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TRANQUILIZING EFFECT OF N-MONOMETHYLTRYPTAMINE PREPARED FROM *ABRUS PRECATORIUS* ON THE TRIGEMINAL NERVOUS SYSTEM IN CAT

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ABSTRACT

Chin-Yih Wu and Si-Chih Chen (1973). *Tranquilizing effect of N-monomethyltryptamine prepared from* Abrus Precatorius *on the Trigeminal Nervous System in Cat.* Bull. Inst. Zool., Academia Sinica, **13**(1): 1-13. The effect of an i.v. injection of N-monomethyltryptamine (NMT) compared with 5-hydroxytryptamine (5-HT) and norepinephrine (NE), on neuron circuit of masseteric monosynaptic reflex were investigated electrophysiologically.

1. Stimulation of trigeminal mesencephalic nucleus produces a potential which consists of 2 peaks on the masseteric nerve. The first peak is an antidromic and the second peak is an orthodromic potential.

2. NMT and 5-HT exerted a profound depression of the orthodromic potential of the masseteric monosynaptic reflex recorded along masseteric nerve in response to stimulation of trigeminal mesencephalic nucleus. However, administration of NE, depressed both spike components of the masseteric monosynaptic reflex.

3. The time course of NMT and 5-HT induced depression of the masseteric monosynaptic reflex were very similar. When the dose applied was increased, the depression was much profound and only partial recovery could be found.

4. The orthodromic monosynaptic spike of trigeminal motor nucleus induced by stimulation of ipsilateral mesencephalic nucleus was depressed by administration of NMT, 5-HT and NE. However, the antidromic spike evoked by stimulation of trigeminal motor nucleus recorded on mesencephalic nucleus was only affected by NE.

5. NMT depressed the electrically evoked orthodromic potential of masseteric motor nucleus.

6. NMT depressed the last peak of the triphasic potential evoked by stimulation of masseteric nerve recorded on trigeminal Gasserian ganglion. The two former peaks remainded un- or little changed.

Evidence presented here indicates that:

I. Both 5-HT and NE may be inhibitory transmitters on masseteric motor nucleus, but only NE has this possibility on trigeminal mesencephalic nucleus.

II. NMT mimics 5-HT at post-synaptic sites in the CNS.

N-monomethyltryptamine (NMT) was prepared by decarboxylation of N-monomethyltryptophan and isolated from Abrus precatorius growing wild in the southern part of Taiwan[10,31,34,38].

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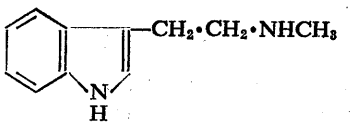
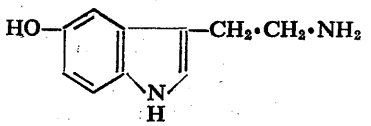
Probably due to the similarity with 5-hydroxytryptamine (serotonin, 5-HT) in structure containing an indole nucleus (Table 1), they were found to possess tranquilizing action on human and other animals[10,11,22,39]. In a recent study of tranquilizing effects of NMT on the neo-, paleo- and archicortex, as compared with 5-HT, in chronic electrode-implanted cats, NMT has a calmative action which might be caused by lowered activation of the amygdaloidal nucleus[39].

TABLE 1



NMT



5-HT

However, in lower brain stem, the possible mechanism of this drug is still unknown.

In 1948, using histological methods, Szentágothai[27] described a monosynaptic reflex arc in the brain stem, i.e. a stretch reflex arc of the masticatory muscles and he concluded that it was excitatory in nature. This was confirmed electrophysiologically by McIntyre[19] and others[7,16,20,21,40].

With the development of histochemical and sensitive biochemical techniques for the localization of monoamines, it has become increasingly evident that these substances may function as synaptic transmitters in the central nervous system. According to Fuxe[12] and Sladek[24], nerve terminals which contain nor-epinephrine (NE) or 5-HT has been observed in trigeminal motor nucleus, but only adrenergic nerve fibers were found in trigeminal mesencephalic nucleus. These terminals make closely contact with the cell bodies and processes of the nuclei.

NE and 5-HT applied iontophoretically from multiple-barrelled micropipettes depressing spinal motoneurones[9,22,23,35]. Because of the anatomical similarity between spinal motoneurones and trigeminal motor nucleus[12,27], similar results of the effect of NE and 5-HT on trigeminal motor nucleus might be expected. In the major part of this investigation, attempt was made to find out the possible mechanisms of the tranquilizing action of NMT, compared with 5-HT, on the trigeminal neurone circuit. In some parts of this investigation, the effects of monoamines on the trigeminal mesencephalic and the masseteric motor nucleus were studied in order to establish whether their actions on nerve cells are compatible with a transmitter function[32,33], and this may reveal some of the possible mechanisms of the tranquilizing actions of NMT in the central nervous system.

MATERIALS AND METHODS

Experiments were performed on twelve cats. Tracheotomy and cannulation of the femoral vein were performed under ether inhalation. Then anesthesia was maintained by repeated injection of thiopental sodium (5mg/kg) every 15 minutes, throught the period of surgical operation.

The preparation of ipsilateral masseteric nerve and the general experimental arrangements have been described in previous investigations on jaw-clossing reflex[15,21,40]. The schematic representation of experimental setup is shown in Fig. 1.

