J. SCUVÉE-MOREAU and A. DRESSE *(Institut de Pathologie, Laboratoire de Pharmacologie, Université de Liège, B-4000 Sart Tilman par Liège 1).*

Attenuation of the inhibitory effect of binedaline and desipramine on the firing rate of locus coeruleus neurons after chronic administration : time-course study (3 figures).

Introduction

Binedaline (Lindilan) (Fig. 1) is a new antidepressant drug characterized by a selective action on catecholaminergic systems.

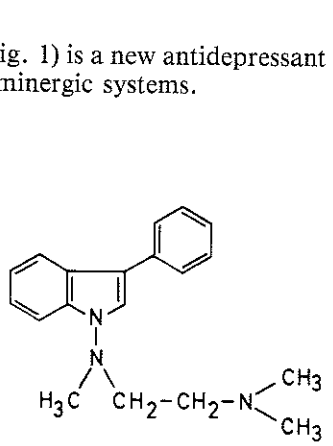

FIG. 1. *Chemical structure of binedaline.*

Biochemical studies show that it is a potent inhibitor of noradrenaline uptake without action on serotonin uptake. Electrophysiological studies *in vivo* confirm this selectivity of action : binedaline is a potent inhibitor of the firing rate of central noradrenergic neurons but does not modify the firing rate of central serotonergic neurons. Binedaline is also a weak inhibitor of the firing rate of central dopaminergic neurons. Clinically binedaline is reported to differ from classical antidepressants (AD) by its rapidity of action. In order to give experimental support to this observation chronic electrophysiological studies were initiated. It was previously demonstrated that the chronic administration of various AD like imipramine, desipramine, clomipramine and nomifensine results in an attenuation of their inhibitory effect on the firing rate of the central noradrenergic neurons of the locus coeruleus (LC) (SVENSSON & USDIN, 1978; SCUVÉE-MOREAU, 1981). This attenuation is probably related to a modification in the sensitivity of some adrenoceptors (SULSER, 1978; SCUVÉE-MOREAU & SVENSSON, 1982). As it is usually assumed that the delayed onset of the therapeutic effectiveness of AD is related to the development of these adaptation processes, the time-course evolution of the attenuation of the inhibitory effect of binedaline and desipramine on the firing rate of LC neurons was studied.

Methods

Male Wistar rats were given daily i.p. injections of binedaline or desipramine (5 mg/kg) during 3, 6, 9 or 14 days. Electrophysiological studies were performed 24-30 h after the last administration. Acute experiments were also performed. The animals (200-300 g) were anaesthetized with chloral hydrate (400 mg/kg i.p.) and mounted in a stereotaxic apparatus. The electrical activity of LC neurons was

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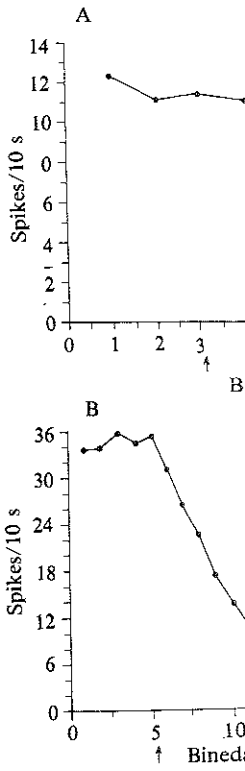

FIG. 2. *Inhibitory effect of an intravenous per*
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recorded with extracellular nickel-chrome microelectrodes implanted at the following coordinates : 1.8-2.2 mm posterior, 1.1-1.3 mm lateral to lambda. Action potentials were passed through an impedance adapter and an amplifier into a *Tektronix* oscilloscope. Signals were also passed into an amplitude discriminator and a digital counter. LC neurons were characterized by a regular firing rate of 0.5-5 spikes/s and a typical response to noxious stimuli (GRAHAM & AGHAJANIAN, 1971; KORF *et al.*, 1974). The electrical activity of the cell was recorded during a control period of a few min afterwhat binedaline or desipramine were perfused into the jugular vein by means of a perfusion pump (flow 6 ml/h). The total doses required to produce a 50 % (ID_{50}) and a 100 % (ID_{100}) inhibition of the frequency of discharge were calculated. Each experiment was performed on 6 animals minimum. Binedaline HCl *(Roussel Uclaf)* and desipramine HCl *(Ciba-Geigy)* were dissolved in saline. Doses refer to the bases. Statistical analysis of the results was performed using Student's *t* test.

