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Dendrobine, an antagonist of β-alanine, taurine and of presynaptic inhibition in the frog spinal cord

Yoshihisa Kudo, Atsuko Tanaka & Kiyoyuki Yamada*

Mitsubishi-Kasei Institute of Life Sciences, Machida, Tokyo 194 and Department of Chemistry*, Nagoya University, Chikusa-ku, Nagoya 464, Japan

1 The effects of dendrobine and nobiline, alkaloids isolated from *Dendrobium nobile*, on the electrical activity and on amino acid-induced depolarizations of primary afferent terminals were tested on the frog isolated spinal cord and were compared with those of picrotoxinin and strychnine.

2 Dendrobine (3×10^{-5} M) caused a slight hyperpolarization in both dorsal and ventral roots and this hyperpolarization was accompanied by the augmentation of the dorsal root potential (DR-DRP) and the ventral root potential and reflex (DR-VRP and DR-VRR). The amplitude of the dorsal root reflex (DR-DRR) however, was reduced significantly. Nobiline (3×10^{-5} M) had no significant effect on either the root potentials or the reflexes.

3 Dendrobine (3×10^{-5} M) reduced the dorsal root potential induced by repetitive antidromic stimulation of ventral root (VR-DRP) as well as diminishing the maximum rate of rise of the dorsal root potential induced by the stimulation of adjacent dorsal roots (DR-DRP), during which time the amplitude of the DR-DRP was seen to be augmented.

4 Dendrobine (3×10^{-5} M) reduced the β-alanine- and taurine-induced depolarizations of primary afferent terminals, while having little effect upon GABA- and glycine-induced depolarizations.

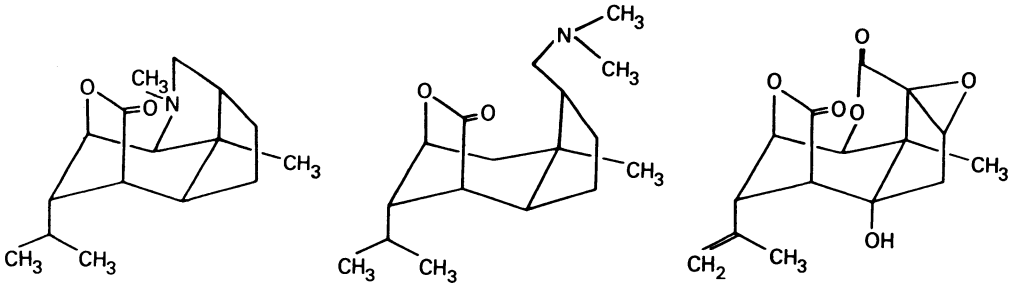
5 Dendrobine (10^{-5} M) reversibly blocked the presynaptic inhibition caused by antidromic conditioning stimulation of the ventral root.

6 These effects of dendrobine were qualitatively similar to those of strychnine but were somewhat different from those of picrotoxinin, a molecule having the same picrotoxane skeleton.

7 The present results are discussed with reference to the likely neurotransmitters involved in presynaptic inhibition in the frog spinal cord, and with respect to the structure-activity relationship of picrotoxane compounds as amino acid antagonists.

Introduction

Dendrobine is an alkaloid isolated from an Orchidaceae plant, *Dendrobium nobile*, which is a constituent of the Chinese medicinal herb 'Chin-Shin-Hu' (Suzuki & Keimatsu, 1932). The chemical structure of the compound, identified as being an alkaloid with a picrotoxane skeleton (Figure 1), was deter-



Dendrobine Nobiline Picrotoxinin

Figure 1 Chemical structures of dendrobine, nobiline and picrotoxinin.

mined simulataneously by three separate groups of Japanese chemists (Inubushi, Sasaki, Tsuda, Yasui, Konita, Matsumoto, Katarao & Nakano, 1964; Onaka, Kamata, Maeda, Kawazoe, Natsume, Okamoto, Uchimaru & Shimizu, 1964; Yamamura & Hirata, 1964). The pharmacological properties of the compound were examined first by Chen & Chen (1935) as early as a half century ago. These investigators reported that the compound possessed analgesic action, hypotensive and hypothermic activity and lethal tonic convulsive actions. Since the compound bears the same picrotoxane skeleton as does pictotoxinin, a well known γ-aminobutyric acid (GABA) antagonist, it would be expected to have some antagonizing actions on inhibitory neurotransmitters. However, precise neuropharmacological studies have never been reported with only one exception, which showed that the compound has strychnine-like antagonizing actions upon the inhibitory effect of glycine at spontaneously firing interneurones of the cat spinal cord (Curtis, Duggan, Felix & Johnston, 1971).

