Effect of Electrical Stimulation of the Spinal Cord on Pressor Response in the Cat[1]

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=국문초록=

고양이 척수의 전기적 자극에 의한 심맥관 반응

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전기적 자극법은 심맥관계기능의 신경성조절을 이해하기위해 널리 이용되는 방법이며, 일반적으로 중추신경에는 고빈도, 말초신경에서는 저빈도 자극에 의해 최대반응이 유발된다고 알려지고 있으며, 이는 흥분파의 빈도가 말초로 내려오며 감소되기 때문이라 해석되고 있다. 또한편 신경계의 어떤 부위에서건 자극빈도가 어느 한계를 넘으면 유발된 반응은 유지되지를 못하고 감쇠소실되는 것으로 이는 주로 시냅스간 흥분파전달능 부전에 기인될 것이라고 믿어지고있다. 그러나 고위주추계와 말초를 연결하고 있는 척수에 있어서는 아직 최적전기적 자극조건도 분명히 알려져 있지 않을 뿐 아니라 이 부위에서도 고빈도자극시에 반응이 어느 정도 감쇠하는지에 대한 보고가 없기에 이를 추구코자 저자는 고양이의 상부경수를 연수와 연결부에서 완전 절단하기 전후 여러가지 자극조건으로 자극하여 몇가지 결론을 얻었기에 보고하는 바이다.

1) 연수와 연결부에서 완전절단을 하기 전에는 경수(C_1~C_2)의 백질, 회백질의 여러부위에서 심맥관반응이 유발되었으나 절단 후에는 백질중의 단 두부위(좌 2~3 mm, 배면으로 부터 0.3~1.0 mm 및 2.5~3.5 mm)에만 반응이 유발되었으며, 이 두 부위는 심맥관계기능을 지배조절하는 원심성 섬유의 통로라고 사료되었다.

2) 최대반응은 자극조건(빈도 자극파지속시간 강도) 100/sec-1 mesc-3V 및 20/sec-3 msec-3V 에서, 최장지속반응은 20/sec-3 msec 에서 유발되었으므로, 후자가 척수부에 있어 심맥관계반응을 유발키 위한 최적자극조건으로 생각된다.

3) 자극빈도 20/sec 이하에서 반응유지가 잘된다는 결과는 생리적 조건하에서 척수를 통과하는 흥분파의 빈도가 20/sec 를 넘지 않을 것이란 것을 시사한다.

4) 반응지속정도는 최초의 최대반응의 반으로 감쇠되기까지 소요되는시간 즉 50% 반응감쇠시간으로 표시하였으며, 척수에서는 대뇌피질 및 간뇌에서보다 심맥관계반응의 50% 반응감쇠시간이 현저히 긴 것을 알 수 있었다.

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Electrical stimulation was carried out in the left half of the C_1~C_2 segment of the spinal cord of 40 cats, sixteen of which had total cord transection between the medulla and C_1. Cardiovascular responses were elicited by stimulation of numerous points in both gray and white matter of the cord. However, only two points consistently induced responses after

transection.

These two points (left 2~3mm from medial line and at depth of 0.3~1.0mm and 2.5~3.5mm respectively from the dorsal surface of the cord) are believed to mark descending cardiovascular fibers. Parametric sets of 20/sec-3msec and 100/sec-1msec were found optimal for production of the largest responses while the most sustained responses were associated with 20/sec-3 msec.

Both systolic pressure and heart rate progressively declined from maximum levels attained early in the period of stimulation. The rate of decay in the pressor response was quantitated by calculating 50% response decay time as the time in which response progressively declincd to 50% of the maximum respons. The average repsponse decay rate from spinal cord was compared with that reported during cerebral cortex and hypothalamus stimulation.

As a means of understanding nervous control of cardiovascular system, extensive stimulation studies have been carried out at various levels of the neuraxis. Investigators have reported that widely varying stimulation parameters are required for elicitation of cardiovascular responses from different structures with in the central nervous system.

