Section I - CNS Agents

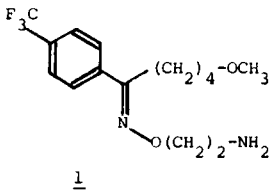
Editor: Leslie G. Humber, Ayerst Laboratories, Montreal, Canada

Chapter 1. Antidepressants

Ivo Jirkovsky and Wilbur Lippmann, Ayerst Laboratories, Montreal, Canada

In 1977, interest has continued in the discovery and evaluation of compounds which are relatively selective blockers of serotonin (5-HT) or noradrenalin (NA) uptake in view of the concept of subclasses of depression. Agents that block dopamine (DA) uptake or 5-HT receptors also received attention as potential antidepressants. For the first time, a clinical efficacy of relatively selective 5-HT uptake blockers has been demonstrated. Repeating the pattern noted last year, studies were carried out on the mode of action of antidepressants at the molecular level. New pharmacological methods to identify or to further distinguish between antidepressant agents were reported. Several compounds have remained in the focus of interest for a number of years, and the reader would find value in consulting the past issues of this series[1,2] for background information. Specific reviews on chlorimipramine,[3,4] doxepin,[5] maprotiline,[6] viloxazine,[7] lofepramine,[8] nomifensin,[9] and TRH[10,11] have appeared. Current knowledge on the depressive disorders[12] and serotonin neurons in the CNS[13] have been summarized. Also, clinical use of lithium in psychiatry[14] and antidepressant therapy by sleep deprivation[15] have been reviewed.

Fluvoxamine (1) was demonstrated to exhibit almost exclusive 5-HT uptake inhibiting properties being effective both *in vitro* and *in vivo* in rat brain.[16] The potency of 1 was similar to or greater than that of imipramine. It showed activities related to this action such as decreasing rat brain 5-HT turnover and potentiating the 5-HTP behavioral syndrome in the mouse. NA uptake *in vitro* and *in vivo* in rat brain and related pharmacological activities were unaffected, or only slightly inhibited; also, no inhibition of displacement of DA from rat brain *in vitro* was exhibited. A preliminary clinical trial was carried out with 1 in endogenous depressed patients employing a 5-week treatment (rising dose) with mean daily dosages of approximately 150 mg.[17] A marked improvement of the overall and detailed psychopathology was observed as early as the end of the first week of treatment and leveled off from the third week on. Bipolar patients tended to improve more than the unipolars, retarded depressions more than agitated ones.



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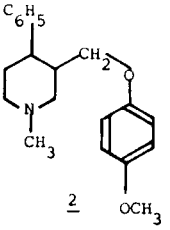

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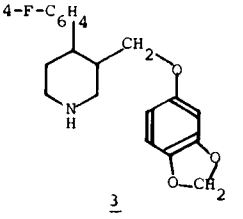

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Femoxetine (FG-4963, 2) was found to be significantly inferior (at 3x200 mg/day) to amitriptyline (at 3x50 mg/day) in treatment of endogenously depressed patients over a 6-week period.[18] Effects of 2 on tyramine and NA pressor responses were weaker than those of amitriptyline. An analog FG-7051 (3) produced hypermotility and an anticonvulsant effect in combination with 5-HTP when given 1-6 h (0.4-1 mg/kg) or 24 h (5-15 mg/kg) prior to 5-HTP.[19] Chlorimipramine was active only at 20-50 mg/kg and 1-2 h before 5-HTP administration.

