# CHAPTER 1

## INTRODUCTION

The name "nucleus accumbens (septi)", as meaning literally, a nucleus leaning against the septum was suggested by Arien Kappers (1907). It situates in the telencephalon in between the olfactory nucleus rostrally. the bed nucleus of the stria terminalis caudally and the caudato-putamen dorso-laterally and the septum dorsomedially (Ariens Kapper, 1907; Jonhston, 1913; 1923; Konig and Klippel, 1970). On the basis of its location and fiber connections, functional role of the nucleus accumbens has been variously included in the olfactory, limbic and striatal systems.

According to Koikegami and his colleques. the nucleus accumbens could be devided into 4 subnuclear groups, which composed of two dorsal and two ventral nuclei. In the dorsal groups, the group of cells clustered proximal to the caudate nucleus was referred to as the nucleus accumbens caudati and the cells grouping proximal to the lateral septal nucleus was called the nucleus accumbens septi. The two ventral nuclei were those larger cells clustered ventral to the dorsal groups which were identified as the nucleus accumbens principalis pars lateralis and pars medialis (Koikegami et al, 1967).

Nevertheless, this classification has not been used by other investigators.

## 1.1 Afferent connections of nucleus accumbens

Previous studies by degeneration techniques in the rat, rabbit, cat and monkey have demonstrated preterminal degenerations in the nucleus accumbens following hippocampal lesion (Carman et al, 1963; Raisman et al, 1966; Webster, 1961). This hippocampal-accumbens projection was found to be topographically organized (Carman et al, 1963; Raisman et al, 1966; Webster; 1961). Furthermore, ventral portion of the subiculum and the adjacent part of field CA 1 of the hippocampus was shown to project to the nucleus accumbens of rat by an autoradiographic technique (Swanson and Cowan 1975).

Amygdala projection to the nucleus accumbens was demonstrated by degeneration technique in the rat (Cowan et al, 1965), by autoradiographic technique in the rat and cat (Krettek and Price, 1978), and by HRP technique in the hamster (Newman and Winans, 1980). In details, the nuclei accumbens of the rat and cat recieved afferent projections from both basolateral and basomedial amygdaloid nucleus (Krettek and Price, 1978) but basomedial amygdaloid projection to the nucleus accumbens in the hamster was reported to be absent (Newman and Winans, 1980).

Cowan and Powell (1955) have suggested that the parataenial thalamic nucleus might project to the nucleus accumbens of rabbit. This projection was also found by an anterograde transport of tracing substance. After a very small injection of [$^3$H] proline was made into the bilateral parataenial and paraventricular nuclei, there was a dense aggregation of silver grains on both sides over the medial part of the nucleus accumbens. On the basis of autoradiographic study, anterograde and retrograde transport of HRP. other areas reported to project to nucleus were the olfactory cortex of rat (de Olmos and Ingram, 1972), the reuniens nucleus of rabbit and monkey (Cowan and Powell, 1955; Powell and Cowan, 1956); the dorsal raphe of rat (Bobillier et al, 1976); the prelimbic, the anterior cingulate and rostral sulcal cortices of rat (Beckstead, 1979).

Newman and Winans (1980) made a systematic investigation concerning afferent projections to the nucleus accumbens of hamster. They made conclusions that the nucleus accumbens of hamster received ipsilateral projection from the telencephalon; diencephalon and brainstem. These projecting areas included the posterior agranular insular, perirhinal, entorhinal and primary olfactory cortices; the subiculum and hippocampal field CA 1 and the anterior and posterior division of basolateral amygdaloid nucleus of the telencephalon, the centromedial, paracentral and parafasicular intralaminar nuclei, the midline nuclei including the parataenialis, paraventricularis and anterior nucleus of the diencephalon; the ventral tegmental area and the dorsal raphe nucleus of the brain stem. In addition, many of these projections were demonstrated to be topographically organized.

More recently, nucleus accumbens of rats was shown to receive input from the entorhinal cortex and amygdala (Kraynisk et al, 1981). Small injection of tritiated leucine and proline confined to ventral tegmental area and substantia nigra. pars compacta were shown to label fibers ascending to the nucleus accumbens in rat (Beckstead et al, 1979). Anterograde transport of HRP indicated projection from the ventral tegmental areas to the nucleus accumbens in rat and rabbit (Chronister et al, 1980). Subsequent neurophysiological study showed that some ventral tegmental neurons were antidromically activated after stimulation of the nucleus accumbens (Deniau et al, 1980).

It was documented that the nucleus accumbens received dopaminergic innervation from two different sources: major innervation from the ventral tegmental area while minor innervation from substantia nigra, pars compacta (Chronister et al, 1980; Fallon and Moore, 1978: Moore and Bloom, 1978; Dahlstrom and Fuxe, 1964; Newman and Winans, 1980). Radioenzymatic assays demonstrated a high dopamine level in nucleus accumbens and such levels were not significant different in the antero-posterior dimension of the nucleus accumbens (De France et al, 1983).