For maximum pressor and cardioaccelerator responses, higher stimulation frequencies are generally thought to be required for intracranial stimulation while lower frequencies are necessary at the sympathetic outflow. During cortical, hypothalamic and medullary stimulation, parameters of 100/sec-1 msec have been more frequently employed[1,2,18] while 20~10/sec and 10~5 msec are preferred for stimulation of the peripheral sympathetic ganglia and nerves[10,15,16]. Bronk et al[4] observed that impulses originating from the hypothalamus show reduced frequency somewhere between the hypothalamus and preganglionic nerves.

However, there is relatively little information on the optimal stimulation parameters for the descending cardiovascular fibers in the spinal cord.

In order to locate vasomotor and vesicomotor pathways in the cervico-thoracic segments of the spinal cord, Kerr and Alexander[13] employed parameters of 60/sec-2 msec. Optimal stimulation parameters for maintenance of long sustained elevations in pressure and cardioacceleration are also essentialy unknown.

On the other hand, it has been reported often that during prologed electrical stimulation of nervous structures, ensuing cardiovascular responses are rarely prolonged despite continuous application of the stimulating current.

Such progressive decline in response is often associated with fatigue, and is well known during cortical [8,12], hypothalamic[3,6,17], and peripheral sympathetic nerve [10,16] stimulation.

In the latter, response decay is sometimes attributed to synaptic transmission failure related to high frequency stimulation. There is little or no information concerning optimal stimulation parameters or cardiovascular response decay during electrical stimulation of the spinal cord. Since this is the site of at least one, and perhaps multiple synaptic stations in descending cardiovascular pathways, it is conceivable that such connections serveas step-down frequency converters.

Therefore the porposes of the present study were 1) to establish optimal stimulation parameters for elicitation of maximum cardiovascular responses from the descending autonomic fiber in the cervical spinal cord as well as the determination of those necessary for prolonged maintenance of such responses, 2) to learn whether comparable response decay phenomenon occur during spinal cord stimulation and 3) to quantitate and compare such decay rates with those known to characterize responses elicited from the cerebral cortex, hypothalamus and stellate ganglia.

Material and Method

Experiments were carried out in 40 cats of either sex weighing 2~3.5kg. After premedication with 1mg/kg of Phencyclidine hydrochloride (sernylan), all animals were anesthetized with alpha chloralose(30mg/kg) and maintained on positive pressure respiration. All animals were given 0.8mg/kg of atropine every two hours for vagal blockade and 0.05 mg/kg of decamethonium bromide(syncurine) every 30 to 60 minutes to prevent motor mvements. Two points in the left half of cervical spinal cord (between C_1 and

C_2 segments, 2~3 mm left from midline, and at a depth of 0.3~1.0 mm and 2.5~3.5 mm respectively from dorsal surface of the spinal cord) were stimulated by means of electrodes positioned stereotaxically. Care was exercised to maintain the longitudinal axis of the spinal cord so that electrodes penetrated the cord perpendicularly. This was achieved by fixing animals on an animal board adjusted to the stereotaxic apparatus. Concentric bipolar electrodes consisted of 22 gauge hypodermic needle tubing as reference, with teflon insulated nichrome wire fitted snugly as the active electrode. Integrity of insulation was tested routinely.

In 16 of these animals the spinal cord was stimulated before and after complete transection at C_1 in order to identify descending sympathetic pathways. Approximately 20 minutes after rapid hemisection, the remaining half of the cord was slowly cut over an additional 10~20 minutes. Throughout the entire transection period, sympathetic tonus was increased by the continuous stimulation of cervical segment of the spinal cord. In order to prevent bleeding the cut area was tamponed with a thin piece of gelform, and of course, heparin was not used for flushing of the carotid artery catheter until transection was completed.

