EMPHASIS OF LIMBIC SYSTEM IN NEURAL CONCEPT OF EMOTION

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SUMMARY

Anatomy and functions of limbic system and neural circuits within amygdala and hippocampus are discussed in this review. As a conclusion it should be said that limbic system structures in the cortical regions are responsible for associative functions while the subcortical part is included in the control of behavioral patterns.

Key Words : Limbic cortex, amygdala, hippocampus, behaviour.

INTRODUCTION

The word limbic means "border" and the word limbic cortex was introduced firstly by Paul Broca. In the past, limbic system was used to describe the brain structure that lies in the border region between the hypothalamus and its related structures and the cerebral cortex. In 1937, Papez described the limbic circuit, as well as Heinrich Klüver and Paul Bucy reported their finding that bilateral destruction of the temporal lobe including several limbic structures such as hippocampus and amygdala, produced dramatic changes in the emotional behaviour of monkeys. From these studies; Papez, Klüver and Bucy submitted the background for many later theoretical and experimental approaches to the neurobiology of emotions. Modern anatomical studies have supported Papez's outline of the limbic system and added new connections (Fig. I).

ANATOMY and FUNCTIONS OF LIMBIC SYSTEM

The limbic lobe includes the parahippocampal gyrus, the cingulate gyrus and the subcallosal gyrus which is the anterior and inferior continuation of the cingulate

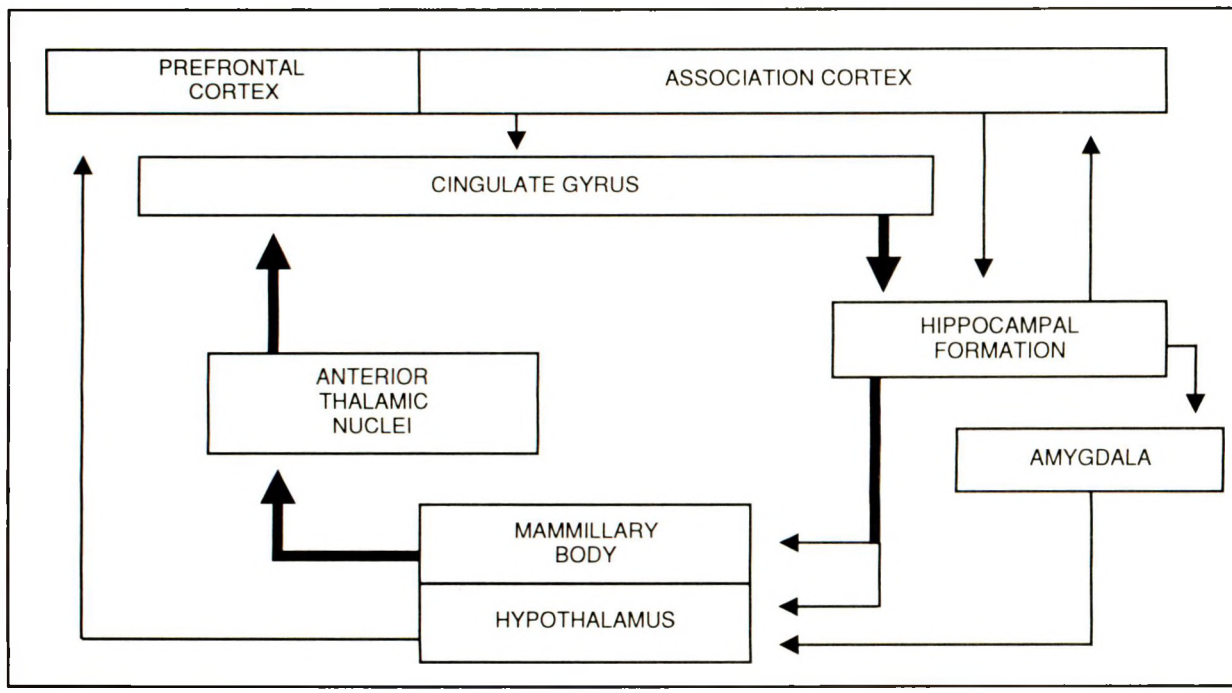

Fig 1. A proposed neural circuit for emotion. The circuit originally proposed by Papez is indicated by thick lines; more recently described connections are shown by fine lines. A pathway interconnecting the amygdala to limbic structures is shown. (From Kandal ER, Schwartz JH, Jessel TM; Principles of neural science, third edition)