In the present study we examined the neuropharmacological properties of dendrobine and the related alkaloid, nobiline, isolated from the same plant, on the isolated spinal cord of the frog and compared these with the actions of picrotoxinin and strychnine.

Methods

The isolated, intra-arterially perfused spinal cord of the bullfrog was used and recordings were made of the root potentials and root reflexes by a sucrose gap method.

Bullfrogs (*Rana catesbiana*) weighing 100–180 g were obtained from October 1980 to February 1981. The technique for preparing the isolated, intra-arterially perfused spinal cord preparation was the same as that described elsewhere (Kudo, Abe, Goto & Fukuda, 1975). An arterial cannula was inserted into the ventral spinal artery and the isolated spinal cord was perfused with amphibian Ringer solution composed of (mM): NaCl 115, KCl 2.7, $CaCl_2$ 1.8 (in Ca^{2+}-free medium $CaCl_2$ was omitted and replaced by $MgCl_2$ 9.0) and glucose 5.5, with pH adjusted to 7.6 by addition of $NaHCO_3$. The perfusion rate was approx. 0.3 ml/min. The experiments were performed at a temperature of 20 ± 2°C.

The potential differences between the spinal cord

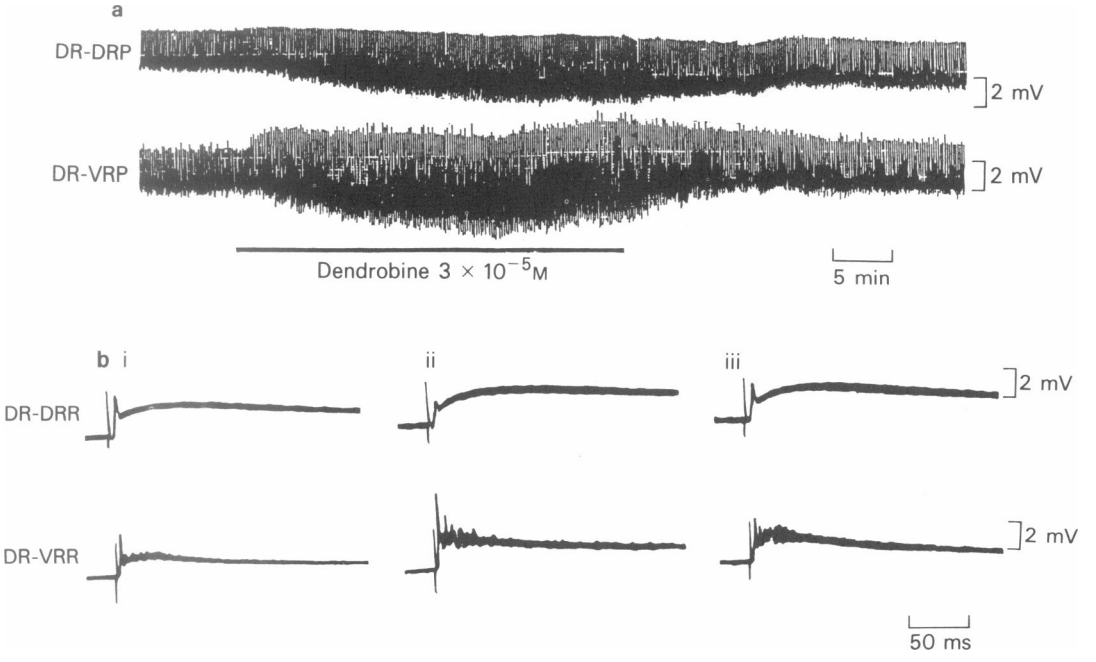


Figure 2 Effects of dendrobine on the root potentials and reflexes induced by stimulation of the dorsal root in the frog isolated spinal cord. (a) Effect of dendrobine on the root potentials. Upper and lower tracings show the dorsal (10th) and ventral (9th) root potentials, respectively. The stimulation was given to the 9th dorsal root. (b) Effects of dendrobine on the root reflex and potential complex. Upper and lower tracings in each set of figures indicate the dorsal (10th) and ventral (9th) root responses, respectively. (i) before the application of dendrobine (3×10^{-5} M); (ii) 20 min after the application; (iii) 30 min after washing.