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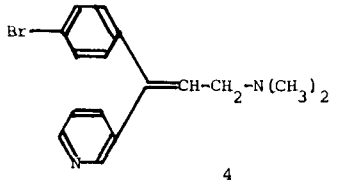

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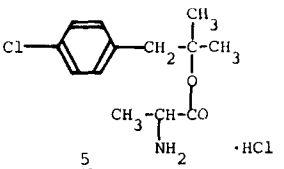
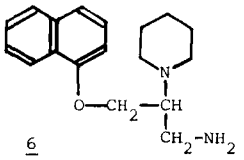


5

Zimelidine (H-102-10, 4) enhanced the spontaneous efflux of 5-HT from rat brain synaptosomes, but significantly inhibited its induced increase.[20] An initial clinical trial[21] with 4 in depressed patients utilized biochemical methodology and indicated potential usefulness of the drug. The 5-HT uptake was markedly inhibited in vitro by the plasma samples drawn from the patients. The study also confirmed that the desmethyl metabolite is approx. 10x as potent as the parent drug in inhibiting 5-HT uptake. Zimelidine was found to be a less potent cardiac depressant (myocardial contractility in dogs) than amitriptyline, although higher doses, by infusion, produced serious circulatory depression.[22] In an open clinical study,[23] 4 was administered for 20 days (150 mg/day) to 10 depressed female patients and good to moderate therapeutic responses were observed in 7 patients between the 4th and 12th day. The treatment had to be discontinued in 3 cases because of agitation symptoms. Alaproclate (A-23189, 5) was 3-30x less effective than chlorimipramine in increasing the induced efflux of 5-HT from rat brain synaptosomes.[20] The kinetics indicated competitive antagonism between 5 and p-chloroamphetamine. In blocking 5-HT uptake, 5 was less potent than chlorimipramine (8x in vitro and 2.5x in vivo).[24] Interestingly, 5 exhibited a 100-fold greater potency in blocking 5-HT than NA uptake. The SAR studies of alaproclate analogs suggested that the presence of the geminal dimethyl moiety was critical for the activity.



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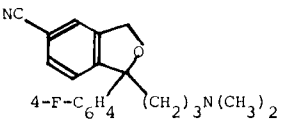

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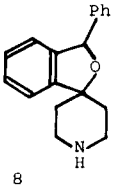
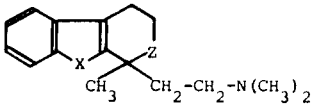


8

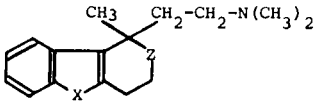
Compound 6, a derivative of (naphthalenyloxy)propanediamine, was reported to be a potent and specific inhibitor of the 5-HT neuronal uptake mechanism.[25] Similarly to chlorimipramine, 6 antagonized the depletion of rat brain 5-HT induced by various agents in vivo, potentiated the behavioral effects of 5-HTP and antagonized fenfluramine-induced anorexia. Compound 6 decreased rat brain 5-HT turnover. In vitro 6 was also equivalent in potency to chlorimipramine in blocking 5-HT uptake into rat brain. In vivo 6 and chlorimipramine did not block rat brain catecholamine uptake; 6 did not inhibit NA uptake in mouse heart whereas chlorimipramine was effective. Compound 6 did not exhibit appreciable anticholinergic effects or MAO inhibition in the mouse.

Citalopram (Lu 10-171, 7) is a new phthalane derivative exhibiting selective and potent inhibitory action on 5-HT uptake mechanism.[26] In this regard 7 was 2-10x more active than chlorimipramine in vitro or in vivo in different animal species and preparations. The metabolites of 7, i.e., the desmethyl-, didesmethyl-derivative and the corresponding N-oxide, showed generally weaker inhibitory activities. Compound 7 and its metabolites were devoid of NA uptake inhibiting activity, in contrast to chlorimipramine, and inhibited DA uptake only at extremely high concentrations; chlorimipramine exhibited the latter inhibitory activity at lower concentrations.