NMT, 5-HT and NE were dissolved into 0.9% NaCl solution (the concentration of NMT or 5-HT was 2 mg/ml, and that of NE was 20 μg/ml) then applied intravenously from femoral vein. When NE was applied, the injection rate was kept approximately at .4 μg/kg/min to avoid any significant cardiovascular change[17].

Responses were recorded with a contineous recording camera on a cathode ray oscilloscope by superimposed 6-10 responses, and usually the submaximum stimulation was applied.

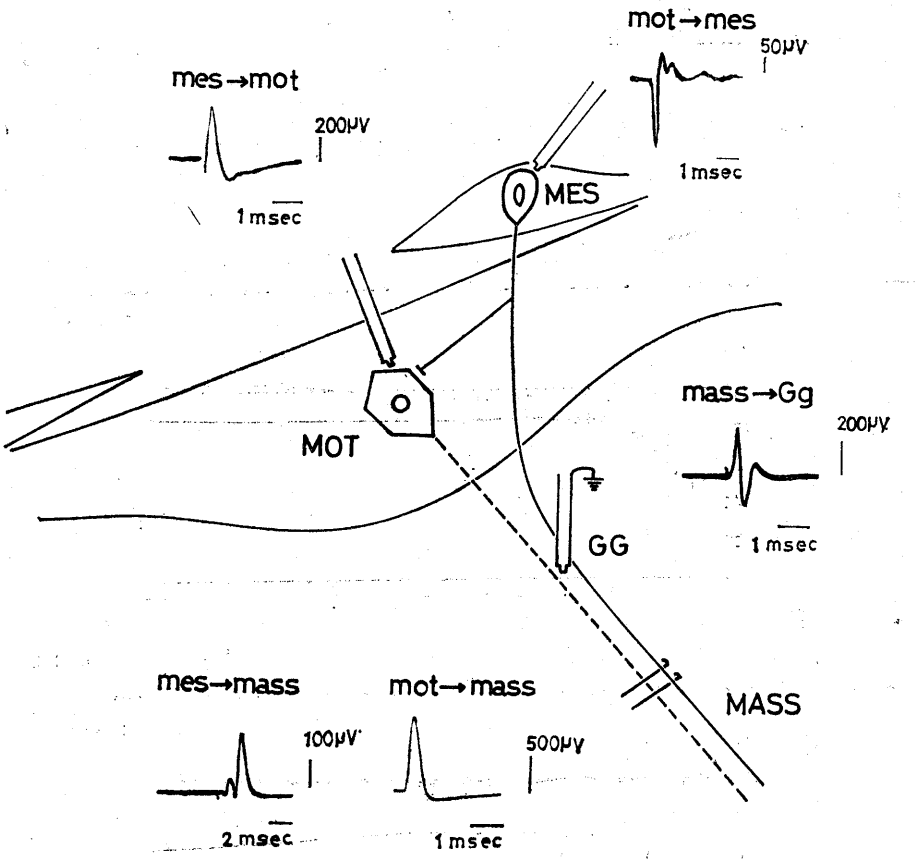
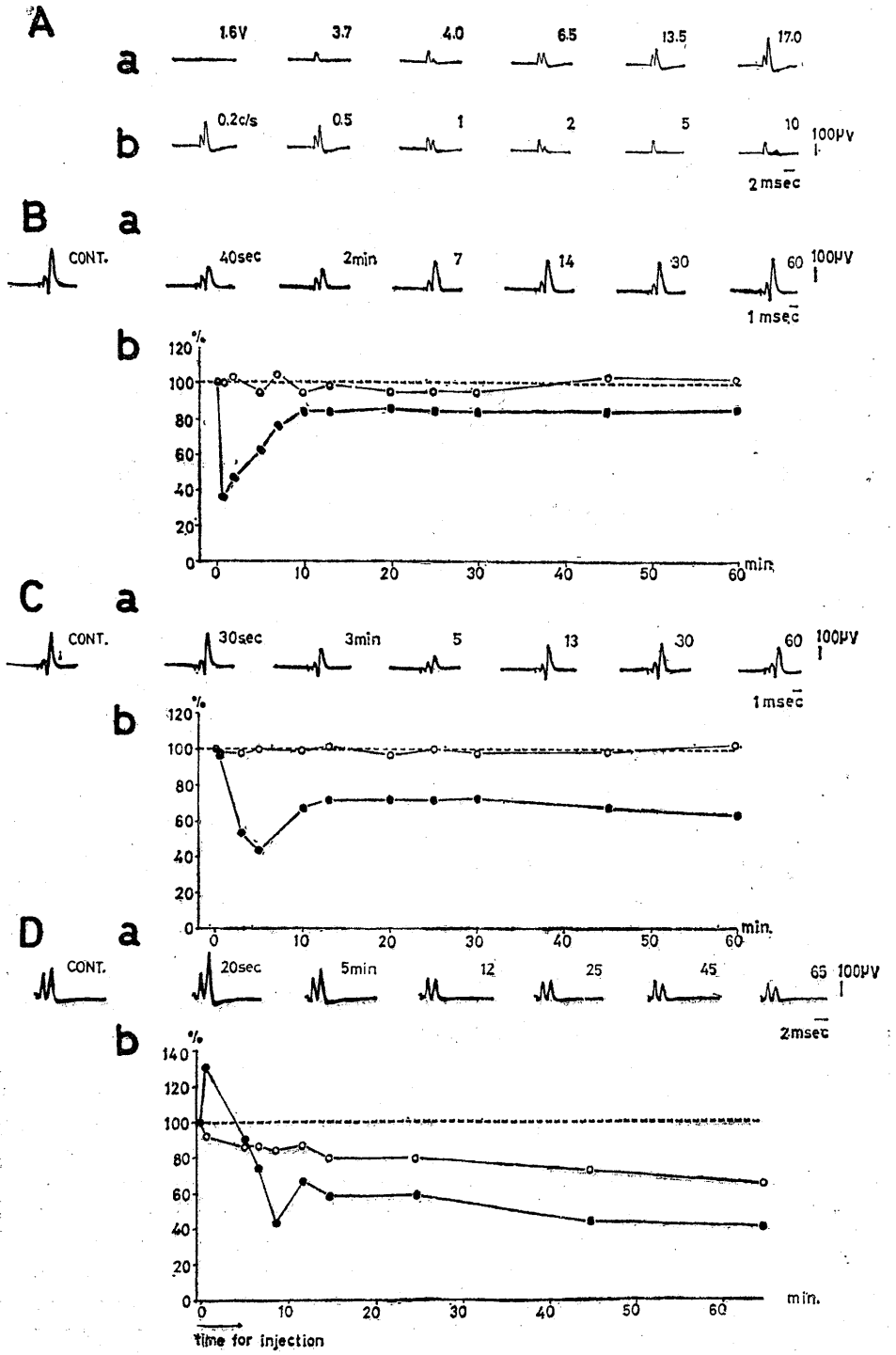


