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Antagonism of Behavioural Depression Produced by Clonidine in the Mongolian Gerbil: a Potential Screening Test for Antidepressant Drugs

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Abstract. The effects of various antidepressant drugs and some other therapeutic agents on the depression of locomotion and exploratory activity induced by clonidine (0.1 mg/kg IP) were investigated in the Mongolian gerbil (*Meriones unquiculatus*). In parallel experiments, the effect of yohimbine on clonidine-induced sedation was observed. The following behavioral components were analysed: ambulation, rearing and novel object investigation. Yohimbine antagonized the effects of clonidine in a dose-dependent manner. All antidepressants similarly antagonized the effect of clonidine on ambulation but they differed to a greater extent in their potency in counteracting the clonidine action on exploration, particularly the novel object investigation. On the other hand diazepam and neuroleptic agents such as pimozide and flupentixol failed to antagonize the clonidine effects. The antagonism of clonidine-induced behavioral depression might be used in the selection of antidepressants.

Key words: Clonidine – Antidepressants – Yohimbine – Presynaptic adrenoceptors – Exploration – Locomotion – Screening of antidepressants – Mongolian gerbil

A great deal of evidence suggests that brain norepinephrine (NE) neurons play an essential role in mechanisms of affective disorders. Daily excretion of urinary 3-methoxy-4-hydroxyphenylglycol (MHPG), the major metabolite of brain NE is decreased in patients with endogenous depression (Maas et al. 1968). The turnover rate of brain NE in the ascending NE system is decreased in rats repeatedly exposed to stress (Kitayama et al. 1980). Drugs which enhance NE synaptic transmission e.g. desmethylimipramine attenuate depression. On the other hand, clonidine which is known to inhibit NE release due to stimulation of presynaptic α_2 adrenoceptors (Langer 1974; Starke et al. 1975) has been recently reported to possess antimanic activity (Jouvent et al. 1980).

Clonidine produces numerous symptoms of behavioral depression in laboratory animals. Sedation and suppression of exploratory behavior have been reported in rats and mice treated with this drug (Drew et al. 1977; Delini-Stula et al. 1979). Other depressive effects such as suppression of avoidance behavior (Robson et al. 1978; Kostowski et al. 1981) and inhibition of self-stimulation (Franklin and Herberg 1977) have been described in clonidine-treated rats.

The sedative action of clonidine is mediated through α_2 adrenoceptors since it is blocked by α_2 adrenoceptor antagonists such as yohimbine and piperoxan (Drew et al. 1977; Delini-Stula et al. 1979; Gower and Marriott 1980). There is, therefore a correlation between the α_2 agonistic property and the central depressive action of clonidine.

Some biochemical and neurophysiological findings also indicate that the action of clonidine is closely related to brain NE neurons. Tang et al. (1979) and Warsh et al. (1981) found decreased brain MHPG concentrations in rats treated with clonidine. This indicates reduced turnover of brain NE. Moreover, Svensson et al. (1975) reported that this drug was able to reduce the firing of ascending NE neurons in the brain. The rate of firing was decreased when clonidine was either injected intravenously or applied directly in the vicinity of the locus coeruleus pericarya, the well known group of NE cell bodies.

The depressive effects of clonidine may provide a new approach to finding improved antidepressant drugs and be suitable for use as a simple animal model of depression (Gower and Marriott 1980; Kostowski and Malatyńska 1980; Kostowski 1981). In fact, preliminary data suggests that both clonidine-induced inhibition of NE release and clonidine-induced behavioral depression could be antagonized by antidepressants (Dubocowich et al. 1979; Gower and Marriott 1980; Kostowski and Malatyńska 1980; Spyraki and Fibiger 1980).

In the present report, we describe the results of experiments which indicate that antidepressants antagonize clonidine-induced sedation in the Mongolian gerbil (*Meriones unquiculatus*). This rodent has gained increasing acceptance as an experimental animal in behavioral tests (Thiessen 1973; Cheal 1978) since it is easy to maintain, shows high intensity of locomotor activity and readily explores and investigates objects in the environment.

Materials and Methods

Animals. Mongolian gerbils (*Meriones unquiculatus*) were housed in plastic cages, 40 × 30 × 20 cm, in mated pairs. After weaning the gerbils were maintained in groups of 5–6 (per cage) of the same sex in normal laboratory conditions (temperature 20–22° C, natural day-night cycle) with free access to food and water. Male animals were tested when adults (60–70 g). All experiments were performed between 10.00 a.m. and 1.00 p.m.