Citalopram reduced rat brain 5-hydroxyindoleacetic acid for 1-24 h, maximally at 2-6 h, whereas that of 5-HT was practically unchanged.[27] Thus, 7 decreased the turnover of brain 5-HT and this was confirmed in other models. In pharmacological tests, 7 potentiated the activities of 5-HT, 5-HTP and tryptophan in various species *in vivo* and *in vitro* and was 5-10x more active than chlorimipramine; the various metabolites were generally of lower potency.[28] Compound 7 induced or potentiated hyperthermia in animals treated with agents which increased 5-HT. Induced ptosis and immobility were only very weakly antagonized; very weak *in vitro* anticholinergic and antihistaminic activities were observed. These weak activities are in contrast to those of tricyclic antidepressants.[28] The spiro(isobenzofuran-piperidine) 8 (HP-505) was reported to prevent tetrabenazine ptosis and to inhibit brain NA uptake at lower concentrations than desipramine.[29] Relative to chlorimipramine, 8 was 2.5x less potent in blocking 5-HT uptake. Analogs of 8 containing a heteroatom attached to the nitrogen were prepared, and only the N-hydroxy derivative was equipotent with 8 in preventing tetrabenazine ptosis.[30]

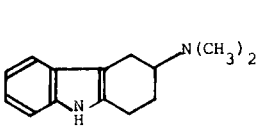


9	X = N-Et	Z = S
10	X = N-Et	Z = CH_2
11	X = CH_2	Z = O



12	X = N-Et	Z = S
13	X = CH_2	Z = O

Tandamine (AY-23,946, 9) was shown to inhibit DA uptake into human blood platelets.[31,32] In healthy subjects, 9 exhibited anticholinergic effects, and it was twice as active as desipramine in inhibiting tyramine pressor responses. Pharmacological screening of tandamine and related compounds demonstrated[33] that the desmethyl derivative, a major metabolite of 9, is considerably less potent than 9 in reversing reserpine hypothermia. The reversed annelation of thiopyrano and indole rings (compound 12) modified both chemical and biological properties to a great extent.[33,34] In depressed patients, various studies with 9, i.e. clinical, psychometric and EEG studies, suggested that the drug has no anticholinergic effects, it is well tolerated, and may be of benefit in retarded depressions.[35] An improvement in the depressive symptomatology became statistically significant between the 1st and 2nd week of therapy. The potency of a related tetrahydrocarbazole 10 with respect to the inhibition of NA uptake *in vivo* was similar to that of desipramine.[36] Several modifications of the pirandamine molecule (11) have been reported,[37] and the biological results indicate that within this series there are no stringent structural requirements in regard to antidepressant-like properties.[37,38] The reversed annelation of pyrano and indene rings (compound 13) caused only moderate changes in activity.



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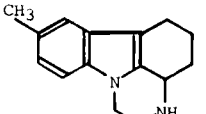

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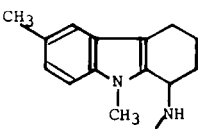
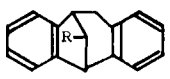
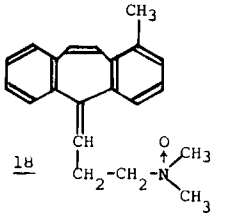


16

Cycloindole (WIN 27147-2, 14),a structurally modified dimethyltryptamine, prevented both the reserpine ptosis and amphetamine stereotyped behavior at 10 mg/kg.[39] Its 6,8-difluoroderivative is a chlorpromazine-like compound. In an uncontrolled clinical study with 14 (200-600 mg/day), all patients showed an improvement and adverse effects were not severe.[40] A placebo controlled trial confirmed that 14 has antidepressant-anxiolytic effects and sedative properties.[41] Recently, studies with 14 were discontinued due to toxicity problems (thrombocytopenia and bleeding). Pyrazidol (15) was 10x less potent than imipramine in inhibiting brain NA uptake; in contrast to imipramine, 15 also inhibited GABA uptake.[42] This compound prevented reserpine ptosis, increased phenamine group toxicity, potentiated 5-HTP head shaking, inhibited pressor response to tyramine, and inhibited NA uptake in isolated rat heart.[43] The seco-analog 16 exhibited a comparable activity only in the potentiation of 5-HTP. The SAR studies within this series have demonstrated the importance of the 8-methyl group.[43] A single injection of pyrazidol had no effect on brain or heart NA, but chronic administration or a higher dose increased heart NA levels.[44]