Fig. 1. Schematic representation of experimental setup. Concentric needle electrodes were used for stimulation or recording except that used in masseteric nerve where bipolar silver wire electrode was used. The core of the concentric needle electrode in Gasserian ganglion was used for monopolar recording. Abbrevitions: MASS, mass—masseteric nerve; GG, Gg—Gasserian ganglion; MES, mes—trigeminal mesencephalic nucleus; MOT, mot—trigeminal motor nucleus. Efferent fibers from motor nucleus are shown by broken lines. The abbreviations on the bilateral sides of arrows indicate the locations of stimulation and recording respectively, and their responses, time bases and calibrations are shown.

RESULT

1. Effect of NMT, 5-HT and NE on the masseteric monosynaptic reflex.

Stimulation of the trigeminal mesencephalic nucleus elicited in the masseteric nerve a monosynaptic reflex[16,19,25,40]. The evoked potential consisted of two peaks, an initial small spike and a following large one (Fig. 2Aa). The latency of the onset of the first spike and second spike were about 0.74±0.02 msec and 1.59±0.03 msec, respectively. The second spike was susceptibly to repetitive stimulation. With the increase of repeated stimulation the second spike was gradually suppressed (Fig. 2Ab), Stimulus frequency of 5/sec completely abolished the second spike. However the first spike was not altered even after changes in stimulus frequency up to 100/sec. The first


A
a
1.6V
3.7
4.0
6.5
13.5
17.0
b
0.2c/s
0.5
1
2
5
10
100μV
2msec
B
a
CONT.
40sec
2min
7
14
30
60
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1msec
b
%
120
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80
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40
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0
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CONT.
30sec
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140
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100
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20
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min.
time for injection

Fig. 2. The effect of NMT, 5-HT and NE on ipsilateral masseteric monosynaptic reflex. A: Masseteric monosynaptic reflex evoked by stimulation of mesencephalic nucleus. Aa: Directly evoked antidromic spike and monosynaptically evoked orthodromic response. Stimulation: left trigeminal mesencephalic nucleus (0.2/sec, 0.1 msec); applied intensities expressed at right upside in each record. Record: masseteric nerve. Ab: Effect of repetitive stimulation (0.1 msec, 16 V) on masseteric monosynaptic reflex. Applied frequencies expressed at right upside in each record. All are 10 sweeps superimposed. B, C, D: Effects of NMT (2mg/kg), 5-HT (2 mg/kg) and NE (22 μg/kg) on masseteric monosynaptic reflex, respectively. Ba, Ca, Da: Sample, records. Stimulation: left mesencephalic nucleus 0.2/sec, 0.1 msec, 17.3 V for B, C, 20.3 V for D. Record: ipsilateral masseteric nerve. Bb, Cb, Db: Time courses after drugs administration. Abscissa: time elapsed. Ordinate: amplitude of antidromic (empty circle) and orthodromic (filled circle) potential (control: 100%). All are 6 superimposed.

spike which has a brief latency, and has been due to impulses propagated antidromically down the masseteric nerve. The second spike with longer latency and susceptible to change in stimulus frequency were an orthodromically evoked monosynaptically reflex via the motor nucleus[8,16,20,27,40]. The orthodromic spike potential increased almost linearly with the stimulus intensity up to 10 times the threshold ($\times$T) of mesencephalic nucleus excitation, but the antidromic potential reached a maximum at 2.5$\times$T.