Apparatus and Procedure. All tests were conducted in the Universal Motility Meter (UMA-1-06, COTM, Białystok, Poland) consisting of a transparent circular plastic arena

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(27 cm in the diameter) surrounded by a wall 16 cm high and equipped with vertical and horizontal movement detectors. Each impulse produced by horizontal movements (ambulation) and vertical movements (rearing) was automatically recorded by an electronic counter. Experiments were performed in a special sound-proof room separated from the observer by a one-way glass window. The apparatus was illuminated by a 25 W bulb. The animals were not previously adapted to the apparatus.

Gerbils were placed singly in the apparatus and both ambulation and rearing were recorded (as a number of counts) over a period of 10 min. Then to induce interest following habituation, the "novel object" (a wooden block, $5 \times 5 \times 5$ cm) was placed in the center of the arena and the animals explored this object vigorously. Investigation was defined as direct orientation of the animals to the object while touching, sniffing or licking the object. The duration of investigation of the object was recorded with a stopwatch accurate to 0.1 s. The total time that the animal spent investigating was recorded over a period of 5 min.

Clonidine (0.1 mg/kg IP) was injected 30 min before testing. Since relatively consistent behavioral effect with small variations between the groups was observed at a dose of 0.1 mg/kg, this dose was used for subsequent interaction studies. Generally, other drugs were given subcutaneously once a day (10.00–11.00 a.m.) for 4 consecutive days preceding the clonidine and the last dose was given 30 min prior to clonidine (for doses see Fig. 3). Yohimbine was injected in a single doses (1.0 and 2.5 mg/kg) 30 min prior to clonidine. Flupentixol was injected twice – 2 mg/kg SC 4 days before clonidine and 1.0 mg/kg 24 h before clonidine. The effects of drugs alone without interaction with clonidine were assessed in a separate experiment. Control animals received saline (0.1 ml SC) once a day for 5 consecutive days. The animals were tested 30 min after last injection.

Drugs. The drugs used were clonidine (Boehringer-Ingelheim, FRG), yohimbine HCl (Merck, Darmstadt, FRG), amitriptyline (Hoffmann-La Roche, Basel, Switzerland), desipramine HCl (Ciba-Geigy, Basel, Switzerland), mianserine HCl (Organon, Oss, The Netherlands), imipramine HCl (Ciba-Geigy), clomipramine HCl (Ciba-Geigy), nomifensine hydrogen maleate (Hoechst AG, Frankfurt am Main, FRG), D(+) amphetamine sulphate (Smith Kline and French Laboratories, Philadelphia, PA, USA), diazepam (POLFA, Kutno, Poland), pimozide (Janssen Pharmaceutica N.V., Beerse, Belgium), flupentixol decanoate (Flupentixol depot. Lundbeck, Copenhagen, Denmark). With few exceptions drugs were dissolved in 0.9% NaCl and injected in a volume of 2 ml/kg. Diazepam was suspended in a 1% carboxymethyl-cellulose aqueous solution, flupentixol was suspended in rape oil.

Statistics. Statistical analysis of the data was performed using the Mann-Whitney two-tailed test.

Results

In a dose of 0.05 mg/kg IP clonidine already decreased both locomotor activity (ambulation) and exploration of the novel object but only slightly reduced rearing. There were further reductions at higher doses (Fig. 1). As previously mentioned, a dose of 0.1 mg/kg was chosen for subsequent interaction studies. The clonidine dose-dependent depressant effect is

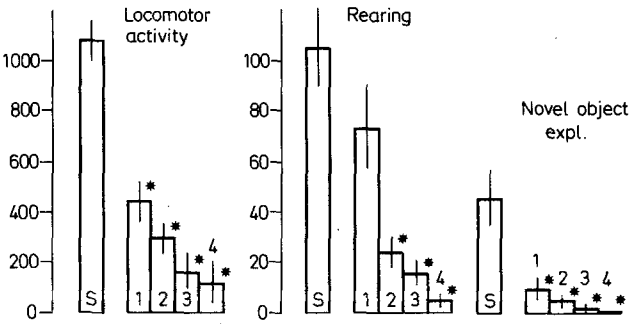

Fig. 1. Effect of clonidine on behavior of gerbils. Mean counts ± SEM of locomotor activity (ambulatory movements), rearing and exploration of the novel object (see text for details). The number of animals tested at each dose level was 12–16. All animals received single daily injections of saline (0.1 ml IP) for 4 consecutive days and then on day 5 saline (*S*) or clonidine in progressive doses: *1*, 0.05 mg/kg, *2*, 0.1 mg/kg, *3*, 0.15 mg/kg, *4*, 0.2 mg/kg, $P<0.01$ as compared with saline-treated animals (Mann-Whitney, two-tailed test).