17 R = CH_2-$N(CH_3)_2$



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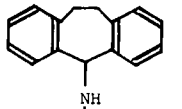
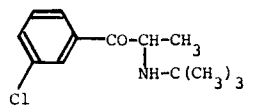


19

The phramacological profile of R-806 (17) was found to be similar to that of imipramine, except that 17 displays less anticholinergic activity.[45] Compound 17 potentiates the pressor response to NA, and in vitro, inhibits the NA uptake into rat brain more effectively than imipramine. In an open clinical trial[46] in endogenously depressed patients, treatment with 17 (10-30 mg/day) proved to be beneficial, and no anxiolytic or sedative effects were observed. The 1-methyl derivative of cyclobenzaprine N-oxide (Ro-8-1998, 18) was compared clinically with imipramine in a double-blind study[47] with a dose relationship of 2:1. The patients markedly improved in both groups and there was no difference in the overall results. The study did not confirm the expectation (based on animal experiments) that 18 might cause less anticholinergic side-effects than imipramine. After 10 days of treatment with 18, a significant decrease of systolic blood pressure and leucocytes was observed. The aminoacid S 1694 (19) produced an increased locomotor activity in mice, competitively inhibited DA uptake, and also caused a significant release of DA at low concentrations.[48] Similar effects on NA and 5-HT uptake and release mechanisms were obtained with higher concentrations of 19.



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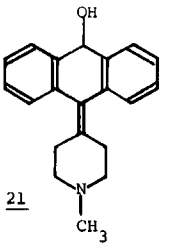

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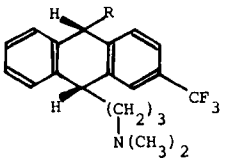


22 R = CH_3

23 R = H

Bupropion (Wellbatrin, 20) was reported to prevent tetrabenazine-induced sedation and ptosis in mice, and to antagonize reserpine hypothermia, although at slightly higher doses than amitriptyline.[49] In contrast to amitriptyline, 20 reduced both the intense motor activity and mortality caused by amphetamine. In in vitro rat brain preparations, bupropion had little

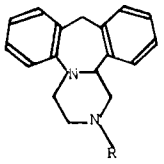
effect on 5-HT uptake, and it was 60x less potent than imipramine in inhibition of NA uptake. On the other hand, as an inhibitor of DA uptake, 20 was 6-fold and 20-fold more potent than imipramine and amitriptyline, respectively. When tested clinically in endogenous depression (double-blind, 20 vs placebo), therapeutic responses were noted after 1 week.[50] Danitracen (WA-335, 21), a base structurally related to cyproheptadine and pimethixen, elicited strong binding to 5-HT and histamine receptors.[51] Compared to imipramine, 21 was considerably less potent in reversing the reserpine hypothermia, but its sedative and anticholinergic effects were greater.[52] In healthy subjects, low doses of 21 caused quantitative EEG alterations that were typical for antidepressants.[53] In a double-blind trial with 3x1 mg/day of 21 vs 3x50 mg/day of amitriptyline, two-thirds of the patients showed a 50% improvement (Hamilton score) in both groups after 20 days.[54] Similar results were reported with a low dose of 21 (3 mg/day), however, a dose of 6 mg/day produced marked sedation.[55] Recently, 21 has also been shown to antagonize the action of oxotremorine[56] and the 5-HTP syndrome.[57]

The structure of fluotracene (SKF-28175, 22) bears resemblance to that of melitracene and dimethacrine. Interestingly, 22 exhibited properties of both antidepressant and antipsychotic agents.[58] It was more potent than imipramine in preventing reserpine ptosis and hypothermia, and its neuroleptic profile was comparable to that of thioridazine. Preliminary uncontrolled clinical studies with 22 indicated that this compound might be useful in both depressive and psychotic states. The 10-desmethyl analog (SKF-25971, 23) had a full range of neuroleptic properties in animals, and it was considerably more potent than chlorpromazine in many of the tests.

