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Role of brain cholinergic systems in cognitive function: A review

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It is widely known that acetylcholine (ACh) plays important roles in the central nervous system (CNS) as well as in somatic and autonomic motor neurons. The onset of studies on human brain cholinergic systems as an essential component for learning and memory dates back to the 1980s, when neuron loss within cholinergic systems was found in patients of Alzheimer's disease. The contributions of ACh in the CNS to memory processes have been investigated with several techniques, including cholinergic neuro/immuno-toxin administration, cholinergic ligand administration, a high-performance liquid chromatography (HPLC) technique, and an immunohistochemical technique. Brain tissue lesion studies have shown that the hippocampal formation has crucial roles in various cognitive functions. Accordingly, the majority of research on cholinergic functions has focused on the hippocampal cholinergic system. Recent studies regarding consciousness and attentional processes have, however, focused on the brain stem cholinergic system, as its ascending projections are believed to be involved in conscious awareness. Moreover, the striatal cholinergic system has also drawn interest because of the densest distribution in the brain. In the present review, the brain cholinergic functions including recent hypotheses concerning cholinergic functions in learning and memory processes are introduced.

Key words: ACh, acetylcholine, cholinergic system, striatum, hippocampus, learning, memory.

Preface: General function of brain cholinergic systems

Acetylcholine (ACh) is the 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. ACh released from terminals bind postsynaptic receptors. ACh also bind to presynaptic receptors, process of which functions as a part of 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). Mammalian cholinergic neurons in the prosencephalon (forebrain) are generally classified into the 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 innervations to the cortex. Other input to the cortex comes from neurons in the midbrain reticular system and the dorsolateral potine tegmentum) (Vincent, Satoh, Armstrong & Fibiger, 1983); and the interneurons in the striatum.

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 CNS 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 suggested 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 to be 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 the brain cholinergic systems in cognitive processes 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) activity, choline acetyltransferase (ChAT) activity, 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 learning and memory processes.

1. Early studies on function of brain cholinergic systems

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 alternation, 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, studies described above are based on electrolytic or radiofrequency lesions that its non-selective effects on other neurotransmitter systems are speculated. Thus, studies focusing on the brain cholinergic systems gradually shifted to the use of neurotoxic excitatory amino acids such as ibotenic and kainic acids. However, these chemical tools also carry danger to produce non-selective effects. Though ibotenic and kainic acids destroy neuronal perikarya at 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 within the injection site except for the neurons passing there. Furthermore, higher doses of kainic acid into the nucleus basalis of Meynert can damage the area surrounding the ventral and medial globus pallidus as well as the cholinergic cells within the nucleus basalis of Meynert (Salamone, Beart, Alpert & Iversen, 1984). Thus, drugs to produce selective decrease on the brain cholinergic activity, such as ethylcholine mustard aziridinium ion (AF64A) and 192 IgG-saporin were developed. However, these selective toxic drugs also carry danger for its selectivity on cholinergic neurons. Thus, studies on the 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.

2. Toxin administration

2.1. Ethylcholine mustard aziridinium ion (AF64A)

Ethylcholine mustard aziridinium ion (AF64A) is a cholinergic neurotoxin that has been used as a strong tool for a selective lesion on cholinergic neurons. 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 appropriate. AF64A does not pass through blood-brain barrier. Therefore, it is necessary to be injected directly into the CNS. As mentioned above, 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. 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 be 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 demonstrates that AF64A 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 the brain cholinergic neurons are complex. If administered into rat's ventricle, ChAT and AChE activities decrease in the hippocampus, whereas those activities in the septum increase. AChE activities are not altered. 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 of the mRNA levels is explained that 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 (Hanin, 1996). Since AF64A is a sensitive tool in the sense it might destroy brain tissues when its dose and volume are inappropriate, 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 choice rate compared to the control animals. Jarrard, Kant, Meyerhoff & Levy (1984) measured working and reference memory components. First, animals were trained in the radial maze 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-rewarded 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 in 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 without impairing 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 at spatially fixed position throughout trials and the cued procedure in which escapable platform was attached to a visual cue were 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 the septo-hippocampal cholinergic neurons (Fisher, et al., 1982). The findings above suggest that the septo-hippocampal cholinergic system plays a 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 described above. To a closer examination of cholinergic neurons in each region of the CNS, direct administration of AF64A into the highly responsible area for learning and memory such as the hippocampus and striatum is necessary. However, direct administration technique has not been completed yet with regard to its injection dose and volume, so 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) regardless of its critical roles in cognitive function demonstrated in tissue lesion studies. Therefore, brain regions containing cholinergic neurons are necessary to be investigated employing the technique of direct AF64A injection. Then again, injection dose of AF64A should be determined carefully.