30–50 sec after the application of NMT (2 mg/kg) or 5-HT (2 mg/kg) the second peak was depressed very significantly, although the antidromic potential remained intact (Fig. 2Bab, Cab). The depressive effect reached maximum within 1–5 min after the drug administration. Recovery was found after 10 minutes. Whereas administration of NE (22 μg/kg) by i. v. injection resulted the depression of both the components. But before this depressive effect was found, the amplitude of the orthodromic potential of the reflex had increased abruptly within the first 20 sec, then decline quickly as that of the antidromic potential did (Fig. 2Dab). There exists a linear relationship between the depressive effect and time elapsed. 60 minutes after NE injection, even partial recovery could not be found, orthodromic potential was depressed more profoundly than antidromic potential.

II. Time course of the effect of NMT, 5-HT at different doses on the masseteric monosynaptic reflex.

An i. v. injection of NMT (2 mg/kg) or 5-HT (2 mg/kg) induced a prolonged depresseion of the masseteric monosynaptic reflex (Fig. 3). The depression commenced at about 30 sec after administration but the most intensive depression occurred at about 10 minutes later. At higher doses (NMT: 5 mg/kg, 5-HT: 4 mg/kg) a complete depression was usually obtained. The depression continued to about 120 minutes, then approaching the control value gradually. It was more profound and longer when the dose of NMT or applied 5-HT was increased. Recovery from the depression was shown, but incomplete. At same dose, exerted 5-HT much profound effect than NMT did. When the dose applied was more than 5 mg/kg (NMT) or 4 mg/kg (5-HT), the antidromic potential was also depressed. This was mostly due to a non-specific action between drug applied and the receptor sites[4,5,6,36].

III. Depressive effects induced by NMT, 5-HT and NE on synaptically evoked potential of masseteric motor nucleus.

The masseteric motor nucleus responded to stimulation of the trigeminal mesencephalic nucleus with a synaptic potential[20]. The latency of this potential was about 0.70$\pm$0.02 msec. After application of NMT (4 mg/kg), 5-HT (2 mg/kg) or NE (40 μg/kg), all these potentials were depressed in 30–50 sec. The time courses of these depressive effects were similar with that of masseteric monosynaptic reflex by NMT, 5-HT or NE respectively (Fig. 4A, B, C. lower record).

A close correlation between the NMT, 5-HT or NE induced inhibition of monosynaptic spikes in masseteric motor nucleus and the depression of massteric monosynaptic reflex was observed

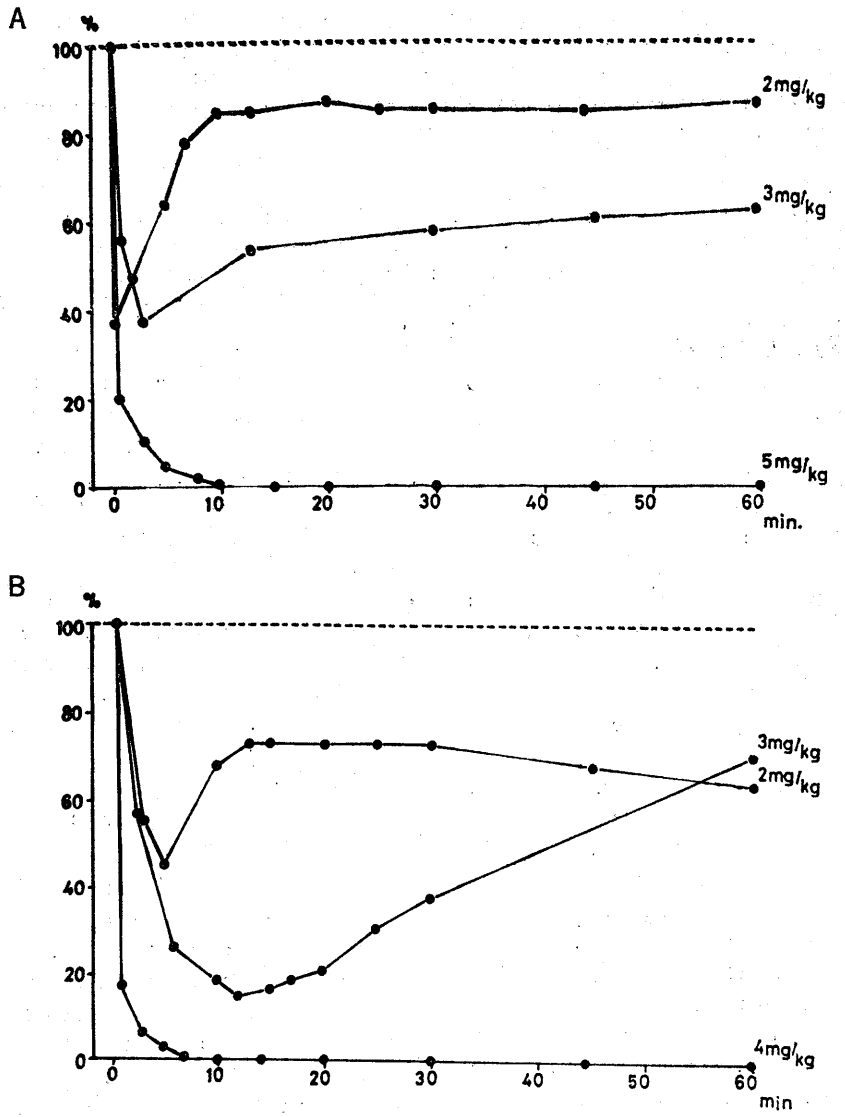

Fig. 3. Time course of the effect of NMT(A), 5-HT(B) at different doses on the masseteric monosynaptic reflex. Abscissa: time in minute. Ordinate: amplitude of orthodromic reflex potential depressed (control: 100%).

and when they were simultaneously recorded. As in Fig. 4, it was shown that when a shock was delivered to the trigeminal mesencephalic nucleus in the depressed phase after the administration of NMT, 5-HT or NE, both the monosynaptic spike and the masseteric reflex were inhibited.