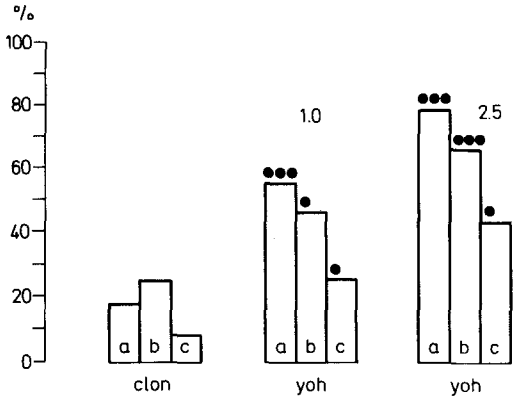

Fig. 2. Effect of yohimbine on clonidine-induced behavioral depression in gerbils. The height of the bars represents the mean response calculated as a percent of control reaction of saline-treated animals. All animals were pretreated 4 days with saline (see Fig. 1) and on day 5 received either saline or yohimbine (*yoh*) 30 min prior to clonidine (*clon*) at the dose of 0.1 mg/kg. Doses of yohimbine marked on the diagram (mg/kg). The number of animals tested in each group was 12–14. Abbreviations are: *a*, ambulation; *b*, rearing, *c*, exploration of the novel object. The raw control scores (saline treated animals) from which the percentages were derived are: ambulation 1082 ± 150.0, rearing 104 ± 20.0, exploration of the novel object 45 ± 6.1 (mean values ± SEM from 20 animals). ● = $P<0.05$, ●●● = $P<0.01$ in respect to clonidine (*clon*) group (Mann-Whitney. two-tailed test)

presented using raw data. However, to avoid variations between the groups the interaction data are presented as percentage changes (although the statistics were performed on raw data).

Yohimbine antagonized the clonidine-induced behavioral depression in a dose-dependent manner (Fig. 2). The gerbils pretreated with antidepressants were less susceptible to clonidine. However, there were substantial differences between particular drugs. The differences involved mostly the exploration of the novel object. Desipramine, imipramine, clomipramine and mianserine clearly antagonized all of the behavioral effects of clonidine, whilst amitriptyline and nomifensine did not have any particular influence on exploring the novel object. Similarly, amphetamine (given in a single dose) antagonized the inhibition of ambulation and rearing

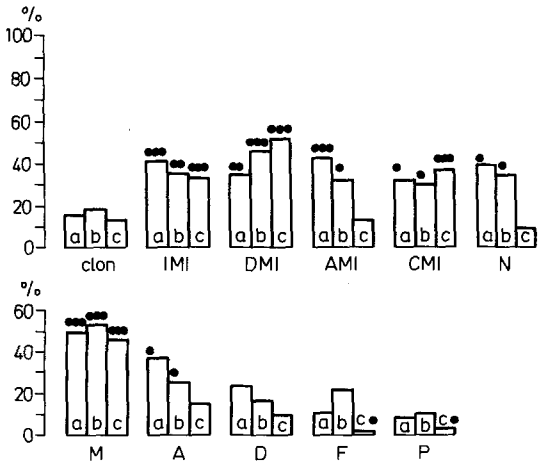

Fig. 3. Effects of drugs on clonidine-induced suppression of locomotion and exploratory activity in gerbils. The height of the bars represents the mean response calculated as percent of control response of saline treated animals (for raw values see Fig. 2). All drugs were given in single daily doses for 4 consecutive days and then the last dose was given 30 min before clonidine (for dosage of flupentixol see text). The number of animals tested in each group was 12–16. Abbreviations are: *a*, ambulation; *b*, rearing; *c*, exploration of the novel object; *IMI*, imipramine (single daily dose 2 mg/kg); *DMI*, desipramine (2 mg/kg); *AMI*, amitryptiline (2 mg/kg); *CMI*, clomipramine (2 mg/kg); *N*, nomifensine (4 mg/kg); *M*, mianserine (2 mg/kg); *A*, amphetamine (1 mg/kg); *D*, diazepam (1 mg/kg), *F*, flupentixol; *P*, pimozide (0.2 mg/kg); *clon*, clonidine-treated animals pretreated with saline (see Fig. 2), ● = $P < 0.05$, ●● = $P < 0.02$ and ●●● = $P < 0.01$ in respect to clonidine (*clon*) group (Mann-Whitney, two-tailed test)