Melanocyte-stimulating hormone release inhibiting factor I (MIF-I), H-Pro-Leu-Gly-NH_2(L,L), given orally in double-blind studies with a placebo control, caused substantial improvement in endogenously depressed patients and this was observed within a few days.[59,60] The improvement was greater at lower doses (e.g., 60 and 75 mg/day) than at higher doses (e.g., 150 and 750 mg/day). This biphasic pattern of response was similar to that observed clinically with MIF-I in Parkinson's disease[60] and in tardive dyskinesia.[61] Improvement in the mood of parkinsonian patients receiving MIF-I has also been reported.[62,63] Various pharmacological studies in animals suggested the antidepressant activity of MIF-I;[64] the biphasic pattern was also reported. Neurochemically, some studies,[65,66] but not others,[67,68] demonstrated that MIF-I increases DA turnover. Recently, novel synthetic analogs of MIF-I were reported.[69] Some of the analogs exhibited a MIF-I-like behavioral potentiation (DOPA response in the mouse) with the most potent being H-Pro-MeLeu-Gly-NH_2(L,D) although it was less potent than MIF-I (the L-MeLeu analog being inactive).[70] The biphasic pattern of response was observed with the analog. In other pharmacological evaluation it was shown to be active orally.[70] Neurochemically, the analog at a higher dose than MIF-I, increased rat brain DA turnover.[66] Neither the analog nor MIF-I affected rat brain 5-HT turnover or the 5-HTP-induced behavioral syndrome in the mouse. The analog decreased rat brain NA turnover, while in contrast, MIF-I was ineffective even at a higher dose. It is of relevance in this regard[66] that tricyclic antidepressants, such as desimipramine,[71] also decrease NA turnover after a single dose.

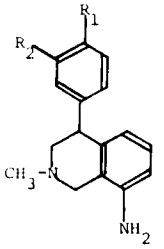
Mianserin (Org GB 94, 24), a clinically effective antidepressant,[72-76] does not exhibit an antidepressant-like profile in conventional animal screening tests.[77] Compound 24 possesses 5-HT receptor blocking properties like methysergide and cinanserin.[78] In a determination in rats of the ability of 24 and other drugs to antagonize the incapacitating effect of morphine on the performance of a two-way active avoidance response, 24 caused a significantly greater number of

escapes and intertrial responses than in placebo-treated animals.[79] The restoration of activities was also exhibited by methysergide and cinanserin, although not to as great an extent. However, the antidepressants amitriptyline and imipramine were ineffective. This further demonstrates a pharmacological difference between 24 and the tricyclic antidepressants. In vitro, 24 blocked the noradrenergic uptake mechanism being similar in potency to imipramine and amitriptyline.[80] In vivo, 24 was less active than tricyclic antidepressants in preventing the induced-decrease in rat heart and brain NA. Like tricyclic antidepressants, 24 was essentially devoid of the ability to block dopaminergic uptake mechanism in vitro and in vivo. The blockade by 24 of the 5-HT uptake mechanism in vitro was appreciably less than that of the tricyclic antidepressants and the drug was essentially devoid of activity in vivo. The lack of an appreciable effect in vivo on NA uptake would be consistent with an inability to block tyramine-induced effects in human subjects.[81] Compound 24 has been suggested to act by blocking presynaptic noradrenergic α-receptors, similar to phentolamine and phenoxybenzamine.[82] This would result in an increase in concentration of NA in the synaptic cleft. In regard to the latter, 24 blocked the NA uptake mechanism which would also lead to an increase in the NA concentration. Various additional observations[83] also suggest that the increase in the turnover of catecholamines is a specific action of 24 which is not exhibited by other antidepressants. Compound 24 also possessed post-synaptic α-receptor blocking activity under certain conditions; however, the role of such an activity in the overall action of the drug has yet to be defined.[82] Furthermore, the importance of the presynaptic α-blocking activity in the central action of the drug is not yet clear. Compound 25 was found to be a major metabolite of 24 in several animal species and in man.[84] This metabolic path seems to be general for similar compounds possessing a piperazine ring, and the N-oxide and the N-desmethyl derivative of 24 were also precursors of 25. Further studies indicated a role of microsomal enzymes in the formation of 25.[84]