gyrus (1). It also includes the underlying cortex of the hippocampal formation. The hippocampal formation consists of the hippocampus proper, the dentate gyrus and the subiculum. Subiculum is the origin of fibers in the fornix that innervate the hypothalamus. The amygdala is composed of many nuclei that are reciprocally connected to the hypothalamus, hippocampal formation, neocortex and thalamus. It also receives an important afferent input from the olfactory system.

The hypotalamus and limbic system mainly function together as a total system. It is also important that many of the behavioral functions elicited from the hypothalamus and other limbic system structures are mediated through the reticular formation of the brain stem. Hypothalamus is a coordinating center that integrates various inputs to ensure appropriate set of autonomic and somatic responses. Since these responses are similar to those seen during some types of emotional behaviours, Hess suggested that the hypothalamus integrates and coordinates the behavioral expression of emotional states. In animals, some of the behavioral effects of stimulation of hypothalamus are the following: 1) Stimulation in the lateral hypothalamus causes thirst, eating, overt rage and fighting; 2) Stimulation in ventromedial nuclei causes satiety and tranquility; 3) Stimulation of a thin zone of periventricular nuclei results in fear and punishment reactions. Lesion of these nuclei, in general, causes the opposite effects.

The hypothalamus and limbic systems are intimately concerned with emotional expression and with the genesis of emotions which have both mental and physical components such as cognition, affect, conation and physical changes like sweating. There are particular neural circuits for numerous emotions localized in either localized brain lesions or electrical stimulation of specific areas. Neuro-pharmacological studies have tried to determine the role of specific transmitters in particular emotions. Brain lesion studies involving experimentally-produced lesions in animals have focused on some dramatic syndromes of emotional change, such as the taming of monkeys following temporal lobe lesions. Brain stimulation studies have generated brain maps for various emotional responses, especially those involving aggression.

NEURAL TRANSMISSION

Role of Dopamine

Papez's proposed circuit has been the source of many experimental work. Each region in the circuit has been lesioned or electrically stimulated to determine the relation to emotional processing. Such stimulation may produce either rewarding or aversive effects or may elicid sequences of emotional behaviour. More recently the maps of self stimulation sites have been done. This work has emphasized on limbic system sites. Maps show that very discrete components of both autonomic and behavioral responses are represented at selected loci in the limbic system and hypothalamic regions. From these maps, the dopamine is the transmitter in reward circuits. In a major review of the extensive research on reward, Wise and Rampre defined that dopamine plays an important role in the rewarding effects of stimulating many brain regions but not of stimulating either the frontal cortex or the nucleus accumbens (2). The latter effects depend on another transmitter (or transmitters); dopaminergic systems probably play a rather general role in motivation and movement. 10 years later in the light of these studies, Stevens pioneered a new approach about the role of dopamine in the neuroanatomy of schizophrenia (3). Postmortem studies documented increased dopamine concentration in the left amygdala in patient with schizophrenia. Furthermore postmortem investigations of limbic cortical and subcortical structures have abnormalities in the hippocampus, amygdala and cingulate gyrus. MRI studies demonstrated structural abnormalities in the temporal lobe including a decreased volume of amygdala and hippocampus (4,5). In parellel with these studies Weinberger concluded to describe the hyperdopaminergic limbic pathophysiology of psychosis and the hypodopaminergic dorsolateral prefrontal pathophysiology of negative symptoms of psychosis or schizophrenia. As an important development in treatment of schizophrenia, clozapine which is an antipsychotic and used in patients with persistent psychosis despite adequate classical neuroleptic treatment has an interesting action. What interesting is its weak affinity for D_2 dopamine receptors and its limbic selectivity.