and the peripheral root stumps (9th dorsal root and 10th ventral root) were assessed by means of a sucrose gap method (Kudo *et al.*, 1975; Kudo, 1978). The 10th dorsal root was stimulated to evoke the dorsal root potential (DR-DRP) and root reflex (DR-DRR) and to evoke the ventral root potential (DR-VRP) and root reflex (DR-VRR). In some experiments the ventral root (9th) was stimulated repetitively (50 Hz, 20 pulses) to evoke the VR-DRP in the 9th dorsal root.

Drugs used were dendrobine (isolated and purified from *Dendrobium nobile* by K.Y., mol. wt. 263, m.p. 135–136°C), nobiline (isolated and purified form *Dendrobium nobile* by K.Y., mol. wt. 293, m.p. 87–88°C) (cf. Yamamura & Hirata, 1964), picrotoxinin (Sigma) and strychnine nitrate (Sigma). All agents were dissolved in Ringer solution and applied by exchanging the perfusion medium with a drug containing solution through the anterior spinal artery. Amino acids used were GABA (Wako pure Chem.), β-alanine (Wako pure Chem.), taurine (Wako pure Chem.), glycine (Wako pure Chem.) and monosodium L-glutamate (Wako pure Chem.). All amino acids were dissolved in a Ca^{2+}-free, Mg^{2+} (9.0 mM)-containing Ringer solution. Three of these (3×10^{-3} M) routinely were perfused in a sequential manner for 5 s at a rate of 0.01 ml/s once every 5 min by a multiperpex pump (LKB 2155) having three electric valves operated by a timer. The compounds flowed through 3 separate fine polyethylene tubes which were placed in a glass cannula, having previously been inserted into the spinal artery.

Results

Effects on root potentials and reflexes

Dendrobine (10^{-5} M and 3×10^{-5} M) augmented the amplitudes of DR-DRP and DR-VRP, and this effect was accompanied by a hyperpolarizing shift of the d.c. base-line in both roots. Following the application of dendrobine (3×10^{-5} M), the amplitudes of DR-DRP and DR-VRP increased to $147.5 \pm 18.6\%$ ($n = 4$) and $212.7 \pm 19.9\%$ ($n = 4$) of the pre-application controls, respectively (Figure 2a). The first spike potential in the DR-VRR increased to $167.6 \pm 33.4\%$ ($n = 4$), while the DR-DRR was reduced to $59.3 \pm 11.6\%$ ($n = 4$) of the control responses (Figure 2b). These effects were reversed within 30 min of washing with a drug-free Ringer solution. On the other hand, picrotoxinin (10^{-5} M) caused gradual depolarizations in both ventral and dorsal roots, which accompanied the reduction in size of the DR-DRP and DR-VRP. The first spike potential in DR-VRR was augmented during the initial 5 min, and was then followed by a reduction concomitant with an increase in the polysynaptic component and of spontaneous firing; during this time the size of DR-DRR was reduced significantly. These effects could still be observed residually even after 60 min of washing with drug-free Ringer solution. At a concentration of 10^{-6} M, strychnine caused a marked depolarization of both ventral and dorsal roots within 5 min of application. The depolarized d.c. base-line gradually returned to the resting level during the application of the drug. During the recovery phase, spontaneous electrical activities of both roots increased markedly. The first spike potential in the DR-VRR was greatly augmented, while the DR-DRR was abolished. The effect of strychnine remained unchanged even after 60 min of washing with drug-free medium. Nobiline (3×10^{-5} M) showed no significant effect on either the root potentials or on reflexes.