IV. The effect of NMT, 5-HT or NE on antidromic potential of trigeminal mesencephalic nucleus evoked by stimulation of trigeminal motor nucleus.

Stimulation of the trigeminal motor nucleus evoked, in the ipsilateral trigeminal mesence-

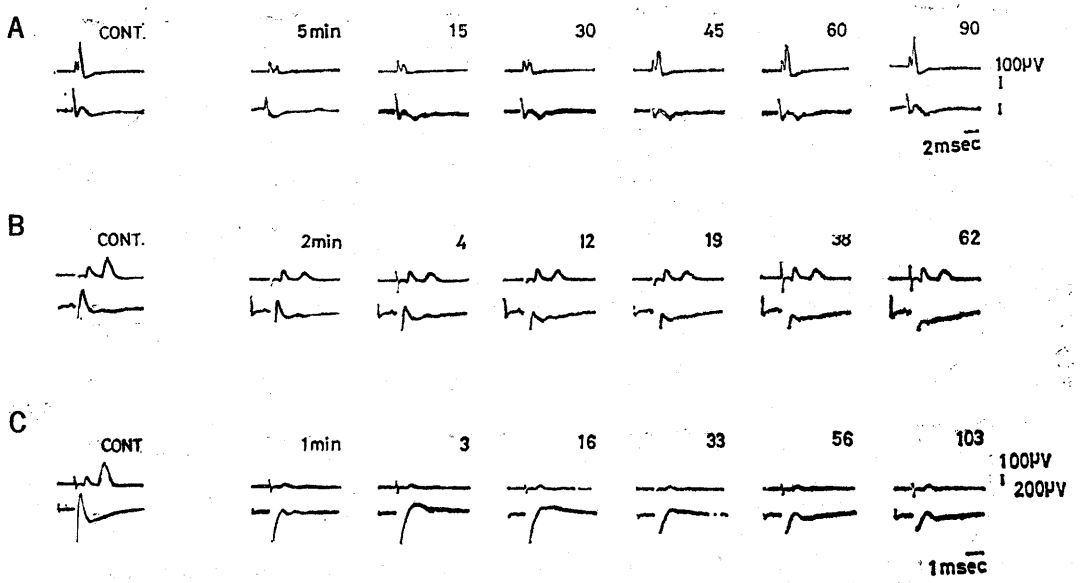

Fig. 4. Effect of NMT, 5-HT and NE on the masseteric reflex and trigeminal motor nucleus. A: NMT 4 mg/kg. Stimulation: Trigeminal mesencephalic nucleus 0.5/sec, 0.1 msec, 25 V. Record: ipsilateral masseteric nerve (upper row) and motor nucleus (lower row). B: 5-HT 2 mg/kg. Stimulation: 0.5/sec, 0.1 msec, 21 V. Record: as A. C: NE 40 μg/kg. Stimulation and Record as B. All are 6 sweeps superimposed. The first record is control. The time elapsed after drug application was expressed at right upside in each record. Time base and calibration in C applies to B. In A, the calibration is applied to upper and lower row.

phalic nucleus, an antidromic spike followed by a rhythmic potential consisting of 2-3 peaks with an brief latency (Fig. 5). The latency of stimulus onset and first peak was about 0.7 msec, and followed by 2 or 3 peaks at 1.8-2 msec intervals. The duration of this antidromic potential was 6-8 msec.

Administration of NMT (2 mg/kg) or 5-HT (3 mg/kg) had no effect on it. However at dose of 20 μg/kg, NE depressed these potentials completely and profoundly (Fig. 5A, B, C).

V. The effect of NMT on evoked orthodromic potential of masseteric motor nucleus.

Stimulation of the trigeminal motor nucleus evoked in the masseteric nerve an orthodromic spike potential. The amplitude of this potential increased almost proportionally with the intensity of stimulus up to 20 times the threshold (×T) of the spike potential. This potential was not altered even after changes in stimulus frequency up to 100/sec (Fig. 6A, B). After application of NMT (4.5 mg/kg), this potential was depressed significantly and profoundly (Fig. 6C).

VI. The effect of NMT on responses in Gasserian ganglion to stimulation of masseteric nerve.

Stimulation of masseteric nerve evoked a triphasic potential in the ipsilateral Gasserian ganglion (Fig. 7A). The first peak was positive followed by an negative potential and then a small positive infection. The latency of the onset of the first negative peak was about 0.16 msec. The amplitude from the first positive to the negative peak increased almost proportionally with the intensity of stimulus up to 2 times the threshold (×T) of the nerve and then reached a quasi-plateau until 4×T (Fig. 7A).