Role of Acetylcholine

Another neurotransmitter functioning in limbic structure is acetylcholine. It has both excitatory and inhibitory neuromodulator effects in the hippocampus. Some cholinergic pathways are intrinsic to the hippocampus but more than 90% of hippocampal cholinergic fibers arise from mostly the medial septum and adjacent basal forebrain nuclei (6-9). Hippocampus is a useful model system that provides selective investigation. Since there is recent evidence that autoreceptor antagonists may have therapeutic utility for forebrain cholinergic neurodegeneration such as Alzheimer's disease (10, 11), it is thought that one of the mechanisms for regulation of acetylcholine release involves inhibitory muscarinic autoreceptors (12).

On the other side, several studies have shown that the nucleus basalis gives rise to a major cholinergic innervation of the neocortex, reticular thalamic and basolateral amygdaloid nuclei (13, 14). It is hypothesized that in Alzheimer's disease and in aging process there is a deficit in functions of the muscarinic and nicotinic receptors and nucleus basalis cholinergic projections (15, 16). Such studies have reported that lesioning of the nucleus basalis area by infusing ibotenic acid, an agonist of the

N-methyl-D-aspartate subtype of glutamate receptors, decreases cortical cholinergic activity producing behavioral deficits to asses learning and memory functions (17-20). Another study related with cholinergic effect on limbic structures was done by Riekkinen et al. They examined on the hypothesis that passive avoidance performance is modulated via the amygdala by drugs acting on muscarinic and nicotinic cholinergic receptors (21). Results of these studies support the hypothesis and suggest that muscarinic and nicotinic receptor active drugs are effective on passive avoidance performance but importance of the nucleus basalis to amygdala cholinergic muscarinic and nicotinic system may be neglible in spatial learning (21).

The wellknown muscarinic cholinergic antogonist scopolamine which produces memory impairment has been used to determine which muscarinic cholinergic receptor subtypes in hippocampus and cortex. It is likely that scopolamine may affect memory impairment acting at more than one muscarinic receptor subtype. Although it is generally thought not to have receptor subtype selectivity, several lines of evidence suggest that muscarinic receptors of M_1 subtype are important in memory processes (22-24). M_1 subtype predominates in the hippocampus and cortex where cholinergic transmission plays an essential role in memory processes. At presynaptic autoreceptors, scopolamine blocks feedback inhibition of acetylcholine release, resulting in acetylcholine release enhancement and leads to decrease brain acetylcholine levels in tissue (25-27).

In the study done by Bymaster et al. (28) trihexyphenidyl and sistemically administered pirenzepine disturbed memory performance in rats like scopolamine. Scopolamine and trihexyphenidyl but not pirenzepine or mecamylamine produced large dose-related decreases in levels of acetylcholine in both striatum and hippocampus as a result of blockade of muscarinic M_2 autoreceptors and increased neurotransmitter release into the extracellular fluid (28). The lack of effect of mecamylamine suggests that acetylcholine is not tonically released onto presynaptic nicotinic receptor in striatum and hippocampus. Alternatively nicotinic receptors are relatively few in that region of brain, they may play little role in modulating neurotransmitter release (28).

ABOUT AMYGDALA

The amygdala is a complex of nuclei. This complex concerned to a great extent with association of olfactory stimuli from the other part of the brain. In their study, Mc Gregor and Herbert have suggested that B-endorphin in the amygdala impairs the processing of female-specific olfactory information (29). Bilateral infusions of B-endorphin into the amygdala specifically interfere with the precopulatory phase of male's sexual behaviours during which male persues the female. Amygdala could monitor all modalities of sensory information. Olfactory impulse from the main and accessory olfactory bulbs arrives within the corticomedial region while visual, auditory and somatosensory information is received by the basolateral region.

Due to the multiple connections, the amygdala has been called the "window" through which the limbic system sees the place of the person in the world. Amygdala receives impulses from all portions of he limbic cortex, orbital surfaces of frontal lobe, the cingulate gyrus, the parahippocampal gyrus, neocortex of the temporal, parietal and occipital lobes and auditory and visual associational areas. On the other hand it transmits signals back into these same cortical areas, the hippocampus, the septum, thalamus and the hypothalamus. For example amygdala receives imputs from auditory processing areas of the thalamus and the cortex.