Thus, Kobayashi (2000) employed the technique of direct AF64A injection, and found that both striatal and hippocampal injections of AF64A impaired the radial arm maze behavior. In addition, the reduction of the striatal ACh resulted in an impairment in egocentric localization (EL) behavior which appears to be mainly due to the deficit in encoding of the EL-task-solving strategy, whereas the reduction of hippocampal ACh lead to a serious impairment of allocentric localization (AL) behavior which may result from the deficit in both retrieval and encoding of the AL-task-solving strategy (Kobayashi and Iwasaki, 2000). EL is illustrated as a spatial localization technique to localize
themselves depending on animals' body position, whereas AL is the technique to localize themselves regardless of their body position. Based on the idea that parallel information processing of EL and AL support spatial localization, the striatal and hippocampal cholinergic systems appear to function simultaneously that each function of both systems is indispensable for an efficient performance in spatial localization.

2.2. 192 IgG-saporin

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 effects are quite high that a large body of studies on the brain cholinergic function in learning and memory have been carried out with 192 IgG-saporin. Dornan, McCampbell, Tinkler, Hickman, Bannon, Decker & Gunther (1997) 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 medial 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 to locate the spatial goal. In addition, those septal lesioned animals showed egocentric strategy in the Morris water maze that 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 with 192 IgG-saporin intraventricularly. Johnson, Zambon & Gibbs (2002) also reported that selective lesion of cholinergic neurons in the medial septum by 192 IgG-saporin resulted in impairment in a delayed matching to position (DMTP) task using T-maze. Male Sprague-Dawley rats were trained in a standard matching to position paradigm where animals are required to choose the identical arm as the one 'chosen' in a forced choice trial on T-maze. Prior to the behavioral testing, animals underwent surgery for 192 IgG-saporin treatments in which either lower (0.22 μg) or higher (1.0 μg) dose of the drug was injected. In the forced choice trial, animals had only to choose one arm out of two arms because only the forced 'choice' arm was open and the other arm was closed with a guillotine door. Then animals were returned to a start arm to make the second choice (test trial) where two choice arms were open. Animals received 8 trial pairs per day. As a result, 192 IgG-saporin impaired the DMTP acquisition dose dependently. DMTP task can be considered as a spatial working memory task, in the point that animals are required to rotate themselves between the forced and test trials using extramaze visual stimulus and working memory, so these studies suggest that the basal forebrain cholinergic systems play a critical role in spatial working memory. On the other hand, there is a report that 192 IgG-saporin injection resulted in no cognitive impairment. Chappell, McMahan, Chiba & Gallagher (1998) investigated the effect of intraseptal injection of 192 IgG-saporin on the spatial working memory task using the radial arm maze 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, spared compensatory task solving strategy might help perform the task without serious impairment. Thus, those no or milder deficits may have been observed in such tasks. Another suggestion is that the cholinergic systems in the basal forebrain appear to be regulated by GABAergic and glutamatergic inputs (Pepeu & Blandina, 1998) and cognitive functions as spatial working memory are not seriously impaired as long as a part of interaction among plural neurotransmitter systems is spared. Recently, GABAergic systems in the basal forebrain have also been the focus regarding cognitive functions represented by spatial working memory, it may be that non-cholinergic systems also contribute to the spatial performance either in essential or compensatory way. 192 IgG-saporin treatment does not affect levels of GABA and glutamate when injected with an appropriate dose, so it may also account for the previous no or milder deficits.

3. Ligand administration

Gammon & Thomas (1980) investigated the effect of cholinergic agonist 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 and found that the drug 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 retention of the standard 8-arm radial maze task (Hiraga & Iwasaki, 1984). Recently, novel muscarinic M_2 receptor antagonist, SCH 57790 was found to increase ACh release in the CNS and improve cognitive performance. Carey, Billard, Binch Ⅲ, Cohen-Williams, Crosby, Grzelak, Guzik, Kozlowski, Lowe, Pond, Tedesco, Watkins & Coffin (2001) reported that SCH 57790 (0.1-10mg/kg, p.o.) produced dose-dependent ACh release in the hippocampus, cortex, and striatum, and even lower dose (0.003-1.0mg/kg) of the drug improved performance of passive avoidance learning in rats. The apparatus consisted of black and clear chambers connected by a doorway and a floor of the black chamber was connected to a shock generator. In the training session, rats were placed in the light chamber and entering the dark chamber resulted in an electric shock. Twenty-four hr later, the time for each animal to move from the light chamber into the dark chamber (step-through latency) was recorded. SCH 57790 significantly increased the mean step-through latency whether given before of after the training session. Similar results were obtained in the same study that SCH 57790 improved cognitive performance employing working memory operant task (fixed ratio discrimination with titrating delay) in squirrel monkeys, suggesting that M_2 receptor blockade improves cognitive performance.

