Then again, injection dose of AF64A should be determined carefully.

Recently, an immunotoxin, 192 IgG-saporin, is employed to destroy the basal forebrain cholinergic systems. 192 IgG-saporin is taken from p75-nerve growth factor receptors by endocytosis and shows its toxic effect after axonal transport. However, its selective effect is limited to the basal forebrain cholinergic systems since p75-nerve growth factor receptors are not found in the striatum and the nucleus accumbens (Pappas, Davidson, Fortin, Nallathamby, Park, Mohr, & Wiley, 1996). Its selectivity and effect are quite high that a large body of studies on the brain cholinergic function in learning and memory have been investigated with 192 IgG-saporin. Dornan, McCampbell, Tinkler, Hickman, Bannon, Decker, & Gunther (1998) investigated the effect of 192 IgG-saporin injection into the medial septal area, nucleus basalis magnocellularis, and both two regions on the Morris water maze and radial arm maze tasks. They found a mild impairment in the radial maze behavior but no impairment in the Morris water maze behavior. Janis, Glasier, Fulop, & Stein (1998) reported that intraseptal injections of 192 IgG-saporin resulted in deficits for strategy selection in spatial memory tasks. Animals were trained on the standard radial maze task and then given injections of the drug into the me-

dial septum and vertical limb of the diagonal band. Animals were then retested postoperatively on the radial maze task. Consequently, animals injected with 192 IgG-saporin in the medial septum were impaired in allocentric strategies used to locate the spatial goal. In addition, those septal lesioned animals showed egocentric strategy in the Morris water maze which was further tested. Leanza, MartinezSerrano, & Bjorklund (1998) also found a long lasting, substantial impairment in both the acquisition of spatial reference memory in the Morris water maze task and delay-dependent short-term memory performance in delayed matching-to-position task in rats injected 192 IgG-saporin intraventricularly. There is also a report that 192 IgG-saporin injection resulted in no impairment. Chappell, McMahan, Chiba, & Gallagher (1998) investigated the effect of intraseptal injection of 192 IgG-saporin on the spatial working memory task and found no impairment compared to the control animals even when delays ranging from 60s to 8 hr were imposed within a trial.

Thus, there has been both findings on the effect of 192 IgG-saporin injection suggesting no or milder impairment and serious impairments in various learning situations. Here, it should be noted that the effect of 192 IgG-saporin is limited to the basal forebrain lesion and cholinergic systems in the striatum and nucleus accumbens are not destroyed. It is presumed that cholinergic systems function in a complementary manner among several region-involved cholinergic systems as learning tasks become more complex. The Morris water maze and radial arm maze tasks may require plural learning functions such as EL and AL as described previously, thus those no or milder deficits may have been observed.

Another suggestion is that the cholinergic systems in the basal forebrain appear to be regulated by GABAergic and glutamatergic inputs (Pepeu & Blandina, 1998). 192 IgG-saporin treatment does not affect levels of GABA and glutamate, so it may also account for the previous no or milder deficits.

1.2.2. Ligands administration

Gammon & Thomas (1980) investigated the effect of physostigmine that enhance central cholinergic tone by inhibiting the catabolic enzyme AChE and found that one way active avoidance learning was facilitated by physostigmine injection. Meyers & Domono (1964) injected muscarinic receptor antagonist scopolamine, which impaired spontaneous alternation in the passive avoidance learning. Whitehouse (1964) found that muscarinic receptor antagonist atropine impaired the continuous discrimination learning. Scopolamine was further tested by Watts, Stevens, & Robinson (1981) that the antagonist had its effect in decreasing correct choices and retarded learning in acquisition of the radial maze task. Furthermore, scopolamine impaired the retention of standard 8-arm radial maze task (Hiraga & Iwasaki, 1984).

These studies have shown that anti-muscarinic drugs such as scopolamine and atropine have deleterious effects on the acquisition and retention of a variety of learning tasks. In contrast, physostigmine enhances performance in learning and memory. These series of pharmacological studies have provided evidence that the brain cholinergic systems, although not specified the region involved, play important roles in certain

types of learning and memory. The function subserved by the brain cholinergic systems is still under controversy. They may be one or more of disruption of behavioral inhibition, working memory, reference memory, attention, movement and strategy selection, and stimulus processing. However, Dunnett & Fibiger (1993) pointed out that it is virtually uncertain that cholinergic mechanisms are involved in a disparate variety of central nervous system functions and that anti-muscarinic –induced deficits are multiply determined, since cholinergic neurons innervate virtually the entire neuraxis and muscarinic receptors are also distributed throughout the central nervous system. Therefore, though muscarinic agents can undoubtedly affect the acquisition and performance of a broad spectrum of acquired behavior, cholinergic anatomy indicates that attempts at unitary accounts regarding the basis of such effects cannot be justified. Thus since the drugs were administered systemically in most studies, it is quite difficult to localize the responsible cholinergic neurons in the brain for these learning behavior.

1.2.3. Aging

Geriatric diseases accompany the decline of cholinergic activities, which drew interests of researchers to accumulate findings showing critical roles of cholinergic systems in learning and memory. Dekker et al. (1991) summarized the geriatric memory dysfunction based on the cholinergic hypothesis of geriatric memory function by Barutus, Dean, Beer, & Lippa (1982) as follows: a decrease in forebrain cholinergic parameters was found in patients with Alzheimer's disease; postmortem analysis of

the brains of patients with senile dementia revealed a decline in cortical cholinergic activity which correlated with earlier mental test scores; cells in the NBM in human may selectively degenerate in patients with senile dementia; similarities have been shown between the learning and memory impairments seen in senile dementia and those produces in young human subjects by anti-cholinergic drugs; cholinomimetic drugs can enhance memory capabilities in patients of senile dementia.

There are more findings using animals to show critical roles of the brain cholinergic systems in learning and memory. Aged mice with impaired performance on the radial arm maze task showed a significant decrease in ACh levels related to normal aging in the striatum and hippocampus (Ikegami, Shumiya, & Kawamura, 1992). Cholineacetyltransferase activity was decreased in the vertical diagonal band nucleus, the dentate gyrus, and the striatum of aged rats with learning deficits in the radial maze (Luine & Hearns, 1990). Fisher, Chen, Gage, & Bjorklund (1992) evaluated the performance in the Morris water maze in rats with the age of 3, 12, 18, 24, 30 months and their ChAT activities and number of the neuro-growth-factor (NGF)-positive neurons in the medial septum, vertical diagonal band nucleus, nucleus basalis magnocellularis, and the striatum. As a result, 8, 45, 53, and more than 90 % of rats with 12-, 18-, 24-, and 30-month-old rats showed retardation in performance of the task, and these animals' ChAT activities and NGF-positive neurons were significantly lower than those with no retardation in the task. Dunbar, Rylett, Schmidt, Sinclair, & Williams (1993) found that the hippocampal ChAT activity correlates with spatial learning in aged rats. They trained aged

animals in the Morris water maze task and measured ChAT activities and uptake levels in HACU site. Consequently, better performance correlated with higher ChAT activities and higher uptake levels in HACU site.

These findings suggest that the forebrain ACh levels fall through aging, which may cause the retardation in performing spatial learning tasks. In addition, cholinergic system in the hippocampal formation is assumed to play a critical role in spatial learning such as the radial arm maze behavior and the Morris water maze behavior.

Thus, cholinergic systems in the forebrain are assumed to play critical roles in spatial learning, yet most of these findings only suggested the involvement of brain cholinergic systems in cognitive processes without specifying brain region. Therefore, further close investigation is necessary in order to classify each cholinergic neural function in the brain.