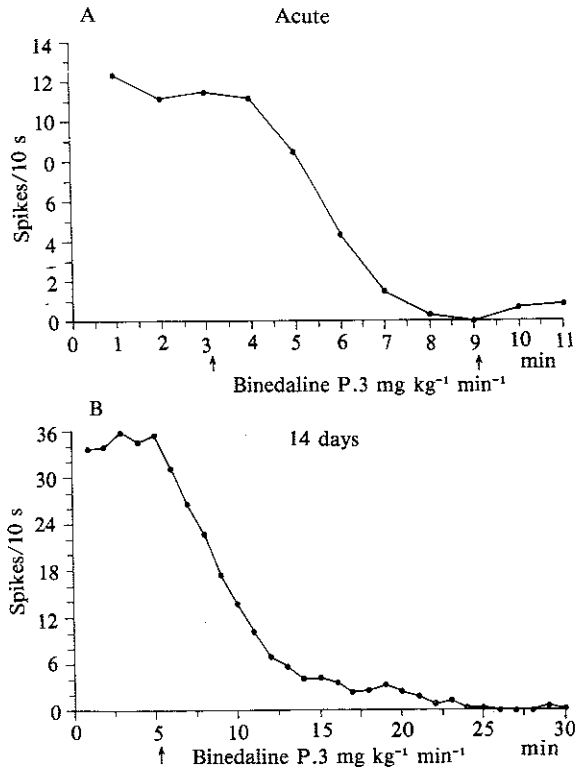

FIG. 2. *Inhibitory effect of an intravenous perfusion of binedaline on the firing rate of a LC neuron :* A) *after acute administration,* B) *24 h after subchronic administration during 14 days;* after that treatment a longer duration of perfusion is required to produce a complete inhibition of the firing rate.

Results

Chronic administration of binedaline results in an attenuation of its inhibitory effect on the firing rate of LC neurons (Fig. 2). This attenuation is reflected by a progressive increase of the ID_{50} and ID_{100} values (Fig. 3A). This increase is already apparent after 3 days of treatment and reaches the statistically significant level after 9 days for the ID_{100} value and after 14 days for the ID_{50} value.

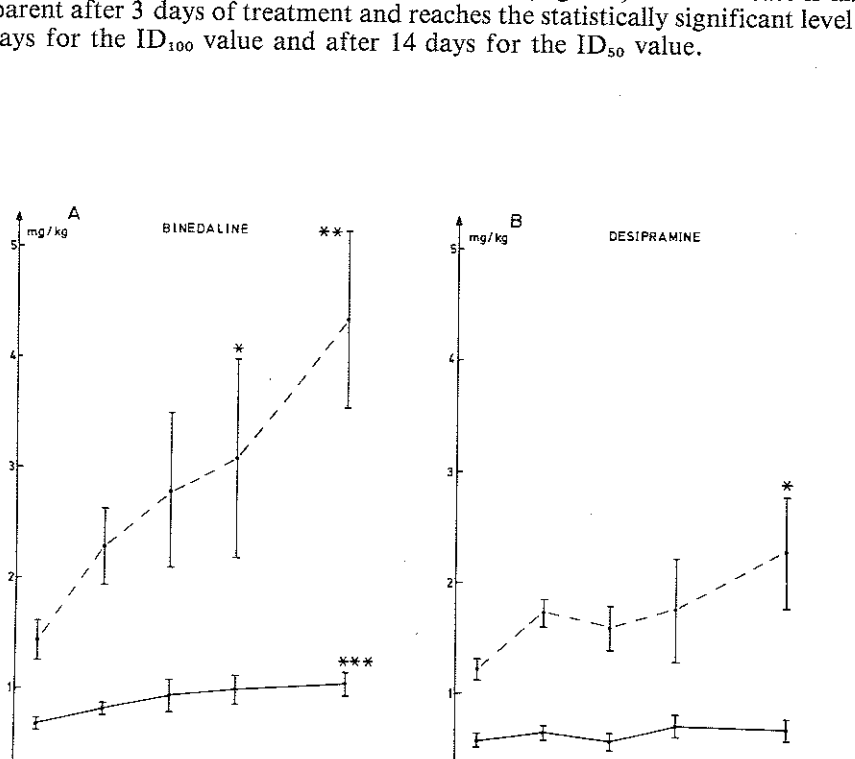

FIG. 3. *Mean total dose (± SE) of binedaline* (A) *or desipramine* (B) *required to produce a 50 % (ID_{50} ——) and a 100 % (ID_{100} - - - -) inhibition of the firing rate of LC neurons after acute administration or 24-30 h after subchronic administration during 3, 6, 9 or 14 days.*
* $P < 0.02$, ** $P < 0.01$, *** $P < 0.005$.

Chronic administration of desipramine also induces an attenuation of its inhibitory effect on the firing rate of LC neurons. This attenuation is however less pronounced than with binedaline. There is no modification of the ID_{50} value after 14 days of treatment. The attenuation is only reflected by a significant increase of the ID_{100} value after 14 days of treatment (Fig. 3B).

