Chapter 5. Anorexigenic Agents

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Introduction - No breakthrough was made in the field of anorexigenic agents during 1967. With few exceptions, research continues to be concentrated on amphetamine like drugs.

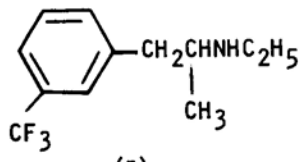
Obesity and weight control received considerable but unfavorable publicity in the lay press regarding the indiscriminate use of the so-called "rainbow pills"; the use of such preparations has been criticized.[1] Obesity, however, continues to be a problem of great concern in the United States and is considered to be a major health hazard.[2] An assessment of how anorexigenic agents are best used and the important role they play in weight control has been made.[3]

Mechanism of Action - The mechanism of action of anorexigenic agents has not been precisely demonstrated, although sufficient evidence has accumulated to fix the probable locus of their suppressant action on the lateral nuclei or feeding center of the hypothalamus. In support of earlier observations with stereotaxically induced lesions in the hypothalamus of the rat,[4] it was found that gold-thioglucose obese mice are not refractory to the anorexigenic effect of amphetamine and therefore not dependent on a ventromedial inhibitory system suggesting that the lateral hypothalamic feeding center is involved in the anorexigenic effects of amphetamine.[5] Inhibition of gold-thioglucose induced obesity by the glucose inhibitor 2-deoxy-D-glucose or its amino analogue led to the conclusion that these inhibitors interact with cells in the "satiety center"; hypothalamic cells possess a high affinity for the inhibitors since an aphagic response was not obtained with stereotaxically induced lesions in mice.[6]

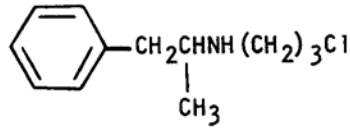
A dose-dependent increase, in electrical stimulation of the lateral hypothalamus, necessary to elicit eating in food-satiated rats, was clearly shown for amphetamine, phenmetrazine (III), methamphetamine (IVa), chlorphentermine (VIa) and diethylpropion (VII). The duration of effect also tended to be dose-dependent for the tested drugs except amphetamine and methamphetamine.[7]

A series of anorexigenic agents injected i.p. into rats 16 hrs. before sacrificing decreased hypothalamic serotonin levels. One of these, fenfluramine (I), protected mice against diarrhea and writhing induced by L-5-hydroxytryptophan. p-Chlorophenylalanine, a specific brain serotonin depletor had no effect on food consumption in normal rats and did not change the anorexigenic response of these animals to drugs. The serotonin depleting properties of these phenylalkylamines are evidently not involved in the mechanism of their anorexigenic action.[8]

Phenalkylamine Derivatives - An examination of the recent clinical experiences with fenfluramine (I) indicates it to be an effective anorexigenic agent without cardiovascular and stimulant effects.[9,10] Its failure, at therapeutic doses, to influence the "critical flicker frequency" correlates well with the clinical observation of lack of central stimulation.[11] A sedative component is suggested since slowing of cortical waves and abolishment of cortical after-discharge were observed in cats.[12]



(I)



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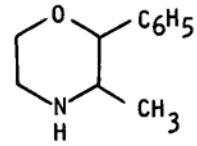
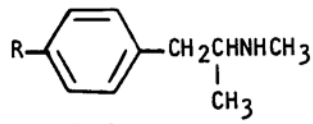


(III)

The computer technique of power spectrum analysis was used to analyze frequency changes induced by d-amphetamine and mefenorex (II) [Ro4-5282] in the EEG of the cat. Unlike amphetamine, mefenorex did not antagonize the EEG depressant effects of sodium pentobarbital in anesthetized cats, suggesting that mefenorex is less stimulating than amphetamine.[13] However, recent clinical studies report CNS stimulation in addition to the usual side effects.[14,15]

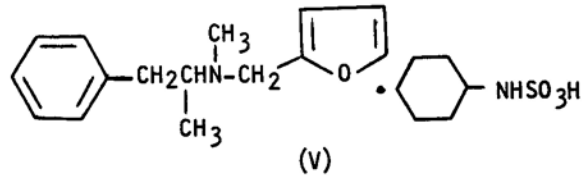
Several new derivatives of methamphetamine have been reported to be effective anorexigenic agents. An alkyl derivative (IVb) is reported to have an anorexigenic effect almost completely dissociated from the cardiovascular activity of its precursor.[16] A N-furfuryl derivative (V) [furfenorex] is reported to be effective in man,[17] and is currently being marketed in France. Its pharmacology[18] indicates it to have sympathomimetic effects in both rats and dogs.



(IV)

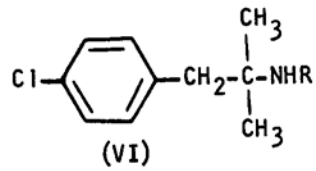
a R = H

b R = n-C_5H_{11}



(V)

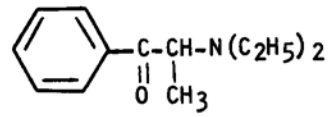
The N-ethylcarbamate of chlorphentermine (VIa) (VIb, cloforex) continues to receive attention and is reported to be an effective anorexigenic without CNS stimulation in both adults[19] and children.[20]



(VI)

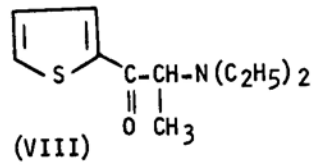
a R = H

b R = $COOC_2H_5$

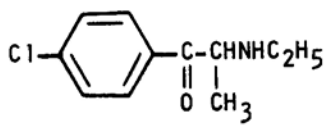


(VII)