Effects on dorsal root potentials induced by repetitive stimulation of either the dorsal or ventral root

In the frog spinal cord the dorsal root potentials could be evoked by stimulation of either the adjacent dorsal root (DR-DRP) or corresponding ventral root (VR-DRP). The effects of dendrobine on these dorsal root potentials were tested. In the present experiments, to make the potentials more obvious, either the dorsal or ventral roots were stimulated repetitively at a rate of 50 Hz (20 pulses). As is shown in Figure 3, such stimulation produced depolarizations of the primary afferent terminals. Dendrobine (3×10^{-5} M) reversibly abolished the VR-DRP, while it augmented the maximum amplitude of the DR-DRP (Figure 3a). The maximum rate of rise of the DR-DRP was clearly reduced. The effects of dendrobine on the DRPs were qualitatively similar to those of strychnine (10^{-6} M), which also abolished the VR-DRP, augmented the maximum amplitude of DR-DRP and reduced the maximum rate of rise of the DR-DRP (Figure 3c). On the other hand, the effects of picrotoxinin (10^{-5} M) on the DRPs differed from those of dendrobine and strychnine. The agent reduced the amplitudes of the DR-DRP and VR-DRP, and this effect recovered partially following 30 min washing with drug-free medium (Figure 3b).

Effects on presynaptic inhibition

Since in the frog spinal cord the antidromic conditioning stimulation of the ventral root causes a presynaptic inhibition on the ventral root reflex potential evoked by the test stimulation of the dorsal root (Holemans & Meij, 1968), the above results suggest strongly that dendrobine may block the presynaptic inhibition. As shown in Figure 4a, dendrobine, at a

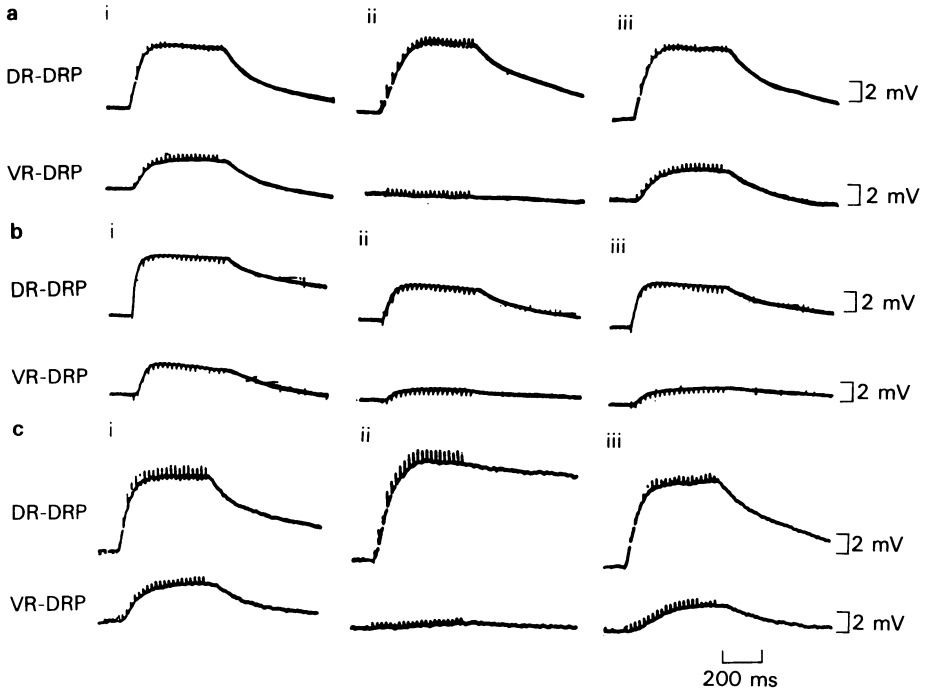


Figure 3 Effects of dendrobine, picrotoxinin and strychnine on the dorsal root potentials. Upper and lower tracings in each set of figures indicate the dorsal root potential induced by stimulation (50 Hz, 20 pulses) of an adjacent dorsal root (10th) and the corresponding ventral root (9th), respectively. (a) Effect of dendrobine (3×10^{-5} M). (b) Effect of picrotoxinin (10^{-5} M). (c) Effects of strychnine (10^{-6} M). In each set of figures; (i) before the application of the agent; (ii) 20 min (a and b) and 10 min (c) after the application of the agent; (iii) 30–40 min after washing.

concentration of 10^{-5} M, blocked the presynaptic inhibition influencing the size of the first spike potential, induced by conditioning stimulation of the ventral root in the same segment. The effect of dendrobine was easily reversible by washing with drug-free medium. At the same concentration (10^{-5} M), picrotoxinin also reduced presynaptic inhibition, but this substance was less effective than dendrobine, and its effect was not reversible within 30 min of washing (Figure 4b). Strychnine, at a concentration as low as 10^{-7} M, blocked presynaptic inhibition. The effect remained unchanged after 30 min of washing with drug-free medium.