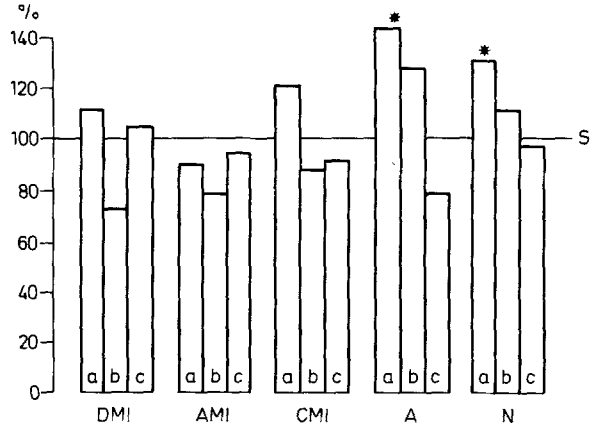

Fig. 4. Effects of drugs given alone on locomotion and exploratory activity in gerbils. All drugs were given in a manner similar to that described in Fig. 3, the only difference was that saline (0.1 ml) instead of clonidine was injected 30 min after the last dose of drug. Animals were tested 30 min later. The number of animals tested in each group was 12–14. The height of the bars represents the mean response calculated as a percent of reaction of saline treated gerbils (solid horizontal line, *s*). The raw values of the saline treated group ($n = 12$) are: ambulation, 890 ± 98.0; rearing, 87.0 ± 18.0 and exploration of the novel object 29.0 ± 8.767. Note that only amphetamine (*A*) and nomifensine (*N*) produced significant change in locomotion (* = $P < 0.05$, Mann-Whitney two-tailed test)

produced by clonidine but failed to antagonize the clonidine effect on investigation of the novel object (Fig. 3).

Other drug classes such as the benzodiazepines (e.g. diazepam) and neuroleptics (flupentixol and pimozide) lacked an anticlonidine action and even potentiated clonidine-induced sedation (Fig. 3). Pimozide potentiated all clonidine effects whilst flupentixol increased clonidine-induced suppression of exploration of the novel object. None of the antidepressant drugs alone influenced the behavior of gerbils (see Fig. 4). The effects of imipramine and mianserine are not shown. The only exception was nomifensine which, like amphetamine, increased by itself locomotion (ambulation) of untreated gerbils.

Discussion

A depressant effect of clonidine on locomotion and exploratory behavior of normal gerbils was manifested by a marked, dose-related decrease in ambulation, rearing and exploration of the novel object. This result is consistent with other observations that clonidine almost uniformly induces behavioral depression in rats and mice (Laverty and Taylor 1969; Delbarre and Schmitt 1973; Strömbom 1975; Hano et al. 1978; Delini-Stula et al. 1979; Gower and Marriott 1980; Kostowski and Malatyńska 1980; Kostowski et al. 1981; Kostowski 1981).

We suppose that all the components of the behavior of the gerbils are at least partially mediated by central presynaptic α_2 adrenoceptors since these are blocked by clonidine and restored with yohimbine, an antagonist of α_2 adrenoceptors (Borowski et al. 1976; Andén et al. 1976). A number of investigators have shown that biochemical and behavioral effects of clonidine can be antagonized by drugs possessing preferential presynaptic α receptor-blocking activity such as yohimbine, piperoxan and tolazoline (Strömbom 1975; Andén et al. 1976; Delini-Stula et al. 1979). It should be noted that the action of yohimbine was not simply the result of an stimulant action of this drug, since yohimbine is known to decrease rather than increase exploration of untreated rats (Delini-Stula et al. 1979) and gerbils (Kostowski and Malatyńska, unpublished results).

Interestingly, not all the components of the behavior of the gerbils were influenced to the same extent by antidepressants and stimulants used in our study. Ambulation was increased by all drugs approximately to the same extent, but substantial differences were recorded when rearing and novel object exploration were measured. Neither amphetamine nor nomifensine restored the latter component in clonidine-treated gerbils. This behavioral component is in our opinion related rather to the "motivational" than "locomotor" aspects of exploration and may be useful in distinguishing drugs acting upon motivational processes from those acting mainly upon locomotor activity. In fact, the pharmacological profile of amphetamine and nomifensine is somewhat different from that of tricyclic antidepressants. Amphetamine is a psychostimulant which inhibits amine uptake and releases catecholamines from nerve terminals (Carlsson et al. 1965; Van Rossum 1970). Nomifensine is known to inhibit dopamine neuronal uptake, and unlike the tricyclic antidepressants (but similarly to amphetamine) produces locomotor excitation and EEG arousal (Hoffman 1973; Gerhards et al. 1974; Samanin et al. 1975; Miller and Wheatley 1978).

