CHAPTER II

BACKGROUND INFORMATION

Cardiovascular Responses Evoked from Fastigial Nucleus

Many reports have shown that electrical stimulation of the rostral fastigial nucleus (FN) of cat (Achari and Downman, 1969,1970 ; Miura and Reis, 1969,1970,1971 ; Doba and Reis,1972$_a$, 1972$_b$; Achari, Al-Ubaidy and Downman,1973;Lutherer and Williams,1986; Bradley,et al., 1987 ; Williams, et al., 1989 ; Huang, Peng and Shieh, 1989), dog (Dormer and Stone, 1976; Dormer, Foreman and Stone, 1977 ; Foreman and Ohata, 1982 ; Dormer, et al., 1986), rabbit (Bradley, Paton and Spyer, 1986; Bradley,et al., 1987),rat (Del bo, Sved and Reis, 1983 : Del bo, et al., 1983), and monkey (Sudsuang, et al., 1990) elicits elevation in arterial blood pressure (ABP) and heart rate (HR)"fastigial pressor response" (FPR). The FPR is characterized by a rise in systolic (SP) and diastolic (DP) blood pressure, pulse prassure (PP), regional vasoconstriction of limb, kidneys and abdominal iscera, a sustained increase in myocardial contractility (Achari and Downman, 1970 ; Miura and Reis, 1970 ; Doba and Reis, 1972$_a$) and increase of pulse pressure also occured (Achari and downman, 1970). This cardiovascular responses has been associated with autonomic neural activity and sympathoexcitation (Dormer, et al., 1982 ; Andrezik, et al., 1984 ; Nisimasu and Kawaguch, 1984) while using sympathetic blocking drug indicate that fastigial stimulation causes sympathetic discharge to the heart and to the peripheral vessels (Achari and Dowman, 1980). Furthermore, Achari and Downman (1970),Miura and Reis (1971) showed that stimulation of the rFN could inhibit a baroreceptor-evoked bradycardia. This apparent inhibition could result from a summation of the tachycardia elicited from the FN superimposed over the baroreceptor mediated bradycardia.

Separate studies have shown that electrical stimulation of FN induces release catecholamine from adrenal medulla and sympathetic neuron (Del bo, et al., 1983) resulting in tachycardia and vasoconstriction (Achari and Downman, 1970 ; Doba and Reis, 1972 ; Dormer and Stone, 1976 ; Koyama, Ammons and Manning, 1980) a sympathetically mediate activation of the renin-angiotensin system (Kayama, Ammons and Manning, 1980). Del Bo, Sved and Reis 1983, 1984_a, 1984_b ;Sved, Scott and Kole, 1985 ; Del bo and Rosina, 1986, reported that FN stimulation increases vasopressin (VP) release into the circulation and in the absence of the sympathoadrenal system, these substanes release elicited by FN stimulation is sufficient to elevate ABP and HR. While lesion of the FN attenuate vasopressin release in response to hemorrhage (Sved, Scott and Kole, 1985), prevent the recovery of blood pressure after hemorrhage (Lutherer, et al., 1983 ; Lutherer, Williams and Everse, 1989), abate the cardiodynamic patterns during the compensatory phase of the orthostatic reflex to upright posture in cat (Kayama, Ammons and Manning, 1981), impairs the tilting response of blood pressure (BP) and HR (Miura and Reis, 1970) and in the dog with rostral fastigial nucleus lesions has consistent decrease in ABP and HR during exercise (Dormer and Stone, 1982; Dormer, 1984).

For many years it has been uncertain whether the FPR represented a response to stimulation of intrinsic neuron of the FN or to excitation of axons projection into or through the nucleus. Recently, however, several studies have attempted to address the above question by using chemical stimulation. Dormer, Foreman and Stone (1977) using very large injections of glutamate into the rostral fastigial nucleus, obtained a pressor response. In the study using microinjection, Bradley, et al. (1987), observed no changes in blood pressure in response to glutamate, and Chida, et al. (1986), observed only a depressor response with chemical stimulation with Kainic acid. Umeadi (1987) preliminary report showed depressor responses with glutamate and increases, decreases and no change in pressure after

kainate, Moreover, bilateral destruction of perikarya in the FN of the rat (Henry and Connor, 1989) with the cytotoxic agent kainic acid didnot alter the pressor effect seen during electrical stimulation of the rostral pole of the FN, suggesting that an axon or terminal reflex is responsible for the blood pressure increase. However, using extracellular recordings from units within the rostral fastigial nucleus, could elicit changes in firing patterns in units within this region (Lutherer and Williams, 1989). these results suggest that neurons within rostral fastigial nucleus involved in cardiovascular function, but some investigators, Chida, et al (1986), Bradley, et al., (1987) reported that pressure responses are elicited by activating fiber of passage arising from some other underscribed site. Moreover, miura and Takayama (1988), reported that the site of pressor responses to electrical stimulation originates in the parabrachial nucleus (Pbl) which projects into the contralateral parabrachial nucleus via the subfastigial fiber bundle. Although some pathways influencing the cardiovascular system may pass through or near the rostral fastigial nucleus. Suggests that a complex neural network may exist that the cerebellum might be involved in integrating the output of the cardiovascular system. Summary of the previous findings of FN influence on eardiovascular function is shown in Table 1.