The results of the present experiments suggest that dendrobine is an antagonist to the neurotransmitter mediating the VR-DRP and presynaptic inhibition. The actions of dendrobine on the effects of neurotransmitter candidates on primary afferent terminals accordingly have been examined.

Antagonizing actions on amino acid-induced depolarization of primary afferent terminals

Table 1 shows the antagonistic actions of dendrobine, nobiline, picrotoxinin and strychnine on the inhibitory amino acid-induced depolarizations of the primary afferent terminal of the spinal cord perfused with Ca^{2+}-free, Mg^{2+} (9.0 mM)-containing solution. Dendrobine (3×10^{-5} M) antagonized the actions of β-alanine and taurine but had little inhibitory effects upon glycine- and GABA-induced depolarizations. The effects of dendrobine were qualitatively similar to those of strychnine (10^{-6} M), which also antagonized taurine- and β-alanine-induced depolarizations of primary afferent terminals, but had no inhibitory effects upon GABA- and glycine-induced depolarizations. Strychnine also had no antagonistic effects upon the glycine-induced depolarization of motoneurones. On the other hand, picrotoxinin reduced the depolarizations induced by GABA, β-alanine and taurine. Nobiline (3×10^{-5} M) showed only a trace of inhibitory action against the effect of taurine and had no antagonistic action on the effect of β-alanine.

As is illustrated in Figure 5, the dose-response curves for β-alanine and taurine on primary afferent terminals were shifted to the right by dendrobine (3×10^{-5} M). The shift was apparently parallel. The antagonistic action of dendrobine on taurine applied for 1 min (Figure 5b) was weaker than that expected

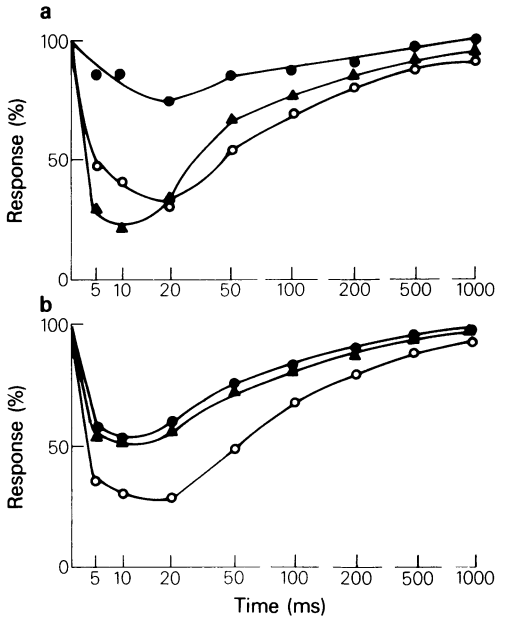


Figure 4 Alteration of presynaptic inhibition on the first spike potential in the DR-VRR. (a) Effects of dendrobine (10^{-5} M). Each point represents the average of five separate experiments. (b) Effects of picrotoxinin (10^{-5} M). Each point represents the average of three separate experiments. Abscissa scale: interval between conditioning (9th ventral root) and test (10th dorsal root) stimulations. Ordinate scale: the percentage amplitude of the first spike potential in the 10th ventral root. (○) Control; (●) 20–30 min after the application of the agent; (▲) 20–30 min after washing.

from the results of the one dose application (5 s) of the agonist (Table I). Since the rising time of the taurine-induced depolarization of the primary afferent terminal was slower than it was for β-alanine, the response induced by the short time application may not be its maximum and thus may be more vulnerable to the antagonist.