It was suggested that neurons in locus coeruleus and subcoeruleus projected to the nucleus accumbens (Chronister et al, 1981). Neurochemical study by the method of mass fragmentography could detect norepinephrine in nucleus accumbens of rat (Koslow et al, 1974; Farley and Walaas, 1981) and human (Farley and Hornykiewicz, 1977). Furthermore, radioenzymatic assays showed that norepinephrin levels were significantly higher in the caudal portion than in the rostral portion of the nucleus accumbens (De France et al, 1983).

## 1.2 Efferent connections of the nucleus accumbens

Efferent fibers from the nucleus accumbens to the substantia nigra have been described by using autoradiographic, degeneration and HRP techniques that they exist in the tamanda (Smith, 1930). the cat (Rioch, 1931), and the rat (Swanson and Cowan, 1975; Conrad and Pfaff, 1976; Domesick et al, 1976). Autoradiographic technique demonstrated a projection from the nucleus accumbens to ventral tegmental nucleus of rat (Nauta et al, 1978). Furthermore, Phillipson (1979) observed labeling neurons in nucleus accumbens after HRP application in the rat ventral tegmental area.

Others efferent connections of the accumbens neurons have been described by using autoradiographic and HRP techniques that they project to the septum and caudate nucleus of the macaque (Lauer, 1945) and the rat (Conrad and Pfaff, 1976; Domesick et al, 1976), the entopeduncular nucleus of the tamanda (Smith, 1930), the hypothalamus, the olfactory tubercle. the frontral cortex. the preoptic area and the thalamic nuclei in the rat (Swanson and Cowan, 1975; Williams et al, 1977; Fallon et al, 1978; Herkenham, 1978), the amygdala of the rat (Gurdjan, 1928; Nauta et al, 1978) and the globus pallidus of the rat (Swanson and Cowan, 1975; Heimer and Wilson, 1975; Domesick et al, 1976), and the hamster (Newman and Winans, 1980).

The nucleus accumbens-globus pallidus projection were suggested to be a GABA ergic (Wood et al. 1976: Pycock and Horton. 1976) which was in accordance with a high GABA concentration found in the nucleus accumbens (Beart et al, 1980).

Early investigators suggested that nucleus accumbens might play a functional role in relation to the basal ganglia (Ariens Kappers, 1907; Jonhston, 1913) particularly as a part of the olfactostriatum (Lauer, 1913). The exact relationship of the nucleus accumbens and other brain areas remained unknown until inputs from the hippocampus were demonstrated to terminate in the nucleus accumbens (Webster, 1961; Carman et al, 1963; Raisman et al, 1966) These findings linked the nucleus accumbens closely with the "limbic system". On the other hand, morphological study of the nucleus accumbens reported its cytoarchitectures to be similar to those of caudatoputamen (Koikegami et al, 1976; Wilson 1972). Major interest in this nucleus arosed when the demonstration of dopaminergic neurons from the ventral tegmental area terminating in the nucleus accumbens was reported (Dahlstrom and Fuxe, 1964; Chronister et al, 1980; Deniau et al, 1980). Subsequent experiment indicated that the nucleus accumbens received dopaminergic innervation not only from the ventral tegmental area but also from the substantia nigra pars compacta (Björklund and Lindvall, 1975).

Other lines of evidence showed that neurons in the nucleus accumbens sent their axons to terminate in the globus pallidus (Swanson and Cowan, 1975; Heimer and Wilson, 1975; Domesick et al, 1976) and these neurons was indicated to be GABA ergic (Pycock and Horton, 1976; Jones and Mogenson, 1979). These two lines of evidence have led to the suggestion that the nucleus accumbens is a part mesolimbic and extrapyramidal motor systems by which its inputs mainly originated from mesolimbic dopaminergic neurons and its outputs send mainly via the GABA ergic neurons to the basal ganglia (Costa and Gessa, 1977; Heimer and Wilson, 1975).

Clinical observation found depletion of DA level in the nucleus accumbens of Parkinson's patients in a similar magnitude as that found in the caudate nucleus (Price et al, 1978). The authors suggested that akinesia in Parkinson's patient might be related to degeneration of mesolimbic dopaminergic projection to the nucleus accumbens. The reduction in inhibitory DA input might exaggerated actions of GABA ergic neurons projecting to the globus pallidus and contributing factor causing akinesia

(Jones and Mogenson, 1980).

Furthermore, DA receptors in the rat nucleus accumbens were shown to modulate the activity of GABA releasing nerve terminal (Beart et al. 1980).

Recent electrophysiological study also suggested that the nucleus accumbens might form a part of interface linking the limbic structure to motor areas (Lopes da Silva et al, 1984).

Although evidence has emphasized the role of nucleus accumbens in motor activity associated with the limbic and mesolimbic system; systematic study concerning afferent connections of the nucleus accumbens has been carried out only in the hamster and cat (Newman and Winans, 1980; Groenewegen et al, 1980) such a study has not been reported in the rat or other mammals. Any additional informations, if avaiable would provide further understanding concerning the role of the nucleus accumbens in relation with the limbic-mesolimbic and the motor system.

The purpose of the present study is, therefore, attempt to systemically elucidate the afferent connections of the nucleus accumbens of the rat by using the widely accepted technique of retrograde axonal transport of HRP.