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 the CNS 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 CNS. 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, it is impossible to localize the responsible cholinergic neurons in the brain for these learning behavior. One interesting study employing local ligand administration technique is by Ragozzino and Tzavos (2002) on effects of scopolamine injection into the dorsomedial striatum on acquisition or reversal learning of response discrimination. The apparatus used in the study was a cross-maze. In the acquisition phase, animals learned to make either right or left turn for 10 consecutive correct choices. In the reversal learning phase, animals were required to perform the task employing the identical task solving strategy except that they had to make a turn to the opposite direction from that required during the acquisition phase. Eight μg of scopolamine produced a reversal (but not acquisition) learning deficit, suggesting an inability to learn the new strategy. Thus, more studies employing local infusion studies are expected to clarify region-specific cholinergic function regarding cognitive processes.

4. 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, dentate gyrus, and 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 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.

Recent studies investigating age related decline of cognitive performance focused on broader spectrum of neurotransmitter systems. Stemmelin, Lazarus, Kelche & Cassel (2000) investigated cholinergic and monoaminergic changes in the comparison of 26-month-old and 3-month-old Long-Evance female rats. Behavioral parameter was also evaluated using the Morris water maze. Aged rats showed reduction of choline acetyltransfrerase-positive neurons in the nucleus basalis of magnocellularis and striatum. Aging also affected concentrations of ACh, norepinephrine and serotonin in the striatum, serotonin in the occipital cortex, dopamine and norepinephrine in the dorsal hippocampus, and norepinephrine in the ventral hippocampus. The reduction of cholinergic marker and ACh concentration in the striatum, as well as concentration of serotonin in the striatum, serotonin and norepinephrine in the dorsal hippocampus, norepinephrine in the frontparietal cortex and other functional markers were shown to have correlation with the water maze performance.

These findings suggest that the forebrain ACh levels fall through aging, which may cause the retardation in performing spatial learning tasks. Cholinergic systems in the hippocampal formation and striatum are assumed to play a critical role in spatial learning such as the radial arm maze behavior and the Morris water maze behavior, so 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. In addition, cognitive deficits through aging involve concomitant alterations of various neurochemical systems in several brain regions, so closer experimental studies are necessary to clarify specific cholinergic functions in cognitive process regarding each brain region.

5. Function of extrinsic and intrinsic cholinergic neurons

The possibility of the dissociable functions of the brain cholinergic systems could be elucidated by the functional dissociation of intrinsic and extrinsic cholinergic neurons. As for the hippocampal systems, the septo-hippocampal cholinergic projection has drawn major attention with regard to learning and memory functions. Most of the hippocampal cholinergic terminals originate in the medial septum-diagonal band complex, but some conceivably may originate from the intrinsic cholinergic neurons (Amaral & Kurz, 1985) based on immunohistochemical studies. Van der Zee &

Luiten (1999) hypothesized, according to the computational model of Hasselmo (1995), that ACh functions as a modulator regulating the level of intrinsically originating versus extrinsic originating signal transduction (i.e. signal transduction arising from local circuits versus afferent, ascending projection nuclei), and switching the hippocampus and neocortex from recall (retrieval) to learning (encoding) mode, respectively. They suggest that cholinergic neurons in the hippocampus and neocortex both contribute to spatial localization and could be differentiated with regard to learning (encoding) and recall (retrieval) processes. The hypothetical dynamics are as follows: a state in which new information is stored (high activity level of extrinsic cholinergic fibers) and a state in which this information is reactivated for recall/retrieval (high activity level of intrinsic cholinergic fibers). The way ACh exerts a shift towards learning (encoding) is by inhibiting transmitter release from intrinsic, local fibers through activation of their presynaptic muscarinic ACh receptors, and activating postsynaptic muscarinic ACh receptors on the target neurons by which input transfer from extrinsic fibers is facilitated.

On the other hand, there are many brain regions including cholinergic local circuit neurons such as the striatum, nucleus accumbens, olfactory tubercle, amygdala, hippocampus, and neocortex (Woolf, 1991) and Van der Zee & Luiten (1999) claimed that intrinsic local cholinergic fibers also play a critical role in memory. Kobayashi and Iwasaki (2000) found that the striatal cholinergic system contributes to acquisition process in egocentric localization, suggesting that intrinsic local circuit of cholinergic neurons in the striatum also play significant roles in certain kinds of cognitive processes.