Stimulation parameters included rectangular pulses of 1, 3, 5 msec duration, frequeneies of 10, 20, 100/sec and intensity of 2~5 volts (0.3~0.8m. A). Squarl wave stimulation pulses were delivered from a Grass model S5 stimulator.

Actual stimulating voltage was read from a cathode ray oscilloscope, while instantaneous currents were ascertained by measuring the IR drop across a 100 ohm resistor with an identical oscilloscope. Total duration of the stimulation period varied from 5 to 60 minutes. Mean arterial and pulse pressures were recorded from the carotid artery with a Statham P23Db transducer while heart rate was continuously registered by an integrating cardiotachometer[14] All recordings were made on a Grass model 7 polygraph. At the end of each experiment electrolytic lesions were made in the stimulated area by means of a Grass model LM3 lesion maker. After fixation of this segment of the cord with 10% formalin, serial sections were made and stained with hematoxyline-eosine to identify precty precise position of the electrodes. The magnitude of responses was represented as the initial maximum peak attained during stimulation. In order to compare maintenance or decay rate of responses, the 50% response decay time was calculated as the time required for responses to fall to 50% of the maximum elevation.

Result

With spinal cord intact, cardiovascular responses were elicited from electrical stimulation of numerous points in both white and grey matter of the C_1~C_2 segments of the cord, while only two points consistently showed good pressor and cardiac rate responses after total transection between the medula oblongata and the first cervical segment. These two points are considered to be sites of descending cardiovascular sympathetic fibers, and are located 2~3mm left from midline and at a depth of 0.3~1.0mm and 2.5~3.5 mm respectively from the dorsal surface of the spinal cord. For convenience of description, one (depth 0.3~1.0 mm) will be called the dorsal point and the other (depth 2.5~3.5 mm) the ventral point.

Typical responses to stimulation at different frequencies are shown in Figure 1. Results of stimulation in the dorsal and ventral points before and after transection are summarized in Tables 1 and 2.

Before transection, pressor responses from both dorsal and ventral points generally increased with stimulation frequency. Pressor responses were smallest with 10/sec and largest with 100/sec. Even with 20/sec, however, the magnitude of pressor response was as large as that induced with 100/sec when pulse duration was 3 msec. Within stimulation intensity range used in the experiment pressor response also increased with greater stimulus intensity. Mean blood pressure dropped, on average, from 120 mmHg to 80mmHg during spinal transection.

After cord transection, however, responses were remarkably decreased especially when low frequency stimulation was employed. Pressor responses to various combination of stimulus parameter could be divided into two groups, according to their magnitude, Large responsces (58~81mmHg) were elicited by 100/sec-1

Table 1. Changes in mean arterial pressure, heart rate, 50 response decay times during stimulation of the dorsal spot in the cervical spinal cord(Depth 0.3~1.0 mm) of the atropinized cats with variouse stimulation parameters.

LOCATION Left:2~3 mm Depth:0.3~1.0 mm	PARAMETER cps-msec-Volt	△BP++ (MEAN±SE)+ mmHg	50% RESP. DECAY (MEAN±SE) Sec.	△HR+++ (MEAN±SE) Beat/min.
BEFORE TRANSECTION	100~1~2.0	74±4.4	290±38	20±2.5
	20~5~2.3	70±10	900±356	19±2.2
	20±3~2.5	88±12	860±174	18±2.6
	20~1~2.1	60±4.8	800±203	19±4.0
	10~5~2.5	65±8.1	810±127	13±1.0
	10~1~2.2	58±7.1	960±223	17±3.2
AFTER TRANSECTION	100~1~4.2	58±8.8	150±26	22±5.3
	20~5~4.3	66±5.0	530±104	17±1.8
	20~3~4.4	58±6.1	620±110	19±2.5
	20~1~4.7	36±4.3	680±104	17±1.6
	10~5~4.2	38±10	440±102	10±1.0
	10~1~5.0	47±27	500±16	.....