Desipramine and mianserine were relatively the most potent among the antidepressants in preventing the clonidine suppression of exploratory behavior and locomotion in gerbils. Desipramine like other secondary amines preferen-

tially inhibits the uptake of NE (Carlsson et al. 1969; Meek et al. 1970). Chronic treatment with this drug has been recently reported to antagonize effects of clonidine on noradrenergic neurons as well as clonidine-induced sedation (Dubocovich et al. 1979; McMillan et al. 1980; Spyraki and Fibiger 1980; Gower and Marriott 1980). Mianserine, a tricyclic compound with an additional "side chain cycle" increased NE neurotransmission by a presumed presynaptic α adrenoceptor blocking action (Baumann and Maitre 1977) and has been also found to reduce both biochemical and behavioral effects of clonidine (Gower and Marriott 1980).

Both imipramine and clomipramine showed an effective anticlonidine activity and antagonized all clonidine effects including suppression of exploration of the novel object. These drugs belong to tertiary amines of tricyclic antidepressants and inhibit strongly the uptake of serotonin (Carlsson et al. 1969; Modigh 1973) being relatively less active upon NE uptake mechanisms.

Antidepressants could inhibit clonidine effects in several ways. If we consider that the depressive action of clonidine is related to reduced release of NE due to stimulation of presynaptic inhibitory α_2 adrenoceptors, antidepressants could counteract this effect by inhibiting reuptake of NE and by blocking (e.g. mianserine) the presynaptic α_2 adrenoceptors. The problem seems, however, to be more complex since at least some of the clonidine effects are related to action upon α_2 adrenoceptors located postsynaptically. Clonidine has been reported to inhibit the firing of the NE neurons of the locus coeruleus either by acting on presynaptic or postsynaptic receptor sites (Svensson et al. 1975; Strömbom 1975). Besides noradrenergic receptors, clonidine affects also other neuronal and receptor systems: it stimulates central epinephrine receptors (Bolme et al. 1974) and histamine H_2 receptors (Audiger et al. 1976). There are also limited effects on central serotonergic and cholinergic neurons (Andén et al. 1970; Svensson et al. 1975; Maj et al. 1975).

More recent studies have shown that chronic administration of antidepressants produced changes in NE neurotransmission owing to the development of compensatory receptor mechanisms. Thus it has been reported that multiple injections of tricyclic antidepressants produce phenomena indicating a reduction of sensitivity of α_2 presynaptic adrenoceptors (Svensson and Usdin 1978; Vetulani et al. 1980; Vetulani et al. 1982) and postsynaptic adenyl cyclase-linked receptor systems (Vetulani et al. 1976; Schultz et al. 1978; Sulser 1979). In light of these observations, antidepressants could counteract the clonidine effect by reducing sensitivity of presynaptic receptors on central NE neurons. It is uncertain, however, whether this mechanism can be considered in relation to our experiment since gerbils were treated with antidepressants for relatively short periods (5 days). Vetulani et al. (1982) found that 4-week but not 1-week pretreatment with imipramine significantly depressed the binding of ^{3}H-clonidine to cortical membranes in rats. Moreover, Spyraki and Fibiger (1980) reported that 15-day but not 2-day pretreatment with desipramine significantly reduced the effect of clonidine on exploratory behavior. On the other hand, Gower and Marriott (1980) reported the inhibition of clonidine-induced sedation in mice by single doses of antidepressants (imipramine, amitriptyline and mianserine) administered orally 1–5 h prior to clonidine. Our results indicate that a 5-day pretreatment with antidepressants was sufficient to produce changes in NE transmission counteracting the clonidine-induced inhibition. Unpublished observations indicate that single doses of antidepressants used by us given 30 min before clonidine failed to produce the same effects as 5-day pretreatment in gerbils. The only exception was nomifensine which significantly improved the locomotor activity (ambulation) but not exploratory behavior (Kostowski and Malatyńska, unpublished results).

Our test seems to be highly sensitive, since relatively low doses of antidepressants were able to antagonize the effects of clonidine. For example Spyraki and Fibiger (1980) used desipramine at a dose of 5 mg/kg twice daily for 15 days, Vetulani et al. (1982) used imipramine at 10 mg/kg for 4 weeks, Gower and Marriott (1980) tested tricyclic antidepressants in single doses from 10 to 80 mg/kg.