Administration of NMT (3 mg/kg) depressed

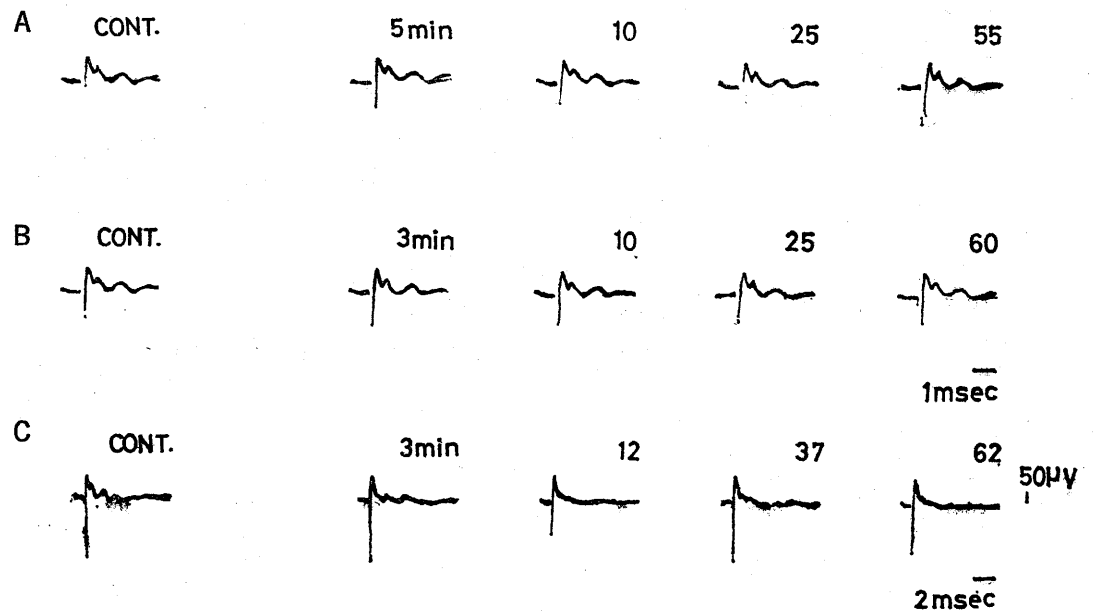

Fig. 5. Effect of NMT, 5-HT and NE on the antidromic potential evoked by stimulation of trigeminal motor nucleus recorded on ipsilateral mesencephalic nucleus. (A: NMT 4 mg/kg, B: 5-HT 3 mg/kg, C: NE 20 μg/kg) Stimulation: left trigeminal motor nucleus (10 V, 0.5/sec, 0.1 msec). Record: left trigeminal mesencephalic nucleus, monopolar recording, postivity shown as upward deflexion, 10 sweeps superimposed. The first record is control. The time elapsed after drug applicaion was expressed at right upside in each record. Time base in B applies to A, B and calibration in C applies to all records in A-C.

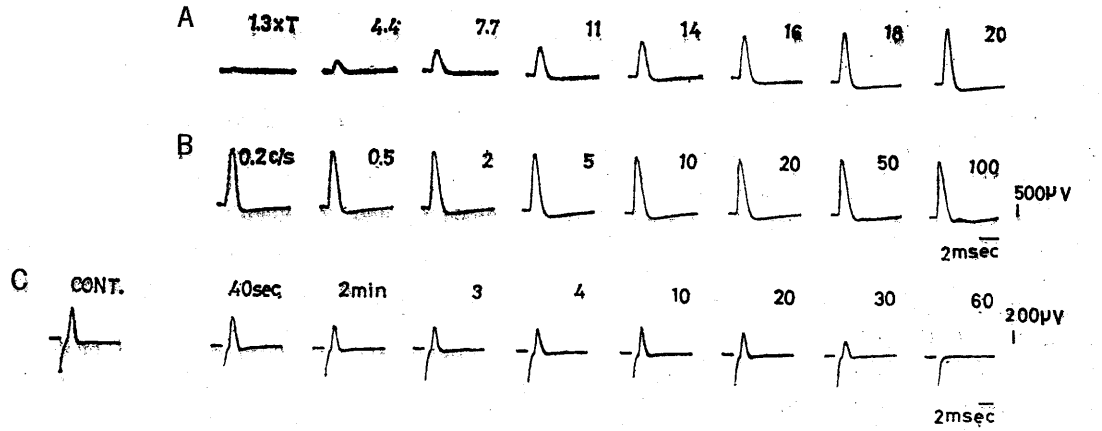

Fig. 6. The depressive effect of NMT on the orthodromic potential of masseteric motor nucleus. A. Orthodromic potential evoked by stimulation of trigeminal motor nucleus. Stimulation: left trigeminal motor nucleus (0.1/sec, 0.01 msec); applied intensities expressed by numerals representing multiples of nerve threshold (×T) in each record. Record: left masseteric nerve. B. Effect of repetitive stimulation (20×T, 0.01 msec) on the orthodromic potential of trigeminal motor nucleus recorded along the masseteric nerve applied frequencies expressed at right upside in each record. C. Effect of NMT on the orthodromic potential of trigeminal motor nucleus recorded along the masseteric nerve. Stimulation: as in A (25 V, 0.1/sec, 0.01 msec). Record: as in A. The first record is control. The time elapsed after NMT (4.5 mg/kg) administration was expressed at right upside in each record. Time base and calibration in B applied in A, B. All records are 10 sweeps superimposed.