Discussion

Although dendrobine has the same picrotoxane skeleton as picrotoxinin, a well known GABA-antagonist, the former showed no antagonistic action against GABA, and had no inhibitory effect upon the DR-DRP. However, in the same manner as that of picrotoxinin, dendrobine (1) blocked the presynaptic inhibition caused by antidromic conditioning stimulation of the ventral roots (Holemans & Meij 1968), (2) reduced the size of DR-DRR and VR-DRP, and (3) also reduced the β-alanine- and taurine-induced depolarization of primary afferent terminals. These neuropharmacological properties of dendrobine on the frog spinal cord were qualitatively similar to those of strychnine, which also blocked presynaptic inhibition, the β-alanine- and taurine-induced depolarizations of primary afferent terminals and VR-DRP and DR-DRR, but had no significant effect upon the GABA-induced depolarization of primary afferent terminals. Dendrobine and also strychnine had no significant antagonistic action upon the glycine-induced depolarization of primary afferent terminals. These results support the idea that in the frog spinal cord, the neurotransmitter involved in the VR-DRP and presynaptic inhibition through this pathway may not be GABA, but could be β-alanine or taurine (Barker, Nicoll & Padjen, 1975b). Since the DR-DRR and the rising phase of the DR-DRP were reduced significantly by dendrobine and also by strychnine, the earlier phase in the dorsal root potential induced by stimulation of an adjacent dorsal root may also be mediated by β-alanine or taurine. However, GABA seems to be involved in the later phase of DR-DRP.

The possibility that GABA and β-alanine/taurine may react with different receptors on the primary afferent terminals in the frog cord has been suggested (Barker, Nicoll, Padjen, 1975a). In our preliminary experiments, the primary afferent terminals which were desensitized to GABA, were also desensitized to β-alanine and taurine, and the converse also was

Table 1 Antagonistic effects of dendrobine, nobiline, picrotoxinin and strychnine upon amino acid-induced depolarizations of primary afferent terminals

Agents	*Dose* (M)	n	*% values of antagonism upon* *GABA*	*BALA*	*Taurine*
Dendrobine	3×10^{-5}	4	7.6±4.7	27.5± 6.0	45.0±5.2
Nobiline	3×10^{-5}	3	2.8±1.4	0.1± 2.7	12.8±4.4
Picrotoxinin	3×10^{-5}	4	34.8±9.4	60.3± 7.6	68.0±7.1
Strychnine	10^{-5}	5	2.8±7.9	43.2±15.6	92.3±4.8

GABA: γ-aminobutyric acid; BALA: β-alanine. Each amino acid in a concentration of 3×10^{-3} M was infused for 5 s at a rate of 0.01 ml/s (1.5×10^{-5} mol) once every 5 min by a microtube pump and a timer-controlled micro-valve system.

Percent values of antagonism were calculated based upon amino acid-induced responses observed following 15–25 min of application of test agents taking the responses before application as controls.