Another possible mechanism of action of antidepressants which may account for facilitatory action on NE neurotransmission is the antiserotonin action. Certain antidepressants such as imipramine, nortriptyline and mianserine possess serotoninergic receptor blocking activity in doses near to those causing amine uptake inhibition (Ögren et al. 1979). Chronic treatment with some antidepressants leads to reduced serotonergic transmission (Fuxe et al. 1977). Since serotonergic neurons are supposed to exert an inhibitory influence upon NE neurons the antiserotonergic action of antidepressants may be considered as "reinforcing" their noradrenergic action (Kostowski 1980, 1981).

Unexpectedly, amitriptyline, like amphetamine and nomifensine did not affect exploration of the novel object in clonidine-treated gerbils. This tertiary amine, like clomipramine is a potent inhibitor of serotonin uptake (Modigh 1973). There is, however, a substantial difference between amitriptyline and other tricyclic antidepressants used in our study. Evidence has been presented which indicates that amitriptyline is several times more potent than other antidepressants in blocking postsynaptic α adrenoceptors in the brain (Palmer 1976; U'Prichard et al. 1978). Moreover, amitriptyline has been shown to be a potent histamine H_1 receptor antagonist (Taylor and Richelson 1980). It has been suggested that both the antiadrenergic and antihistaminic action of amitriptyline may contribute to its sedative action (U'Prichard et al. 1978; Taylor and Richelson 1980).

Our findings indicate that the anti-clonidine action of antidepressants is not simply due to the stimulating action upon the behavior of gerbils. Only amphetamine and nomifensine slightly increased locomotion (ambulation) without effect upon exploratory activity.

Our preliminary data indicate that major and minor tranquilizers and psychostimulants are rather ineffective in antagonizing clonidine-induced behavioral depression in gerbils. Amphetamine failed to prevent clonidine inhibition of exploration of the novel object. It was, however, effective in counteracting the effect of clonidine upon rearing and ambulation. Diazepam remained without effect upon behavioral pattern in clonidine-treated animals, whilst neuroleptics (flupentixol and pimozide) enhanced behavioral depression. Further studies including other drug classes such as monoamine oxidase inhibitors, cholinolytics and antihistaminic agents are obviously needed. Our test also requires most extensive testing of other atypical antidepressants and should be extended to longer treatment and other doses of drugs. Nevertheless, it appears that clonidine-induced behavioral depression in gerbils may be suitable for use as a simple animal model of depression and could provide a method for the selection of drugs suspected to have antidepressant action.

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References

Andén N-E, Corrodi H, Fuxe K, Hökfelt B, Hökfelt T, Rydin C, Svensson T (1970) Evidence for a central noradrenaline receptor stimulation by clonidine. Life Sci 9:513–523

Andén N-E, Grabowska M, Strömbom U (1976) Different alpha-adrenoceptors in the central nervous system mediating biochemical and functional effects of clonidine and receptor blocking agents. Naunyn-Schmiedeberg's Arch Pharmacol 292:43–52

Audiger Y, Virion A, Stawartz JC (1976) Stimulation of cerebral histamine H_2 receptors by clonidine. Nature 262:307–308

Baumann PA, Maitre L (1977) Blockade of presynaptic α receptors and of amine uptake in the rat brain by the antidepressant mianserine. Naunyn-Schmiedeberg's Arch Pharmacol 300:31–37

Bolme P, Corrodi H, Fuxe K, Hökfelt T, Lidbrink P, Goldstein M (1974) Possible involvement of central adrenaline neurons in vasomotor and respiratory control. Studies with clonidine and its interaction with piperoxane and yohimbine. Eur J Pharmacol 28:89–94

Borowski E, Ehrl H, Starke K (1976) Relative pre- and postsynaptic potencies of α adrenolytic drugs. Naunyn-Schmiedeberg's Arch Pharmacol Suppl 293:R2

Carlsson A, Corrodi H, Fuxe K, Hokfelt T (1969) Effects of some antidepressant drugs on the depletion of intraneuronal brain catecholamine stores caused by 4-α-dimethyl-metatyramine. Eur J Pharmacol 5:367–373

Carlsson A, Lundquist M, Dahlström A, Fuxe K, Masuoka D (1965) Effects of the amphetamine group on intraneuronal brain amines in vivo and in vitro. J Pharm Pharmacol 17:521–526