These cardiovascular responses indicate the evidence of their local circuitry between the FN and areas involed in hemodynamic regulation.

Distribution of Cerebellar Fastigial Nucleus Projection.

Several investigators have shown that ascending projections of the contralateral FN pass via the uncinate fasciculus (UF) and ipsilateral juxtarestiform body (JRB) to the brain stem (Thomas, et al.,1956 ; Carpenter, 1959 ; Angaut and Bowsger, 1970 ; Batton, et al,

Table 1. Summary of the previous findings of FN influence on cardiovascular function

No	Experimental procedure	Results	Animal	References
1.	Electrial stimulation of rFN.	Produced pressure response	Cat.	Achari and Downman (1969, 1970), Miura and Reis (1969,1970, 1972_a,1972_b) Achari, al-Ubaiby and Downman (1973), Lutherer and Williams (1986),Bradley, et al.(1987),Hung,Peng and Shich (1989), Williams (1989).
			Dog	Dormer and stone (1976), Dormer, Forman and Stone (1977), Forman and Ohata (1982), Dormer, et al. (1986).
			Rat	Delbo, Sved and Reis (1983), Delbo, et al. (1983).
			Rabbit	Bradley, Paton and Spyer (1986), Bradly, et al. (1987).
			Monkey	Sudsuang, et al. (1990)

2.	Electrical stimulation of rFN.	inhibit a baroreceptor -evoked bradycardia	Cat	Achari and Downman (1970).
3.	Electrical stimulation of rFN.	Inhibited BP response of carotid sinus stimulation	Cat	Miura and Reis (1971).
4.	Electrical stimulation of rFN.	Excitatory spinal sympathetic nerve activity	Dog	Dormer, et al. (1982).
5.	Electrical stimulation of rFN.	Releases renin	Cat	Kayama, Ammons and manning (1980).
6.	Electrical stimulation of rFN.	Releases adrenomedullary catecholamines.	Rat	Delbo, et al. (1983).
7.	Electrical stimulation of rFN.	Releases vasopressin	Rat	Delbo, Sved and Reis ($1983, 1984_a, 1984_b$).
8.	Electrical stimulation of rFN.	Excitatory renal sympathetic nerve activity	Rabbit	Nisimaru, et al. (1984).
9.	Fastigial lesion	Impairs the tilting response of BP and HR	Cat	Miura and Reis (1970).
10.	Fastigial lesion	Abate cardiodynamic pattern during compensatory phase of the orthostatic reflex	Cat	Kayama, Ammons and Manning (1981).

11.	Fastigial lesion	Decrease in ABP and HR during exercise	Dog	Dormer and stone (1982), Dormer, (1984)
12.	Fastigial lesion	Prevent the recovery of BP after hemorrhage	Dog	Lutherer, et al. (1983), Lutherer, Williams and Everse (1989).
13.	Fastigial lesion	Attenuate vasopressin release in response to hemorrhage	Rat	Sved, Scott and Kole (1985).
14.	Chemical stimulation of FN	Glutamate produced a slowly evoluing hypertension with bradycardia	Dog	Dormer, Foreman and Stone (1977).
15.	Chemical stimulation of FN	Kainic acid induced a depressor response	Rat	Chida, et al. (1986).
16.	Chemical stimulation of FN	No changes in BP in response to glutamate	Cat	Bradley, et al. (1987).
17.	Chemical stimulation of FN	Depressor responses with glutamate and inereases, decreases and no change in pressure after kainate	Cat	Umeadi (1987).

18.	Electrical stmulation of subfastigial fiber bundle	Produced pressor response	Cat	Miura and Takayama (1988).
19.	Electrical stimulation after chemical lesion of FN	Produced pressor response after destruction of perikarya in the FN	Rat	Henry and Connor(1989).