Auditory thalamo-amygdala projections originate in the posterior thalamic areas. Classical fear conditioning depends on the transmission of auditory conditioned stimulus information to the lateral nucleus of amygdala. Thus auditory information, including auditory conditioned stimulus information may reach the amygdala via thalamo-amygdala or thalamo-cortico-amygdala projections. Previous studies have shown that auditory fear conditioning in rats is not blocked by bilateral ablation of the auditory cortex (30) but is interfered either by bilateral lesions of the amygdala (31-32) or disconnection of the amygdala from the auditory processing areas of the thalamus. These findings above indicated that cortico-amygdala projections are not necessary and that thalamo-amygdala projections are sufficient as auditory conditioned stimulus transmission routes to the amygdala during fear conditioning to examine further the contribution of thalamo-amygdala and thalamo-cortico-amygdala projections to fear conditioning (33). Thalamo-amygdala and thalamo-cortico-amygdala transmission routes converge in the lateral nucleus of the amygdala (34) and these routes may have complementary functions. However to understand more about the stimulus transmission to the amygdala during emotional process and associative learning organization functions of these pathways should be further examined (33).

Lesioning of amygdala results in inhibition of pituitary-adrenal function (35) and behavioral inactivation and loss of behaviour (36). Amygdala stimulation causes two kinds of effects: First, hypothalamus mediated ones causing involuntary movements; and the second, changes in arterial pressure, heart rate, gastrointestinal system motility and secretion, defecation and micturition. Independent from hypothalamus, amygdala stimulation causes tonic movements (raising head and bending the body), circling mowement, clonic, rithmic movements and movement associated with olfaction and eating. Stimulation of amygdala and hippocampal sites can provoke complex sensory experiences and mood and

behavioral changes (37). Direct stimulation of the amygdala stimulates pituitary adrenal function and provokes arousal and vigilance. Such effects can be similarly reproduced via direct stimulation of amygdala and limbic structure in patients with complex partial seizure (38, 39). The method of kindling discovered by Goddard et al. is commonly induced by repetitive electrical stimulation of limbic areas resulting in seizures that are similar to complex partial seizures with secondary generalization in epileptic patient. Amygdala-kindled rat is a unique model of epilepsy studies. All drugs which are clinically effective againts complex partial seizures supress focal (limbic) seizure in these kindled rats. Previously it was thought that one exception to correlation between clinically effective anticonvulsants and the kindling model was phenytoin (40). However more recent studies proposed that acute administration of phenytoin exerts potent anticonvulcant activity in this model. Rundfeldt and Löscher used amygdala-kindled rat to examine the anticonvulsant efficacy of phenytoin during chronic treatment and their data also provided an additional support from the idea that kindled rat is a useful model for epilepsy with complex partial seizures. They reveal that phenytoin is an efficacious anticonvulsant in amygdala-kindled model after both acute and chronic administration (41).

Effect of some other pharmacological substances on limbic system.

A review of evidence indicating that repetetive administration of CNS stimulants and other releated compounds is associated with progressive alteration of behaviour was presented by Kopanda and Post (42). In that review it is suggested that pharmacological limbic system-kindling mechanism by cocaine and amphetamine produces a psychosis. Another theory was about psychosis model that relates catecholamines with limbic system.

Another observation about relationship between limbic system and pharmacological substances is that there is a similarity between effects of systemically administered local anesthetics and limbic activation either by direct stimulation or during seizures and these results are compatible with data that limbic structures are thought as targets of local anesthetic action in the brain (43). In addition , the data of Racine et al. (1975) demonstrate that procaine tends to activate subcortical limbic sites. It is also notable that because the amygdala has extensive reciprocal connections with temporal cortical region processing in sensory information mostly the auditory and visual modalities are involved in sensory effects of procaine (44). There was a suggestion that local anesthetic-induced limbic action may involve stimulation of CRF (corticotrophin releasing factor) secretion in the CNS, hence icv administration of CRF results in limbic seizures and enhance the effect of cocaine-induced kindling (45). Moreover this local anesthetic-induced increase in CRF secretion was blocked by micromolar concentrations of carbamazepine, a limbic anticonvulsant. Kling et al. presented the study which was based on this phenomena. Their purpose was to examine the clinical effect of stress-responsive neurohormones after i.v. procaine administration. The result is that local anesthetics produce dose-dependent effect on CNS action that may be attributable to a direct effect on limbic structures and action of plasma ACTH, cortisol and prolactin secretion (37).