Cheal ML (1978) Stimulus elicited investigation in the Mongolian gerbil (Meriones unguiculatus). J Biol Psychol 20:26–32

Delbarre B, Schmitt H (1973) A further attempt to characterize sedative receptors activated by clonidine in chicken and mice. Eur J Pharmacol 22:355–359

Delini-Stula A, Baumann P, Büch O (1979) Depression of exploratory activity by clonidine in rats as a model for the detection of relative pre- and postsynaptic central noradrenergic receptor selectivity of α adrenolytic drugs. Naunyn-Schmiedeberg's Arch Pharmacol 307:115–122

Drew GM, Gower A, Marriott AS (1977) Pharmacological characterization of α adrenoceptors which mediate clonidine-induced sedation. Br J Pharmacol 61:468P

Dubocovich M, Langer SZ, Pelay F (1979) Cocaine and desipramine antagonize the clonidine-induced inhibition of ^{3}H-noradrenaline release from the rat cerebral cortex. Br J Pharmacol 67:417P–418P

Franklin KB, Herberg LJ (1977) Presynaptic α adrenoceptors: the depression of self-stimulation by clonidine and its restoration by piperoxane but not by phentolamine or phenoxybenzamine. Eur J Pharmacol 43:33–38

Fuxe K, Ögren S, Agnati L, Gustafsson JA, Jonsson G (1977) On the mechanism of action of the antidepressant drugs amitriptyline and nortriptyline. Evidence for 5-hydroxytryptamine receptor blocking activity. Neurosci Lett 6:339–343

Gerhards HJ, Carenzi A, Costa E (1974) Effect of nomifensine on motor activity, dopamine turnover rate and cyclic 3′,5′-adenosine monophosphate concentrations of rat striatum. Naunyn-Schmiedeberg's Arch Pharmacol 286:49–52

Gower A, Marriott AS (1980) The inhibition of clonidine-induced sedation in the mouse by anti-depressant drugs. Br J Pharmacol 69:287P

Hano J, Vetulani J, Sansone M, Oliverio A (1978) Effect of clonidine, amphetamine and their combinations on the locomotor activity of CD-1 and C57BL/6 mice. Pharmacol Biochem Behav 9:741–746

Hoffman J (1973) 8-Amino-2-methyl-4-phenyl-1,2,3,4-tetrahydroisochinoline, a new antidepressant. Arzneim Forsch 23:45–48

Jouvent R, Lecrubier Y, Puech AJ (1980) Antimanic effect of clonidine. Am J Psychiatry 137:1275–1276

Kitayama I, Nomura J, Hatotani N (1980) Studies on pathogenesis of depression using animal model. Abstracts of the 12th CINP Congress, Göteborg, 1980, Pergamon, Oxford p 205

Kostowski W (1980) Noradrenergic interactions among central neurotransmitters. In: Essman WB (ed) Neurotransmitters, receptors and drug action. Spectrum Publications Inc. New York, pp 47–65

Kostowski W (1981) Brain noradrenaline, depression and antidepressant drugs: Facts and hypothesis. TIPS 2:314–317

Kostowski W, Malatyńska E (1980) Clonidine-induced suppression of exploration and locomotor activity in Mongolian gerbils: A new animal model of depression. Naunyn-Schmiedeberg's Arch Pharmacol Suppl 313:R31

Kostowski W, Płaźnik A, Puciłowski O, Bidzinski A, Hauptmann M (1981) Lesion of serotonergic neurons antagonizes clonidine-induced suppression of avoidance behavior and locomotor activity in rats. Psychopharmacology 73:261–264

Langer SZ (1974) Presynaptic regulation of catecholamine release. Biochem Pharmacol 23:529–538

Laverty R, Taylor KM (1969) Behavioural and biochemical effects of 2-(2,6-dichlorophenyloamino)-2-imidazoline hydrochloride (ST 155) on the central nervous system. Br J Pharmacol 35:252–264

Maas JW, Fawcett J, Dekirmenjan H (1968) 3-Methoxy-4-hydroxyphenylglycol (MHPG) excretion in depressive states. Arch Gen Psychiatry 19:129–133

Maj J, Baran L, Sowińska H, Zieliński M (1975) The influence of cholinolytics on clonidine action. Pol J Pharmacol Pharm 27:17–21

McMillan BA, Warnack W, German DC, Shore PA (1980) Effects of chronic desipramine treatment on rat brain noradrenergic responses to α adrenergic drugs. Eur J Pharmacol 61:239–246