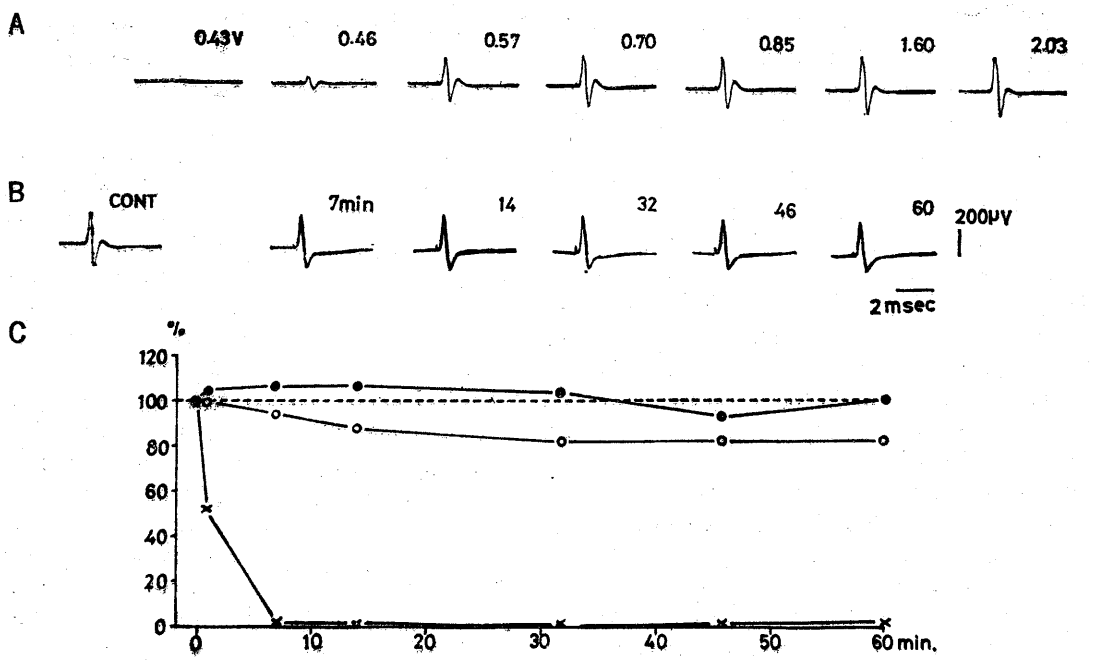

Fig. 7. Effect of NMT on the responses in Gasserian ganglion to stimulation of ipsilateral masseteric nerve. A. Responses in Gasserian ganglion to stimulation of ipsilateral masseteric nerve. Stimulation: left masseteric nerve (0.5/sec, 0.01 msec); applied intensities expressed in each record. Record: left Gasserian ganglion; monopolar recording, positivity shown as upward deflexion. 10 sweep superimposed. B. Effect of NMT (3 mg/kg) on the responses in Gasserian ganglion to stimulation of ipsilateral masseteric nerve. Stimlation: as in A. (0.5/sec, 0.01 msec, 1.25 V) Record: as in A. The first record is control. The time elapsed after NMT application was expressed at right upside in each record. C. Time course of the effect of NMT on the responses in Gasserian ganglion to stimulation of ipsilateral massetic nerve after NMT administration. Abscissa: time in minute. Ordinate: amplitude of each phase between peak and base line. The filled circles, open circles and crossed singns expressed the heights of first, second and third potentials recorded in Gasserian ganglion shown in B (contral: 100%). Time base and calibration in B applied to A, B.

the last component but the second peak was slightly changed and the first one remained intact (Fig. 7B, C). The time course of this depressive effect was similar with that of trigeminal monosynaptic reflex recorded alternatively during the same experiment (Fig. 3A, 3 mg/kg).

DISCUSSION

When drugs are administered intravenously, the presence of diffusional barriers, such as the blood-brain barrier, may creates serious difficulties when attempts are being made to study the pharmacology of centrally located neurones[24]. In addition, because of possible vascular effects peripheral and multiple neural sites of drug action, the interpretation in terms of neuronal mechanisms with the CNS of the systematic administration of these drugs still can not be considered as very persuasive. Further more the depression of potentials generated by many cells are relatively crude methods of assessing alter-

nations in neuronal function. On the other hand, "microiontophoresis" which involve the injection of drugs on to single or small groups of cells from micropipettes are valuable methods for determining the effects of drugs on neurones[23]. However it is impossible to assess whether the sample of neurones tested in a structure is representative of the total population[30]. Because of NMT was found to possess tranquilizing action after systematic administration[10,22,39] and the systematic administration by intravenous injection to a preparation might give us more information on the effects of drugs on a large neuronal pool[30], we decided to apply drugs through the intravenous injection.

We knew that after an intravenous injection of 5-HT or NE, the brain showed comparatively little uptake of these drugs[1,37]. However, in our experiment, in addition to the highly sensitive responses expected when the transmitter react with receptor sites, the time course of the induced depression on the trigeminal masseteric monosynaptic reflex coincident with that of the brain uptake of these drugs[1,37]. After the intravenous injection from femoral vein, the latency of potential changes induced by drugs were about 30–50 sec, but the circulation time elapsed from femoral vein to carotid artery was only about 3.2 sec in cat[26]. Therefore, it was recognized the drugs were reached to CNS already and was most likely that these drugs had direct effects on the nucleus.

However when NE was applied, the amplitude of the orthodromic potential of the masseteric monosynaptic reflex increased abruptly within 20 sec, then decline quickly as that of the antidromic potential did. This change was mostly secondarily due to the cardiovascular effects[9].