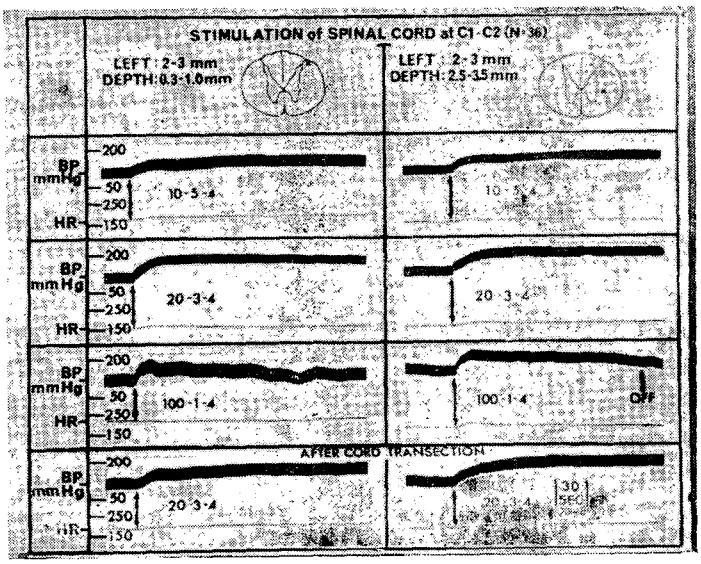
+SE=Standard Error
++△BP=Change in the mean arterial pressure
+++△HR=Change in the heart rate

Table 2. Changes in mean arterial pressure, heart rate, and 50% response decay times during stimulation of the ventral spot in the cervical spinal cord (Depth 2.5~3.5 mm) of the atropinized cats with various stimulation parameters.

LOCATION Left:2~3 mm Depth:2.5~3.5 mm	PARAMETER cps-msec-Volt	△BP++ (MEAN±SE)+ mmHg	50% RESP. DECAY (MEAN±SE) Sec.	△HR+++ (MEAN±SE) Beat/min.
BEFORE TRANSECTION	100~1~2.6	81±4.3	310±33	23±2.4
	20~5~2.6	73±10	1120±219	.....
	20~3~2.9	85±7.5	2240±316	23±5.0
	20~1~2.6	71±4.1	1110±90	22±3.9
	10~5~2.8	65±6.5	1150±170	15±3.3
	10~1~2.9	64±6.4	1300±149	14±2.4
AFTER TRANSECTION	100~1~4.4	63±11	140±44	26±5.5
	20~5~4.5	81±6.5	560±96	25±2.9
	20~3~4.6	80±6.5	730±134	25±2.0
	20~1~50	49±5.5	550±139	18±2.7
	10~5~5.0	41~5.8	480±114	20±1.9
	10~1~5.0	38±6.9	560±133	19±2.9

+SE=Standard Error
++△BP=Change in the mean arterial pressure
+++△HR=Change in the heart rate

msec, 20/sec-5 msec and 20/sec-3 sec while smaller responses (36~49 mmHg) were induced with 20/sec-1msec. The pressor responses were maintained for the shortest period of time during stimulation with 100/sec-1 msec, the 50% response decay time(50% RDT) being approximately 300 seconds in both dorsal and ventral points. In other words response declined to 50% of maximum peak response in 5 minutes. Regar-



[Fig. 1]

dless of the duration of the stimulating pulses, however, the maintenance of pressor responses were almost identical at stimulation frequencies less than 20/sec in both dorsal and ventral points. While stimulating the dorsal point, respones were maintained approximately three times as long as those induced by stimulus parameters of 100/sec-1msec(50% RDT were in the range of 800~1000sec).