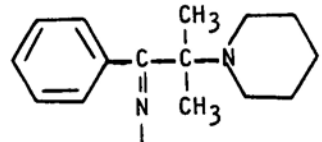
Two diethylpropion analogues (VIII) and (IX) have been described. The thiophene derivative (VIII) and related amino modifications were claimed to have anorexigenic activity comparable to amphetamine with much less CNS stimulation.[21] A chloro-substituted derivative (IX) [SKF-70948, FWH-494] was reported to be one-fifth as potent as diethylpropion in decreasing food intake in dogs; it produced less motor stimulation in the mouse than d-amphetamine, reversed and prevented reserpine induced depression. In the anesthetized cat, a biphasic blood pressure response was observed.[22] A clinical trial of (IX), at daily doses of 75-150 mg, revealed effects similar to those obtained with diethylpropion.[23] A clinical study designed to demonstrate the effect of continuous versus intermittent administration of diethylpropion was shown to favor continuous administration.[24] A related acylimino derivative (X) was reported to have one-half the anorexigenic activity of phenmetrazine in the rat, and equipotent in the dog to phenmetrazine.[25]



(VIII)

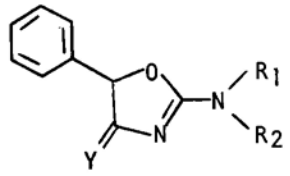


(IX)



(X)

Recent studies with 2-amino-5-phenyl-2-oxazoline (XI) [aminorex] have shown it to be an effective anorexigenic agent with no significant difference in the incidence or degree of side effects observed with marketed agents.[26,27,28]



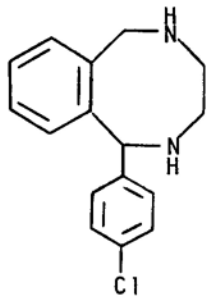
XI, Y = 2H, R_1R_2 = H, aminorex

XII, Y = O, R_1 = H, R_2 = cyclopropyl

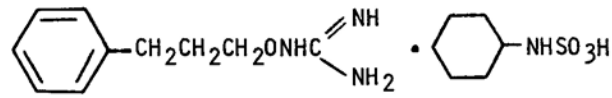
XIII, Y = O, R_1 = CH_3, R_2 = cyclopropyl

The structurally similar 2-cyclopropylamino-5-phenyl-2-oxazoline-4-one (XII) [LD-3695] is also reported to be an active anorexigen with less acute toxicity than d-amphetamine.[29] Its CNS effects are reportedly not due to MAO inhibition and it had no effect on catechol-o-methyl transferase. The N-methyl derivative (XIII) [LD-4202] is reported to be equi-anorexigenic and less stimulating than (XI).[30]

Non-Phenethylamine Derivatives - The search for compounds which bear no structural relationship to phenethylamines and have anorectic properties continues. Current studies on Wy-5244 (XIV) show it to possess only weak sympathomimetic activity in isolated cat atria and rabbit aortic strips; however, the compound apparently does alter adrenergic receptor mechanisms, since the actions of substances such as norepinephrine, d-amphetamine, phenoxybenzamine, and imipramine were profoundly influenced by Wy-5244.[31] The synthesis of (XIV) and related compounds has been described.[32]

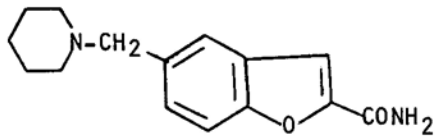


(XIV)

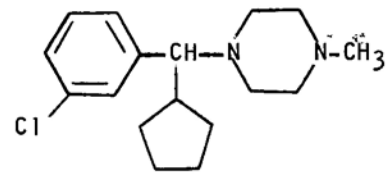


(XV)

3-(Phenylpropoxy)guanidine cyclohexane sulfamate (XV) [U-16,178F] effectively reduced food consumption in dogs, rats and mice. It was one-tenth as potent as d-amphetamine in depleting brain catecholamine levels. Unlike d-amphetamine it had no tryptamine potentiating activity and much less antireserpine activity.[33] A benzofuran derivative, (N-piperidinomethyl)-5-coumarylamide (XVI) [L-4035] has been reported to be comparable to phenmetrazine in activity.[34]



(XVI)



(XVII)

N-(α-cyclopentyl-m-chlorobenzyl)-N'-methylpiperazine (XVII) was shown to reduce food consumption in rats by 44% and caused a 19% weight loss. The compound was devoid of CNS effects.[35]

Miscellaneous - Combination therapy continues to be of interest and recent studies of anorexigenic agents with a sedative,[36] tranquilizer,[37] and a laxative,[38] have been reported. Some of these combinations did not appear to offer distinct advantages over the use of anorexigens alone. Clinical studies have been reported on the effects of anabolic[39] and thyroid analogues[40,41,42] on weight reduction. Further reports on the effects of anorexigenic agents on other metabolic factors such as oxygen consumption,[43] and plasma insulin[44] have appeared.

Methods for the detection, identification and estimation of sympathomimetic amines and their metabolites in human urine by GLC and TLC have been advanced.[45,46] The procedures of Beckett[45] lend themselves to the analysis of a wide variety of basic drugs and their metabolites. Several simple and reliable laboratory procedures have been employed to test the ability of anorexigenic or potentially anorexigenic agents to produce central stimulation in animals; these results correlate well with clinical experience.[47]

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