The masseteric nerve carries both muscle spindle afferents and axons of masseteric motoneuron[7,19]. Stimulation of masseteric nerve evoked a triphasic potential in the ipsilateral Gasserian ganglion. From the lower threshold and the fast conductivity of the masseteric nerve in our previous reports[21,40] it seems to be that the fibers responsible for yielding the earliest potential were muscle spindle afferents which soma was located in the trigeminal mesencephalic nucleus and the masseteric motor fibers would be represented by the last potential.

Administration of NMT depressed the last components, i. e. decreased the excitability of the masseteric motor nucleus, whereas the two former peaks remained un- or little changed. This was mostly due to the direct selective depressive effect on masseteric motoneurones, not to the blocking effect of drugs on nerve conductivity.

In our experiment, the excitability of the trigeminal motor nucleus was depressed by 5-HT, NMT and NE. This depression was manifested by a reduction or abolition of the excitant effects of trigeminal mescencephalic stimulation. Furthermore, NMT induced depression was intensified by a failure of antidromically propagating spike to invade somas of motor neurons; and by a reduction of the excitant effects of electrical stimulation on trigeminal motor neurons. This depressive effect indicate these compounds act post-synaptically[18], though not necessarity on subsynaptic receptors[9,23].

Although several criteria must be satisfied for transmitter identification. The presence of both NE and 5-HT containing nerve terminals in the trigeminal motor nucleus raises the possibilities that they may in fact be inhibitory transmitters in this nucleus[8,12].

Alternatively, they could be acting by stimulating the release of inhibitory transmitter from presynaptic terminals or on non-synaptic receptors on the postsynaptic membrane. Although difficult to rule out entirely, it is unlikely that these compounds are acting presynaptically and, on the evidence currently available, a post synaptic locus of action must be postulated. NMT, 5-HT had depressed the orthodromic components of the masseteric discharge evoked by stimulation of the mesencephalic nucleus. However, NE depressed both of the components. The failure to observe a depression of excitability of neurons tested may indicate that there is no tryptaminergic receptors in the mesencephalic nucleus. These results correspond well with those of Fuxe[12].

Since in the mesencephalic nucleus only preterminals of adrenergic nerve fibers containing catecholamine were found, and in the trigeminal motor nucleus both adrnergic and tryptaminergic fiber was identified[9,12,32,33].

Difference in the relative sensitivities of trigeminal mesencephalic and motor nucleus to the depressent actions of NE may indicate that in the former nucleus, the adrenergic receptors were fewer than the latter. This was also coincide well with those of Fuxe[12].

The rapidity with which 5-HT, NMT and NE affected transmission at the synapse of masseteric motor neurone suggests that these compounds could have direct effect on these neuron and do not interfere with the synthesis and storage of the excitatory transmitter[4,8].

The time courses of potency with NMT and 5-HT were much similar, compared with that of NE. When NE was applied, the gradual increase and the prolonged action may have been due to the slow attainment of an equilibrium concentration around the neurones and a slow rate of removal respectively. These rates may be determined by factors limiting the rate of diffusion to or from the cell membrane[9,29,30]. Attachment of the monoamines to their receptors on the post-synaptic membrane may increase the permeability of the membrane to ions[8], the resultant change in the conductance of the membrane being directly responsible for the stabilization of the membrane[8,9,14]. Further investigation with intracellular recording techniques and a comparison of the reversal potentials of the drug and synaptically induced inhibitory potentials would be required to provide more direct evidence that these compounds are acting as inhibitory transmitters.

Although after intravenous administration of NMT and 5-HT at the same dose, the latter, showed more profound effect on the masseteric monosynaptic reflex, but the comparative activities of these drugs, when they were applied directly, still remained unknown. Since the influence of the blood-brain barrier on the penetration of each drugs might not be the same[4].

The similarity of the potency of 5-HT and NMT upon cells investigated suggested an identical action upon them. The present observations permit one postulate. That is, tryptamine-like compounds with actions upon the CNS are interfering with the synaptic activity of a transmitter[13,28,32,33]. It is also conceivable that at some central synapses 5-HT is a transmitter[2,36] and consequently the effects produced by intravenous injections of tryptamine derivatives will be complex phenomena depending upon which synapses are affected and whether the compounds mimics the action of the transmitters.

Thus, NMT produced a synaptic inhibition. It seems warranted to propose an empirical correlation between the synaptic inhibition and the behavior observed on administration of NMT to the unanesthetized cat. It is concluded that the tranquilizing action of NMT is mostly due to its serotonin-like action on post-synaptic sites, not to any serotonin-releasing activity[3,33].

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N-monomethyltryptamine 對三叉神經系的鎮靜作用

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N-monomethyltryptamine (NMT) 是由臺灣野生植物鷄母珠 (Abrus precatorius) 所提出者，持有輕度鎮靜作用，其構造式甚與 5-Hydroxytryptamine (Serotonin 5-HT) 相似。玆以貓咬肌單突觸反射弧 (monosynaptic reflex arc) 爲例，以欲解釋其作用機制，結果明瞭 5-HT 對三叉神經運動核具有抑制其興奮性，而 NMT 卽在突觸後位置 (post-synaptie site) 模仿 5-NT 的作用，因而具有抑制作用。