ABOUT HIPPOCAMPUS

Functional importance of LTP

Repetetive activation of excitatory synapses in the hippocampus produces a persistent enhancement of synaptic efficiency known as long term potential (LTP). LTP in the dentate gyrus and hippocampus is an extensively studied form of activity-dependent synaptic plasticity and is considered to be a cellular model for changes that underly the memory and learning.

Induction of LTP in the hippocampus and dentate gyrus requires simultaneous presynaptic release of neurotransmitters and sufficient postsynaptic depolarization to cause activation of the NMDA (N-methyl-D aspartic acid) receptor channel complex. GR33 is a presynaptic glutamate receptor with a pharmacological profile similar to that of the postsynaptic NMDA receptors (46). Smirnova et al. have studied the effect of LTP on the expression of GR 33 receptor gene in the rat hippocampus (46). In both anesthezised and freely moving rats, induction of LTP led to a transients increase in the mRNA levels coding for a presynaptic GR33 in dentate granule cells and a NMDA receptor antagonist 2-aiinophosphonovalerate prevented the induction of LTP and increase in GR33 mRNA. These results have potential importance of transsynaptically regulated gene expression in the brain and suggest that the glutamate receptor GR33, which is located presynaptically, functions in this process.

Hippocampal functions on several behavioral patterns

Hippocampus has numerous connections wtih most portion of cerebral cortex as well as limbic system. Thus, hippocampus is an additional channel through which incoming sensory signals can lead to appropriate limbic reaction. Like amygdala, weak electrical stimulation of hippocampus can cause local epileptic seizure including olfactory, visual, auditory, tactile and other types of hallucinations. In epileptic patients the hippocampi have been surgically removed bilaterally for treatment. These people can perform most previously learned activities satisfactorily but cannot learn essentialy new. In 1957, the report of a patient who underwent bilateral removal of hippocampus together with surrounding brain tissue resulted interestingly. Life-threatening epileptic seizures dramatically decreased but another

consequence of the surgery was almost a total anterograde memory loss. This report triggered thousands of experiments aimed at defining the role of the hippocampus in memory processes. Cohen and Eichenboum developed a theory of hippocampal function that the hippocampal formation is responsible for mediating declarative memory while cerebral neocortex, primarily, is responsible for procedural memory (47). Memory is not a single mental faculty but is composed of multiple and seperate abilities that are mediated by distingt brain systems. The major distinction is between declarative (or explicit) memory which depends on limbic and diencephalic structures and provides the basis for conscious recollection of facts and events, and implicit (or various nonconscious) memory abilities, which support skill, habit learning and simple conditioning. Declarative memory refers to recent memory by which, a subject learns about the category that is defined by the items presented. Studies of amnesic patients could illuminate this issues because these patients have severely impaired declarative memory but intact non declarative (implicit) memory (48).

From another focus of view, Bruce McEwen from Rocefeller University and other neuroscientists have shown that prolonged exposure to stress hormones causes atrophy in the hippocampus. Psychiatrist Mark Simith and his colleagues from the National Institute of Mental Health in U.S.A. found that, in adult rats, long-term stress seems to lower production of protein called brain-derived neurotrophic factor (BDNF). Rats are stressed out by immobilization over 7 consecutive days. To determine whether this regimen affected the expression of BDNF the corresponding mRNA is investigated and they found that the expression of BDNF was decreased throughout the brain, but particularly in a region of the hippocampus called dentate gyrus (49).

In summary, till further information is avaliable, it may be the best to state that the cortical regions of the limbic system occupy intermediate associative positions between the functions of the remainder of the cerebral cortex and of the subcortical limbic structures for control of behavioral patterns.