Meek J, Fuxe K, Anden N-E (1970) Effects of antidepressant drugs of the imipramine type on the central 5-hydroxytryptamine neurotransmission. Eur J Pharmacol 9:325–332

Miller AA, Wheatley PL (1978) Effects of some antidepressants on the EEG of the conscious rats. Proceedings of the 7th International Congress of Pharmacology, Abstracts, Pergamon, Oxford p 346

Modigh K (1973) Effects of clomipramine (Anafranil) on neurotransmission in brain monoamine neurons. J Int Med Res 1:274–280

Ögren PO, Fuxe K, Agnati LF, Gustafsson JA, Jonsson G, Holm AC (1979) Reevaluation of the indoleamine hypothesis of depression. Evidence for a reduction of functional activity of central 5-HT systems by antidepressant drugs. J Neural Transm 46:85–103

Palmer GC (1976) Influence of tricyclic antidepressants on the adenylate cyclase phosphodiesterase system in the rat cortex. Neuropharmacology 15:1–7

Robson RD, Antonaccio MJ, Saelens JK, Lebman J (1978) Antagonism by mianserin and classical α adrenoceptor blocking drugs on some cardiovascular and behavioral effects of clonidine. Eur J Pharmacol 47:431–442

Rossum JM Van (1978) Mode of action of psychomotor stimulant drugs. Int Rev Neurobiol 12:307–383

Samanin R, Bernasconi S, Garattini S (1975) The effect of nomifensine on the depletion of brain serotonin and catecholamines induced respectively by fenfluramine and 6-hydroxydopamine in rats. Eur J Pharmacol 34:377–380

Schultz J (1976) Psychoactive drug effects on a system which generates cyclic AMP in brain. Nature 261:417–418

Spyraki Ch, Fibiger HC (1980) Functional evidence for subsensitivity of noradrenergic α_2 receptors after chronic desipramine treatment. Life Sci 27:1863–1867

Starke K, Montel H, Endo T (1975) Relative potencies of sympathomimetic drugs on pre- and postsynaptic adrenoceptors. Naunyn-Schmiedeberg's Arch Pharmacol 287:R5

Strömbom U (1975) Effects of low doses of catecholamine receptor agonists on exploration in mice. J Neural Transm 37:229–232

Sulser F (1979) New perspectives on the mode of action of antidepressant drugs. TIPS 1:92–94

Svensson TH, Bunney BS, Aghajanian GK (1975) Inhibition of both noradrenergic and serotonergic neurons in brain by the α adrenergic agonist clonidine. Brain Res 92:291–305

Svensson TH, Usdin T (1978) Feedback inhibition of brain noradrenaline neurons by tricyclic antidepressants: α receptor mediation. Science 202:1089–1091

Tang SW, Helmeste DM, Stancer HC (1979) The effect of clonidine withdrawal on total 3-methoxy-4-hydroxyphenylglycol in the rat brain. Psychopharmacology 61:11–18

Taylor JE, Richelson F (1980) High affinity binding of tricyclic antidepressants to histamine H_1 receptors: fact and artifact. Eur J Pharmacol 67:41–46

Thiessen DD (1973) Foodhold for survival. American Scientist 61:346–351

U'Prichard D, Greenberg D, Sheean P, Snyders S (1978) Tricyclic antidepressants: therapeutic properties and affinity for α noradrenergic receptor binding sites in the brain. Science 199:197–198

Vetulani J, Pilc A, Rokosz A (1980) The effect of multiple imipramine administration on monoaminergic systems of the rat brain. Pol J Pharmacol Pharm 33:523–530

Vetulani J, Pilc A, Antkiewicz-Michaluk L, Gołembiowska-Nikitin K, Lebrecht U, Rokosz A (1982) Adaptive change of monoaminergic systems in rats treated chronically with imipramine electroshock or serotoninomimetics. In: Marsan CA, Matthies H (eds) Neuronal plasticity and memory formation, Raven, New York, pp 405–424

Vetulani J, Stawarz JR, Dingell JV, Sulser F (1976) A possible common mechanism of action of antidepressant treatments: reduction in the sensitivity of the noradrenergic cyclic AMP generating system in the rat limbic forebrain. Naunyn-Schmiedeberg's Arch Pharmacol 293:109–114

Warsh JJ, Li PP, Godse DD, Cheung S (1981) Brain noradrenergic neuronal activity affects 3,4,-dihydroxyphenylethylene glycol (DHPG) levels. Life Sci 29:1303–1307

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