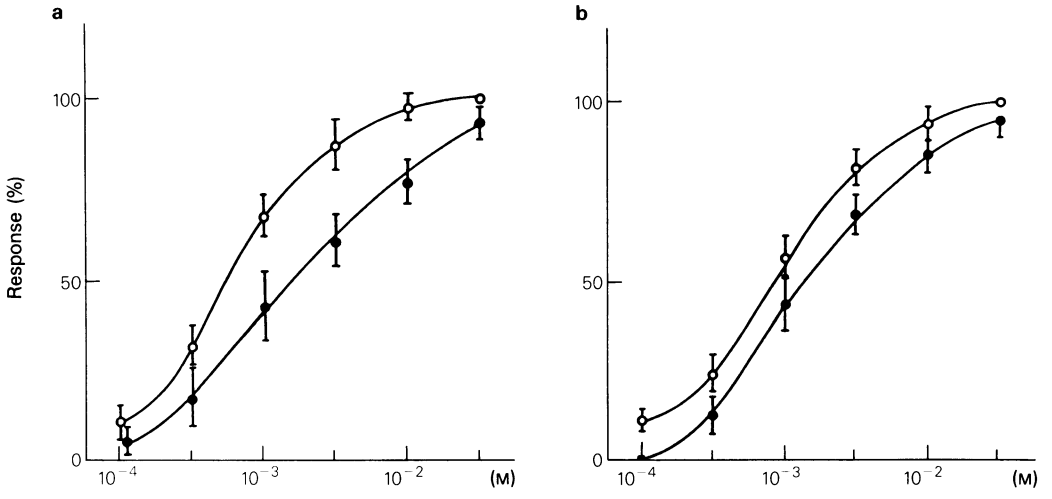


Figure 5 Antagonizing acitons of dendrobine on β-alanine and taurine-induced depolarizations of primary afferent terminals. (a) Dose-response curves for β-alanine before (○) and after (●) the application of dendrobine (3×10^{-5} M). (b) Dose-response curves for taurine before (○) and after (●) the application of dendrobine (3×10^{-5} M). Each concentration of amino acids was applied for 1 min, once every 5 min from lower to higher concentrations. The antagonistic action upon amino acids was tested during 20–50 min following the application of dendrobine. Abscissae scale: concentrations of amino acids in a logarithmic scale. Ordinates scale: percentage responses of amino acid-induced depolarization of primary afferent terminals, taking as 100% the response induced by 3×10^{-2} M amino acid given before the application of dendrobine. Each point represents an average of 4 separate experiments with the s.e. as indicated.

true. Thus the effectors for these amino acids would appear to be common. Picrotoxinin, an effector blocker (Enna, Collins & Snyder, 1977; Olsen, Ticku & Miller, 1978), reduced the depolarizations induced by the above three inhibitory amino acids. On the other hand, dendrobine had little effect on the responses induced by GABA but had antagonistic effects on β-alanine and taurine, dose-response curves of which are apparently shifted to the right in parallel fashion. These observations suggest that although picrotoxinin and dendrobine have structural similarities, their antagonistic actions on amino acid-induced depolarizations of primary afferent terminals are different in nature. Further studies on this point are now being undertaken.

Earlier neuropharmacological studies with dendrobine demonstrated that the agent specifically antagonized the inhibitory effects of glycine on spontaneously firing interneurones of cat spinal cord (Curtis *et al.*, 1971). In the present study, dendrobine had no antagonistic actions upon the glycine-induced depolarization of the primary afferent terminals. However, strychnine, a well known glycine receptor blocker, also had no antagonistic action against glycine-induced depolarization of primary afferent terminals, but antagonized β-alanine and taurine in the frog spinal cord, as has been reported by many authors (Tebecis & Phillis, 1969; Nicoll & Barker, 1973; Evans & Watkins, 1975; Sonnhof, Grafe, Krumnikl, Linder & Schindler, 1975; Barker *et al.*, 1975a). The latter authors attributed the difference to distinct neuropharmacological properties of the glycine receptors of primary afferent terminals and of motoneuronal somata. In the present study, glycine also induced depolarization of motoneurones, and the depolarization was not antagonized by strychnine. Thus the properties of glycine receptors which are distributed in frog spinal cord are different from those which occur in the mammalian central nervous system. Although amino acid receptors similar to those in the mammalian central nervous system are present in the frog spinal cord, it may be suggested that their functions generally are not similar to those of mammals.

Dendrobine has no hydroxyl group at the 6-position of the picrotoxane skeleton, whereas picrotoxinin bears a hydroxyl group at the same position. Since the acetylation of the hydroxyl group at the 6-position of picrotoxinin was found to cause the molecule to lose its toxic action as a convulsant on mice (Jarboe, Porter & Buckler, 1968), the loss of the GABA antagonizing action of dendrobine could be attributed to the absence of hydroxyl group at the 6-position of the picrotoxane skeleton. The other difference between dendrobine and picrotoxinin is the presence of basic nitrogen in dendrobine. We have no direct evidence to substantiate the proposed role of this nitrogen atom in the particular properties

of dendrobine. Nobiline, which has an open ring structure possessing a dimethylamino group, demonstrated no significant effect on the root potentials, nor on the depolarization of the primary afferent terminals induce by amino acids. The presence of the pyrrolidine ring in dendrobine seemed to be important for its neuropharmacological actions. However, tutin and coriamyrtin, compounds lacking the corresponding five-membered ring at the same moiety, have been reported to cause almost the same convulsant action as that of picrotoxinin (Jarboe *et al.*, 1968). The present authors have confirmed in a preliminary study that these two compounds showed almost the same neuropharmacological properties as picrotoxinin in the frog spinal cord. The presence of the five-membered ring at the position in the molecule is not a pre-requisite for an action as amino acid antagonists of picrotoxane compounds. The dimethyl amino group in the nobiline molecule may interfere with the access of the compound to its effector site.