In the ventral point, pressor responses were sustained approximately four times longer than those obtained with 100/sec-1msec (50% RDT was around 2200 sec). In two ainmals the ventral point was stimulated with 20/sec-3 msec for more than one hour resulting in several hours for the 50% RDT. In spinal animals, pressor responses were less well maintained, 50% RDT being reduced to approximately half those obtained before transection. When the spinal cord was stimulated at frequencies above 30/sec, responses declined almost as rapidly as those elicited by frequency of 100/sec. The 50% RDT did not seem to be affected by activation of the vagal system whereas heart rate responses generally were affected. Cardiac acceleration was observed in approximately 75% of the experiments and were generally larger during excitation with higher stimulation frequencies both before and after transection. In spinal animals larger stimulation intensities were required for a comparable magnitude of both cardiac rate and blood pressure responses. After termination of stimulation, blood pressure and heart rate returned promptly to prestimulation level in a majority of animals. In approximately 40% of the experiments, blood pressure and heart rate fell below control levels before recovery and cardiac arrythmias were also observed especially when stimulation intensities were strong.

Discussion

In acute experiments the optimal stimulation parameters are generally associated with parametric sets which involve minimum total energy. Taking this factor into account, optimal stimulation parameters for acute cardiovascular responses from descending sympathetic fibers in the cervical spinal cord appears to be 100/sec-1msec or 20/sec-3msec. No reversal of

pressor to depressor response was observed when stimulation frequency was switched from high to low.

As in the peripheral sympathetic nerve, maintenance of pressor responses was predominantly frequency-dependent, response decay rate being almost identical with all frequencies lower than 20/sec. Considering both magnitude and duration of sustained responses, therefore, 20/sec-3 msec appears to be most optimal parameters for prolonged cardiovascular responses from the cervical spinal cord. Identical response characteristics have been observed during hypothalamic stimulation (unpublished data) except that lower stimulation intensity was required from the spinal cord.

This might be explained by the fact that neural elements are more densely packed or that excitation thersholds are lower in the spinal cord. In comparable studies of stellate ganglion stimulation, maximum responses were induced by 20/sec-5msec whereas 10/sec-5msec was best for prolonged responses(unpublished data).

Comparison of response characteristics of these three levels of the nervous system permits the interesting speculation that there is no frepuency conversion between the hypothalamus and the cervical spinal cord, whereas impulse frequency is reduced between the cervical spinal cord and the stellate ganglion. These studies also suggest that physiological impulse rates in descending cardiovascular sympathetic fibers are low (20/sec or less).

Two points (dorsal and ventral) from which responses could be elicited after total transection are believed to mark descending autonomic fibers mediation cardiovascular responses.

The ventral point appears to coincide with tracts which Foerster[9] found in man while the dorsal point seems to be that which Kerr and Alexander[13] described in low cervical and high thoracic segments in cats and monkeys. After transection there was a marked depression in neural excitability and control blood pressure also dropped average of 30mmHg (from 110 mmHg to 80mmHg). This might be explained by varying degree of anoxia, or decreased metabolism resulting from transection since conduction of impulses along nerve fibers and acsoss synapses are known to be greatly affected by anoxia. Removal of facilitatory effects from higher levels of the central nervous system might also be responsible.

The present study shows that response decay phenomenon also exists during spinal cord stimulation. Compared to cerebral cortex[8,12] and hypothalamus [3,6,17], it is clear that the spinal cord is the best location for the induction of prolonged cardiovascular responses in the various levels of the neuroaxis. The possible explations for response decay may include some combination of the following: 1) tissue damage, 2) defects in stimulating electrodes, 3) Inhibition, 4) exhaustion of effects, 5) reflex inhibition, 6) accumulation of vasodilator substances, 7) inhibitory effect of adrenal secretion on synaptic transmission, 8) exhaustion of nervous tissue and 9) failure in synaptic transmission.

However, at present there is much evidence[5,10,11] that the most reasonable explanations for response decay are 1) failure in excitation of nervous structure probably due to markedly accentuated hyperpolarization which impose a "recovery debt" on the nervous and 2) failure in synaptic transmission probably due to exhaustion of transmitter release mechanism and desensitization of transmitter receptors.

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