24 R=CH_3

25 R=$(CH_2)_2COCH_3$



26 R_1=R_2=H

27 R_1=OH R_2=H

28 R_1=OH R_2=OCH_3

29 R_1=OCH_3 R_2=OH

In a single-blind comparative study[85] in elderly depressed patients with physical disability, both nomifensin 26 (75 mg/kg) and viloxazine[1,7] (150 mg/day) exhibited antidepressant activity. From the second week of treatment on, 26 showed more effect than viloxazine. Physical disability evaluation showed no differences for the two drugs at any period of the trials. No side effects were spontaneously reported by the patients.[85] Of 3 metabolites of 26, compound 27 was the most active one, while 28 and 29 exhibited little or no effect in pharmacological tests in mice.[86] In contrast to 26, the metabolite 27 possessed serotoninergic activity comparable to imipramine and chlorimipramine. In in vitro rat brain, 26 was a potent inhibitor of DA uptake[86] (of competitive type[87]) and of NA uptake;[86,87] 27 was similar in activity with regard to DA[86] and twice as active,[86] or slightly less active,[87] with respect to NA. Compounds 28 and 29 exhibited reduced activities.[86,87] All four compounds were more potent than imipramine, desipramine and chlorimipramine in inhibiting DA uptake.[86]

An *in vitro* study employing crude synaptosomal preparations from various rat brain regions was reported in which relevance of the DA uptake in the mechanism of action of various antidepressants was considered.[88] None of the numerous antidepressant drugs and other biogenic amine uptake blocking agents examined exhibited selective DA uptake inhibition. NA uptake inhibition was always greater, and generally much greater, even with the most potent DA uptake blocker 26.[88,89] It was pointed out[88] that it is difficult to ascribe the antidepressant effect to inhibition of uptake of a particular biogenic amine. The clinical doses of the drugs including 26 were cited to be 50-300 mg/day while there was much greater difference in the inhibitory uptake values. The importance of DA uptake was emphasized; it was also recognized that NA, DA and 5-HT might all be of relevance in the antidepressant effects and that their interactions might also be of importance.

Viloxazine possesses unique psychotropic activity in animals[90-92] and clinical results suggested that it might have a rapid antidepressant effect.[93] However, in a recent controlled trial, viloxazine at 3x100 mg/day was not as effective as placebo at the end of 1 week.[94]

Good therapeutic responses were obtained[95] in the treatment of different types of depression (10,000 patients in general practice) with 75 mg/day of maprotiline.[1,6] The results of 3 separate clinical studies[97] with maprotiline were in variance with the "reversed" catecholamine hypothesis of depression,[96] since no biphasic therapeutic response was observed, and the urinary MHPG concentrations were increased.[97]

In a preliminary open trial with salbutamol (3 mg infused twice daily), a drug which exhibits β_2-adrenergic receptor agonist activities, dramatic antidepressant effect was reported in endogenous depression with the effect appearing as early as 3 days; a distinct improvement in mood, retardation and anxiety was also observed by the third day.[98]