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References

BARKER, J.L., NICOLL, R.A. & PADJEN, A. (1975a). Studies on convulsants in the isolated frog spinal cord. I. Antagonism of amino acid responses. *J. Physiol.*, **245,** 521–536.

BARKER, J.L., NICOLL, R.A. & PADJEN, A. (1975b). Studies on convulsants in the isolated frog spinal cord. II. Effects on root potentials. *J. Physiol.*, **245,** 537–548.

CHEN, K.K. & CHEN, A.L. (1935). The pharmacological action of dendrobine, the alkaloid of Chin-Shin-Hu. *J. Pharmac. exp. Ther.*, **55,** 319–325.

CURTIS, D.R., DUGGAN, A.W., FELIX, D. & JOHNSTON, G.A.R. (1971). Bicuculline, an antagonist of GABA and synaptic inhibition in the spinal cord of the cat. *Brain Res.*, **32,** 69–96.

ENNA, S.J., COLLINS, J.F. & SNYDER, S.H. (1977). Stereospecificity and structure-activity requirements of GABA receptor binding in rat brain. *Brain Res.*, **124,** 185–190.

EVANS, R.H. & WATKINS, J.C. (1975). Ventral root responses of the hemisected amphian spinal cord to perfused amino acids in the presence of procaine. *Br. J. Pharm.*, **55,** 519–526.

HOLEMANS, K.C. & MEIJ, H.S. (1968). An analysis of some inhibitory mechanisms in the spinal cord of the frog (*Xenopus laevis*). *Pflügers Arch. ges. Physiol.*, **303,** 287–310.

INUBUSHI, Y., SASAKI, Y., TSUDA, Y., YASUI, B., KONITA, T. MATSUMOTO, J., KATARAO, E. & NAKANO, J. (1964). Structure of dendrobine. *Tetrahedron*, **20,** 2007–2023.

JARBOE, C.H., PORTER, L.A. & BUCKLER, P.T. (1968). Structural aspects of picrotoxinin action. *J. med. Chem.*, **11,** 729–731.

KUDO, Y. (1978). The pharmacology of the amphibian spinal cord. *Prog. Neurobiol.*, **11,** 1–76.

KUDO, Y., ABE, N., GOTO, S. & FUKUDA, H. (1975). The chloride-dependent depression by GABA in the frog spinal cord. *Eur. J. Pharmac.*, **32,** 251–265.

NICOLL, R.A. & BARKER, J.L. (1973). Effect of strychnine on dorsal root potentials and amino acid responses in frog spinal cord. *Nature, New Biol.*, **246,** 224–225.

OLSEN, R.W., TICKU, M.K. & MILLER, T. (1978). Dihydropicrotoxinin binding to crayfish muscle sites possibly related to γ-aminobutyric acid receptor-ionophores. *Molec. Pharmac.*, **14,** 381–390.

ONAKA, T., KAMATA, S., MAEDA, T., KAWAZOE, Y., NATSUME, M., OKAMOTO, T., UCHIMARU, F. & SHIMIZU, M. (1964). The structure of dendrobine. *Chem. Pharm. Bull.*, **12,** 506–512.

SONNHOF, U., GRAFE, P., KRUMNIKL, J., LINDER, M. & SCHINDLER, L. (1975). Inhibitory post-synaptic actions of taurine, GABA and other amino acids on motoneurones of isolated frog spinal cord. *Brain Res.*, **100,** 327–341.

SUZUKI, H. & KEIMATSU, I. (1932). Alkaloid of the chinese drug, "Chin-Shin-Hu". II. Dendrobine. *J. Pharm. Soc. Japan*, **52,** 1049–1060.

TEBECIS & PHILLIS. (1969). The use of convulsants in studying possible functions of amino acids in the toad spinal cord. *Comp. Biochem. Physiol.*, **28,** 1303–1315.

YAMAMURA, S. & HIRATA, Y. (1964). Structures of nobiline and dendrobine. *Tetrahedron Lett*, **2,** 79–87.

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