1977 ; Andrezik, et al., 1984). Carpenter (1959), reported that complete unilateral destruction of the FN in monkey produced bilateral degeneration in UF, degeneration in the ipsilateral UF represents a summation of uncrossed fibers and fibers from the opposite side which traverse the nucleus. With destruction of the caudal portions of the FN degeneration is seen principally in the contralateral UF while, lesion confined to the rostral portions of the FN provoke degeneration primarily in the ipsilateral UF. Relatively few fiber from the rostral half of the FN appear to cross to the opposite side white matter anterior to rostral pole of FN.

Using autoradiography to detect axonally transported radioactive traced found that rostral fastigial projections to the vestibular nuclei are mainly to ventral portion of the Lateral vestibular nucleus (LVN) inferior vestibular nucleus (IVN) (Botton, et al., 1977 ; Andrezik, et al., 1984) and medial vestibular nuclei (MVN) (Andrezik, et al., 1984). Thomas, et al. (1956), reporded that, direct fastigiobulbar fiber proceed, ventrolaterally from their origin in the FN. Together both crossed and uncrossed, originates in the FN, transverses the restiform body, and passed through the lateral vestibular nucleus to terminate on several nuclei in the lower brain stem.

The anatomical study to delineate fastigial projections demonstrated that the rostral fastigial gived rise to heavy projections to the contralateral medial reticular formations including nucleus reticularis gigantocellularis (NGC) (Moolenaar and Rucker, 1976; Batton,et al., 1977), paramedian reticular nucleus (PRN) (Angaut and Bowsher,1970 ; Batton, et al., 1977 ; Elisevish, Hrycyshyn and Flumerfelt, 1985), to nucleus parasolitarius and to the nucleus tractus solitarius (NTS) (Moolenaar and Rucker, 1976 : Batton, et al., 1977 ; Dietrichs, 1983). Moderate projections to the nucleus ambigous, lateral reticular nucleus and the perihypoglossal nucleus also

described (Moolenaar and Rucker, 1976 ; Batton, et al., 1977 ; Dietrichs, 1983). In tree shrew, FN project to the vestibular nuclei, and reticular formation through the uncinate fasciculus (Ware, 1973). Batton, et al. (1977), reported that fastigiopontine fibers in monkey, emerge with the UF, bypass the vestibular nuclei and terminate upon the contralateral dorsolateral pontine nuclei.

Neuroanatomical studies in monkey (Haines, and Dietrichs., 1984_b) , cat Dietrichs, 1984 ; Dietrichs and Zheng, 1984), and tree shrew (Haines and Dietrichs, 1984_a),using horseradishperoxidase techniqued, have identified direct connections between medial cerebellar nuclei and hypothalamus. Since the paraventricular nucleus (PVN), as well as the supraoptic nucleus, contain neurosecretory neurons which secrete vasopressin and oxytoxin,these nuclei receive neuronal inputs from the FN (Hained, Dietrichs and Sowa, 1984). These studies have revealed direct connection between the FN and the PVN. This cerebello-hypothalamic circuit may be involed in the regulation of the autonomic neuroendocrine system (Kalafuchi and Koizumi, 1990).

By marking the efferents from the rostral fastigial nucleus and cell bodies projecting to the PVN were found in close contact in the region of the locus coeruleus and parabrachial nucleus and in the caudal ventrolateral medulla dorsal to the lateral reticular nucleus (Del bo and Rosina, 1986) which may function as putative relay station of disynaptic pathways linking the rostral fastigial nucleus to PVN. Moreover the fastigial-hypothalamus fiber branch from the main thalamic contingent and apparently terminate in both lateral and posterior hypothalamic areas (Person, et al., 1986). Injections of HRP in lateral hypothalamic area (LHA) found that fastigial cell and neurons of LHA project to spinal cord (Saper, et al., Zemlan, et al., 1979; Hosoya, 1980 ; Dietrichs and Zhing, 1984) presumably terminating in the intermediolateral cell column (IML) (Saper,et al.,1976). At the same time the FN has a direct crossed projection to the spinal cord. These direct fastigiospinal fibers have been documented in a variety

of animals such as the cat (Fukushima, et al., 1977 ; Matsushita and Hosoya, 1978), tree shrew (Ware and Mufen, 1979), and monkey (Takahashi, et al., 1978) that the vast majority of cerebellospinal neurons and that most of them run down in the spinal cord contralaterally, terminate in anterior gray horn cell to the cervical and upper thoracic cord segment.

Pathways for Autonomic Regulation

The pathways through which cerebellar networks mediating the FPR act to influence the output of preganglionic sympathetic neurons in the intermedio-lateral nuclei (IML) of the thoracic spinal cord is not clear. Lesion studies disagree as to the exact route of the fastigiobulbar pathway.