Discussion

Chronic administration of binedaline and desipramine induces an attenuation of their inhibitory effect on the firing rate of central noradrenergic neurons. This is in agreement with previous chronic studies (SVENSSON & USDIN, 1978; SCUVÉE-MOREAU, 1981) and probably reflects the occurrence of adaptation processes at the level of some adrenoreceptors (SULSER, 1978; AGHAJANIAN, 1981; SCUVÉE-MOREAU & SVENSSON, 1982). It is important to point out

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Summary

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References

AGHAJANIAN, G. K. (1981) in *Neuroreceptors* -
& DAVIS, J. M., eds) pp. 27-35, John Wil
GRAHAM, A. W. & AGHAJANIAN, G. K. (1971)
KORF, J., BUNNEY, B. S. & AGHAJANIAN, G. K
SCUVÉE-MOREAU, J. (1981) *Thesis,* Liège Univ
SCUVÉE-MOREAU, J. & SVENSSON, T. H. (1982
SULSER, F. (1978) *Pharmakopsychiat.* 11, 43-5
SVENSSON, T. H. & USDIN, T. (1978) *Science*

E. VANDENBUSSCHE, R. VOGELS (1) ar
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(1) Research Assistant *NFWO.*

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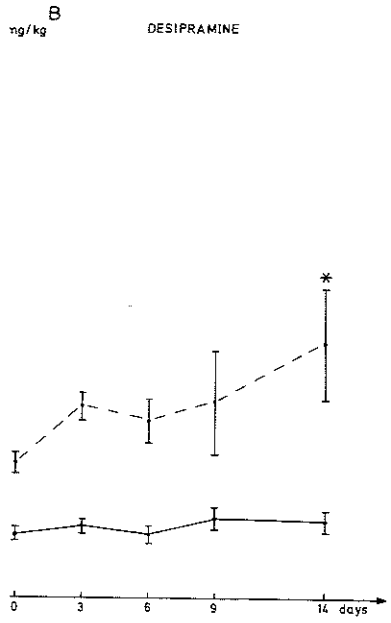

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son, 1982). It is important to point out that the attenuation is principally reflected by an increase of the ID_{100} values without modification or only with a weak increase of the ID_{50} values. The physiological meaning of this observation remains to be elucidated.

The attenuation of the inhibitory effect of binedaline is apparent with statistical significance after 9 days of treatment while the modification of the inhibitory effect of desipramine is only significant after 14 days. These data thus indicate that adaptation processes develop more rapidly with binedaline. If these adaptation processes are important for the therapeutic effectiveness of AD as postulated by several authors, these experiments give support to the clinical data indicating that binedaline has a quicker onset of action than classical tricyclic AD.

Summary

Binedaline is a new AD acting selectively or noradrenergic systems.

Clinically it is reported to differ from classical AD by its rapidity of action. In order to give experimental support to this observation chronic electrophysiological studies were initiated. The chronic administration of various AD results in an attenuation of their inhibitory effect on the firing rate of LC neurons. This attenuation probably reflects modifications in the sensitivity of some adrenoceptors. As it is usually assumed that the delayed onset of the therapeutic effectiveness of AD is related to the development of these adaptive processes, the time-course evolution of the attenuation of the inhibitory effect of binedaline and desipramine on the firing rate of LC neurons was studied. The attenuation was apparent after 9 days of treatment with binedaline and after 14 days of treatment with desipramine. These data indicate that adaptive processes develop more rapidly with binedaline and give experimental support to clinical data.

References

AGHAJANIAN, G. K. (1981) in *Neuroreceptors - Basic and Clinical Aspects* (USDIN, E., BUNNEY, W. E. & DAVIS, J. M., eds) pp. 27-35, John Wiley and Sons Ltd, New York.
GRAHAM, A. W. & AGHAJANIAN, G. K. (1971) *Nature (London)* **234**, 100-102.
KORF, J., BUNNEY, B. S. & AGHAJANIAN, G. K. (1974) *Eur. J. Pharmacol.* **25**, 165-169.
SCUVÉE-MOREAU, J. (1981) *Thesis,* Liège University, Belgium.
SCUVÉE-MOREAU, J. & SVENSSON, T. H. (1982) *J. Neural Transmission* **54**, 51-63.
SULSER, F. (1978) *Pharmakopsychiat.* **11**, 43-52.
SVENSSON, T. H. & USDIN, T. (1978) *Science (Washington)* **202**, 1089-1091.

E. VANDENBUSSCHE, R. VOGELS (1) and G. A. ORBAN *(Laboratorium voor Neuro- en Psychofysiologie, KULeuven, Campus Gasthuisberg, B-3000 Leuven).*

The influence of eccentricity on orientation discrimination : I. Normal vision.

Orientation discrimination of a single line was measured for different orientations using a sequential discrimination task in six normal subjects. Both the

(1) Research Assistant *NFWO.*