In the area of new models for the detection of antidepressant activity of drugs, the potential use of the bulbectomized rat[99] was further studied. Bilateral ablation of the olfactory bulbs of rats resulted in diverse behavioral changes and most of these were reversed by chronic pretreatment with antidepressant drugs.[100] The anxiosoif test is utilized in the assessment of the behavioral changes and the test is essentially a passive avoidance paradigm in which thirsty rats learn to avoid an electrified water spout. Bulbectomized rats showed deficient avoidance behavior. Various antidepressants reversed this effect; in contrast, anxiolytic and neuroleptic drugs aggravated the deficiency. A distinction was made between mianserin and other antidepressant drugs since removal of the olfactory bulbs tended to produce an increase in base-line levels of drinking in most experiments and this effect was reversed by mianserin but not by various other antidepressants.[100] A new behavioral model for detection of antidepressant agents was described based upon behavioral despair in rats[101] and mice.[102] A depressed state was induced by forcing the animals to swim in a narrow cylinder from which they could not escape. After a brief period of vigorous activity the animals adopted a characteristic immobile posture which was readily identifiable. Immobility was reduced by tricyclic antidepressants, MAO innibitors and atypical antidepressants, such as iprindole, mianserin and viloxazine, as well as by electroconvulsive shock. Psychostimulants also reduced immobility, but in contrast to antidepressants, caused marked motor stimulation. Immobility was not affected by minor or major tranquilizers. The mouse assay was more rapid, and thus, more suitable for the primary screening of potential antidepressant drugs.[102]

In a study of the mechanisms of the seizures induced by antidepressants which antagonize the uptake of biogenic amines, baboons with photosensitive epilepsy were employed.[103] Imipramine, chlorimipramine, and maprotiline, lowered the seizure threshold to a comparable extent. In contrast, nomifensin did not enhance myoclonic responses to photic stimulation, thereby being less epileptogenic. The tricyclic antidepressants, which can block 5-HT uptake, did not exhibit the augmentation of photically-induced epileptic responses after administration of 5-HTP. Thus, it was suggested that enhancement of serotoninergic activity following blockade of 5-HT reuptake within the brain is unlikely to be responsible for enhanced myoclonic responses and epileptogenic seizures observed after tricyclic antidepressants.

Antidepressant drugs such as amitriptyline and imipramine inhibited histamine- and dimaprit (S-[3-(N,N-dimethylamino)propyl]isothiourea, a potent and highly specific histamine$_2$-receptor agonist)-activated adenylate cyclase *in vitro* (e.g., homogenates of guinea pig hippocamus); dibenzepin and iprindole were 100x less active than amitriptyline.[104] The blockage of the H_2-receptors, in addition to other activities, may be of relevance for some of the pharmacological effects of the antidepressant drugs. Amitriptyline exhibited higher affinity for the H_2-receptor than the H_2-antagonist cimetidine, a clinically effective antiulcer agent.[105,106] Antidepressants also decrease gastric acidity and ulcers in animals and man (see references in 107;108).

The mode of action at the molecular level of the antidepressant drugs continues to be explored with regard to determining the basis for the discrepancy between the time-course of the biochemical and pharmacological responses which are observed within minutes or hours and their clinical antidepressant action which requires administration of the drugs for weeks in order to attain clinical efficacy.[109] Studies have suggested that the therapeutic action of tricyclic antidepressants may be related to postsynaptic adaptive changes in the sensitivity of the noradrenergic adenylate cyclase receptor system rather than to acute presynaptic events.[110] Chronic administration of antidepressants leads to subsensitivity of NA-stimulated adenylate cyclase *in vivo*.[110] This resistant state of the adenyl cyclase appears to be due to a decrease in the number of β-adrenergic receptors present.[109] In this regard it has been suggested that through regulation of the number of β-adrenergic receptors, the β-adrenergic catecholamines can regulate catecholamine sensitivity of tissues *in vivo*.[111] However, other factors appear to be of relevance. Although findings with the antidepressant desimipramine on the number of β-adrenergic receptors present are in accord, iprindole, which also causes β-adrenergic receptor subsensitivity, only exerts minimal effect at presynaptic neurons (see 109 for references) and thus the concentration of the NA at the synaptic cleft is not the only mechanism for the regulation of β-adrenergic receptor concentration.[109]

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