REFERENCES

1. *Kandal ER, Schwartz JH, Jessell TM. Principles of neural science, third edition. New York: Elsevier, 1991:735-749.*
2. *Wise P. Rompre PP. Brain dopamine and reward. Ann Rew Psyc 1989;40:191-225.*
3. *Carpenter WT, Buchanan RW. Schizophrenia. The N Engl J Med 1994;330:681-688.*
4. *Breier A et al. Brain morphology and schizophrenia. Arch Gen Psychiatry 1992;49:921-963.*
5. *Suddath RL et al. Anatomical abnormalities in the brains of monogzygatic twins discordant for schizophrenia. E Engl J Med 1990;322:789-794.*
6. *Amaral D, Kurz J. An analysis of the origin of the cholinergic and noncholinergic septal projections to the hippocampal formation of the rat. J Comp Neurol 1985;240:37-57.*
7. *Chandler JP, Crutcher KA. The septohippocampal projection in the rat: An electron microscopic horseradish peroxidase study. Neuroscience 1983;10:685-696.*
8. *Kromer LF et al. Regeneration of the septohippocampal parthways in the adult rats is promoted by utilizing embryonic hippocampal implants as bridges. Brain Res 1981;210:173-200.*
9. *Mc Kinney M et al. topographic analysis of the innervation of the rat neocortex and hippocampus by the basal forebrain cholinergic system. J Comp Neurol 1983;217:103-121.*
10. *Mc Kinney M, Coyle JT. The potential for muscarinic receptor subtype-specific pharmacotherapy for Alzheimer's disease. Mayo Clin Proc 1991;66:1225-1237.*
11. *Packard MG et al. Post-training injections of the Ach M2 receptor antagonist AF-DX 116 improves memory. Brain 1990;524:72-76.*
12. *Vickroy TW, Malphurs WL, Degiebre NC. Absence of receptor reverse at hippocampal muscarinic autoreceptors which inhibit stmulus-dependent acetylcholine release. J PET 1993;267:1198-1203.*
13. *Bigl V, Woolf NJ. Cholinergic projection from the basal forebrain to frontal, parietal, temporal, occipital and cingulate cortices. Brain Res Bul 1982;8:727-749.*
14. *Mesulam MM, Mufson EJ, Wainer BH. Central cholinergic parthways in the rat. Neuroscience 1983;10:1185-1201.*
15. *Bowen DM, Smith CB, White P. Davidson AN. Neurotransmitter related enzymes and indices of hypoxia in senile dementia and other abiotrophies. Brain 1976;99:459-496.*
16. *Reinikainen KJ, Riekkinen PJ. Cholinerjic deficit in Alzmheimer's disease. Neurochem. Res 1988;13:135-146.*
17. *Dubois B, Mayo W, Simon H. Profound disturbances of spontaneous and learned behaviours following lesions of the N Basalis magnocellularis in the rat. Brain Res 1985;338:249-258.*
18. *Dunnett SB. Comparative effects of cholinergic drugs and lesions of Nucleus Basalis of fimbria-fornix on delayed matching in rats. Psychopharmacology 1985;87:357-363.*
19. *Mandel RJ, Thal LJ. Physostigmine mproves water maze performance following N Basalis magnocellularis lesions in rats. Psychopharmacology 1988;96:421-425.*
20. *Riekkinen P, et al. Comparison of quisqualic andibotenic acid NBasalis magnocellularis lesions on water maze and passive avoidance performance. Brain Res 1991a;27:119-123.*
21. *Riekkinen P, Sirvio J. Cholinergic drugs regulate passive avoidance performance via the amygdala. J PET 1993;267:1484-1492.*
22. *Bonner TI, Buckley NJ, Young AC. Identification of a family of muscarinic Ach receptor genes. Science 1987;237:527-532.*
23. *Bucley NJ, Bonner TI, Brann MR. Localization of a family of muscarinic receptor mRNAs in rat brain. J. Neurosci 1988;8:4646-4652.*
24. *Levey AI, Kitt CA, Simonds WF. Identification and localization of muscarinic Ach receptor protein in brain with subtype-specific antibodies. J Neurosci 1991;11:3218-3226.*
25. *Bymaster FP, Perry KW, Wong DT. Measurement of Ach and choline in brain by HPLC with electrochemical detection. Life Sci 1985;37:1175-1181.*
26. *Polak RL, Meeuws MM. The influence of atrophine on the release and uptake of ach by the isolated cerebral cortex of the rat. Biochem Pharmacol 1966;15:989-992.*
27. *Serthy VH, Van Woert MH. Antimuscarinic drugs: Effect on brain Ach levels and tremodors in rats. Biochem Pharmacol 1973;22:2685-2691.*