6. Interaction of ACh with other neurotransmitter systems

There is also growing evidence suggesting the critical relationship between ACh and other neurotransmitter systems with regard to memory function (Levin & Rose, 1992). The septal area receives dopaminergic, noradrenergic, serotonergic, and cholinergic afferents from several brainstem structures (Costa, Panula, Thompson & Cheney, 1983; Lindvall & Stenevi, 1978; Mesulam, Mufson, Wainer & Levey, 1983) and glutamate, GABA, DA, norepinephrine and a few peptides have been suggested to be involved in the septal regulation of hippocampal cholinergic activity (Costa et al., 1983; Dekker & McGaugh, 1991). Furthermore, Nilsson, Leanza & Björklund (1992) suggested that especially catecholaminergic and serotonergic systems subserve a critical role in regulating septo-hippocampal cholinergic activity. Noteworthy suggestion on cholinergic function is done by Krnjevic (1993) that ACh plays a critical role in the initiation of long-term potentiation (LTP). He assumes the following three different ways through which ACh affects LTP. The first is through the cholinergic suppression of K currents that oppose cellular depolarization. The second is by the reduction of inhibitory synaptic inputs; most types of stimulation that activate excitatory input also bring into action powerful inhibitory synapses (through feedback or feedforward pathways). The third is a muscarinic facilitation of NMDA-evoked currents. Thus, hippocampal cholinergic system may function under the interaction with other neurotransmitter systems.

As for the striatal cholinergic system, they are intrinsically organized (Woolf & Butcher, 1981) and have drawn little attention in terms of learning and memory. Recently, however, ACh-dopamine interaction has been a focus of interest. Several studies have suggested the involvement of the nigrostriatal DA pathway in learning and memory processes (Carr & White, 1984; Neill, Boggan & Grossman, 1974; Viaud & White, 1989; White, 1988; White & Major, 1978; Zis, Fibiger & Philips, 1974). The striatum receives dense dopaminergic innervations via the nigrostriatal DA pathway, originating in the substantia nigra (Moore & Bloom, 1978), strongly suggesting that DA systems through the pathway be involved in learning and memory. Consolo, Girotti, Zambelli, Russi, Benzi, and Bertoelli (1993) reported that the striatal cholinergic activity is indirectly facilitated by stimulation of D_1 receptors and inhibited by direct stimulation of D_2 receptors. Furthermore, Zhou, Liang & Dani (2001) report

that nicontinic antagonist or depletion of endogenous ACh in the striatum decreased evoked dopamine release by 90 %, suggesting that cholinergic systems within the striatum play a critical role in regulating dopamine release in the striatum. There are more studies suggesting the interaction of ACh and dopamine in the striatum (Suzuki, Miura, Nishimura & Aosaki, 2001; Partridge, Apparsundaram, Gerhardt, Ronesi & Lovinger, 2002), supporting the idea that both cholinergic and dopaminergic systems in the striatum contribute to certain types of learning and memory process.

Discussion

In the present review, studies on the brain cholinergic systems regarding cognitive functions are introduced. It should be noted here that the brain cholinergic systems have been discussed with regard to their roles 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 deficits in pedunculopontine (PPN) cholinergic activity. Patients with dementia with Lewy bodies also show similar 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. Such studies investigating the brain cholinergic function as a neuromodulator are, however, yet to demonstrate whether those deficits in selective attention or conscious awareness cause cognitive deficits. Still, it is presumable that those deficits in consciousness affect various cognitive processes.

As for studies on the brain cholinergic systems regarding their functions on cognitive processes, most issues still remain uncertain regardless of the tremendous amount of studies except for the fact that the brain cholinergic systems play some roles in various cognitive processes. Still, the brain cholinergic systems are no longer regarded as a single function carrier, but play roles depending on specific functions of each region of the brain even though how ACh systems are involved in each region's function is in question yet. One of the recent questions is how they are involved in cognitive processes regarding interactions with other neurotransmitter systems. Are they essential for cognitive processes or do they work as a neuromodulator that helps other neurotransmitters such as NMDA, serotonin, and dopamine in a complementary manner? All these questions are still under investigation. Function of extrinsic and intrinsic cholinergic neurons especially within the septo-hippocampal pathway is one of the recent issues of interest. It is presumable that projections between plural brain regions such as the septo-hippocampal projection play a critical role in encoding process in memory and such studies upon interactions among various neurotransmitter systems have been accumulated promptly. At the same time, it has been demonstrated that local cholinergic interneurons such as the striatal cholinergic neurons play a critical role in certain learning situations, so it is necessary that the brain cholinergic systems be investigated adopting various experimental techniques to clarify each brain region's cholinergic function.

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