Many reports have shown that the PRN of the caudal medulla oblongata, the primary target of the fastigiobulbar tract is a precerebellar principle relay nucleus mediating blood pressure control that receives important inputs from the deep cerebellar nuclei (Carpenter, 1959 ; Miura and Reis, 1970 ; Elisevich and Ciriello, 1988). This nucleus appears to relay the FPR to spinal preganglionic sympathetic vasomotor nucleus (Achari and Downman, 1970). Cardiovascular responses mediated through the FN (FPR) have also been influence by excitation or ablation of the PRN (Miura and Reis, 1969, 1970, 1971 ; Calcaresu and Thomas, 1971). Furthermore, with microelectrode recording neurones were discovered within the PRN which responded to electrical stimulation of the FN (Miura and Reis, 1971). Various aspects of the pathways from the deep cerebaellar nuclei to the PRN have been studied using lesion techniques (Thomas and Kaufman, 1956) and the autoradiographic tracing method (Batton, et al., 1977). Batton, et al. (1977) found that rostral part of the FN, in particular, appeared to contribute all of the fastigial fiber to the contralateral PRN via the uncinate fasciculus (UF). Finally, Neurons in PRN have been shown histologically to project directly to

the region of the intermediolateral nucleus (IML) of the thoracic cord (Elisevich, Hrycyshyn and Flumerfet, 1985).

The bulbar pathways to sympathetic preganglionic nuclei (SPN) originate in the A_5 (Subcoeruleus) norepinephrine-containing ells area of the caudal pons (Dahlstron and Fuxi, 1965) adjacent to the superior olivary nucleus (Dahlstron and Fuxi, 1964 ; Loewy, Mckellar and Saper, 1979 ; Westlund, et al., 1983). Many investigators propose a role of these area serves as the relay to the spinal cord. Loewy, Mckellar and Saper, 1979, Byrum, Stornetta and Guyenet, 1984, showed that the A_5 area projects directly to the intermediolateral nucleus of the spinal cord. Preliminary esion studied on beagles suggested that the cardiovascular sympathoexcitation initiated by the FN may pass through in area homologous to the classically defined monoamine containing A_5 area (Dahlstrom and Fuxe, 1964 ; Dormer, Andrezik and Person,1986) but not through the PRN (Dormer, Andrezik and Person, 1986). Since, substantial radio-frequency lesions were placed in PRN the FN sympathoexitation was not, abolished. However, using both electrolytic and kainic acid lesion placed in the A_5 region obliterated or severely reduced the FN responses (Dormer, Andrezik and Person,1986). Moreover, Lowey, Mckellar and Saper (1979), reported that neurons of this area produce a pressor response when they are stimulated electrically. Nevertheless, the A_5 area does receive a short-latency excitatory input after electrical stimulation of the FN, as shown by electrophysiological recordings from beagles (Ruggiero, et al., 1977).

However,some authors implicate the C_1 (rostral ventrolateral medulla) (RVLM) "glycine sensitive" area is a relay nucleus mediating blood pressure control. These bulbospinal neuron within the rostral ventrolateral medulla neurons are crucial for tonic vasomotor control (Ross, et al., 1984 Mcallen, 1985). Ross, et al., 1983 reported thatthe C_1 areas exert a powerful excitatory control over the activity of preganglionic neurons of the cord and the pathway from

these neurons give rise to a direct and anatomically selective innervation of regions of the intermediolateral cell column of the thoracic spinal cord, the origin of the sympathetic preganglionic neurons (Bosbaum, Clanton and Fields, 1978 ; Ross, et al., 1983 ; ; Ross, et al., 1984).

Electrical stimulation of C_1 region elevates ABP and HR (Ross, et al., 1983) and stimulation of this area with L-glutamate, which excites only neuronal perikarya, produces cardiovascular effects comparable in magnitude to those produced by electrical stimulation (Ross, et al., 1983) whereas its destruction decreases in resting ABP (Guretzenstein and Silver, 1974 ; Dampney and moon, 1980 ; Dampney, et al., 1982). Moreover, electrolytic lesion in RVLM blocked the FN cardiovascular response (Dormer, et al., 1986 ; Chida, ladecola and Reis, 1990) and inactivating neuron of this area : specifically, that tropically applied glycine (Mcallen, 1985) or radio-Frequency lesions (Mcallen, 1985 ; Dormer, et al., 1989) can block the pressor response to electrical stimulation of the FN (Mcallen, 1985) and Kainate surface lesions, the response was substantially reduced but not abolished (Dormer, et al., 1989).

However, very little is known of the pathways and neural mechanism which mediate the cerebellar influence on cardiovascular functions and there is no ducumentation about the role of the FN in mediating cardiolvascular responses in tree shrew. Therefore, the cardiovascular responses produced by fastigial stimulation and lesion of the tree shrew have been investigated in this study.