28. Bymaster FP, Heath I, Hendrix JC, Shannon HE. Comparative behavioral and neurochemical activities of cholinergic antagonists in rats. J PET 1993;267:16-24.
29. Mc Gregor A, Herbert J. The effects of B-endorphin infusion into the amygdala on visual and olfactory sensory processing during sexual behaviour in the male rat. Neurosci 1992;46:173-178.
30. Le Doux JE, Sakaguchi A, Reis DJ. Subcortical efferent projections of the medial geniculate nucleus mediate emotional responses conditioned to acoustic stimuli. J Neurosci 1984;4:683-698.
31. Iwata J, Le Doux JE, Merley MP, Reis DJ. Intrinsic neurons in the amygdaloid field projected to by the medial geniculate body mediate emoional responses conditioned to acoustic stimuli. Brain Res 1986;383:195-214.
32. Le Doux JE, Sakaguchi A, Iwata J, Reis DJ. Intrruption of projections from the medial geniculate body to an archineostriatal field distrupts the classical conditioning of emotional responses to acoustic stimuli in the rat. Neuroscience 1986;17:615-627.
33. Romanski LM, LeDoux JE. Equipotentiality of thalamo-amygdala and thalamo-cortico-amygdala circuits in auditory fear conditioning. J Neurosci 1992;12:4501-4509.
34. Allen JP, Allen CF. Amygdalar participation in tonic ACTH secretion in the rat. Neuroendocrinology 1975;15:115-125.
35. Le Doux JE, Farb CR, Romanski, LM. Overlapping projections to the amygdala and striatum from auditory processing areas of the cortex and thalamus. Neurosci Lett 1991;134:139-144.
36. Kling A et al. A neural substrate for affiliative behavior in nonhuman privates. Brain Behav Evol 1976;13:213-238.
37. Kling MA, Gardner DL, Calogero AE. Effects of local anesthetics on experimential, physiologic and endocrine measures in healthy humans and on rat hypothalamic CRH release in vitro: clinical and psychobiologic implications. J PET 1994;268:1548-1564.
38. Gloor P et al. The role of the limbic system in the experimental phenomena of temporal lobe epilepsy. Ann Neurol 1982;12:129-144.
39. Halgren E et a. Mental phenomena evoked by electrical stimulation of the human hippocampal formation anamygdala. Brain 1978;101:83-117.
40. Mc Namara JO. Development of new pharmacological agents for epilepsy. Epilepsia 1989;30:13-18.
41. Rundfeldt C, Löscher W. Anticonvulsant efficacy and adverse effects of phenytoin during chronic treatment in amygdala-kindled rats. J PET 1993;266:216-223.
42. Kopanda RT, Post RM. Cocaine, kindling, and psychosis. Am J Psych 1976;33:627-634.
43. Garfield JM, Gugino L. Central effects of local anesthetic agents. In: Strichartz, GR, ed. Handbook of experimental pharmacology, Berlin: Springer Verlag, 1987;81:253-284.
44. Amaral DG, Price JL, Pitkanen A, Carmichael ST. Anatomical organization of the primate amygdaloid complex. In: Aggleton JP, ed. The amygdala: neurobiological aspect of emotion, memory and mental dysfunction. New York: Wiley-Liss, 1992:1-66.
45. Weiss SRB, Nierenberg J, Lewis R, Post RM. Corticotropin releasing hormone: Potentiation of cocaine-induced seizures and lethality. Epilepsia 1992;33:248-254.
46. Smirnova T, Laroche S, Errington ML, Hicks AA. Bliss TVP, Mallet J. Transsynaptic expressinon of a presynaptic glutamate receptor during hippocampal long term potentiation. Science 1993;262:433-435.
47. Kimble DP. The structure of memory. Science 1994;263:1300-1302.
48. Knowlton BJ, Squire LR. The learning of categories: Parellel brain systems for item memory and category knowledge. Science 1993; 262:1747-1749.
49. Fiscman J. This is your brain on stress. Science 1993;262:1211.