Neuropharmacology of appetite regulation

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Patient consultations concerning weight problems are frequent but the over-all response to drug treatment is poor. There are many so-called anorexic drugs but the range of unwanted actions is even larger and often with distressing results. The costs to the National Health Service of doctors prescribing appetite-suppressant drugs exceeded £3·5 m in 1975 but there is little evidence of proportional clinical benefit. Much of the pharmacological evidence relating to the central regulation of appetite derives from experimental studies with these same compounds. This review must therefore be read with two admonitions in mind: (1) there is no guarantee that the neuropharmacology described is relevant to the control of appetite in man, and (2) the biological models employed to predict anorexic activity in man are less than adequate.

The governing role of the central nervous system in feeding behaviour is firmly established and the majority of studies identify the hypothalamus as the most important area. The stereotaxic instrument has provided the means of creating discrete lesions and permitting localized electrical or chemical stimulation within this region, the results affording direct and convincing evidence. Yet it is salutary to note that physiologists working in widely different fields have come to similar conclusions about the location of their particular regulating centre. It is evident therefore that electrolytic lesions, electical stimulation or the placement of specific chemical substances may influence a wide variety of physiological variables of which feeding behaviour is but one. Specific interpretations of such experimental information may therefore be misleading.

The elegant studies of B. K. Anand and J. R. Brobeck contributed greatly to present concepts of hypothalamic control of feeding behaviour (e.g. Brobeck, Tepperman & Long, 1947; Anand & Brobeck, 1951). In essence they showed that bilateral electrolytic lesions in the ventromedial nuclei produced hyperphagia: a period of voracious eating behaviour leading to gross obesity in the operated animals. Lesions of the lateral hypothalamus produce virtually opposite results, ablation resulting in aphagia to the point of death by starvation. Electrical stimulation of the same discrete areas has been found to yield similar results (Miller, 1960). Injections of gold thioglucose appear selectively to damage neurons in the ventromedial nuclei, also followed by hyperphagia and obesity (Drachman & Tepperman, 1954). Direct injections of putative neurotransmitters into the brain lends further evidence for the hypothalamic control of food intake (Grossman, 1962; Miller, 1965). Such experimental reports have led to the concept of a satiety

centre, principally concerned with the inhibition of feeding behaviour, located in the ventromedial nuclei, and a feeding centre located laterally. The latter is generally considered the dominant of the two centres. Again it is important to stress that these investigations have not necessarily identified the precise location of the appropriate controlling neurons. To paraphrase Brobeck, whilst it may be true that 'cutting the underground telephone cables outside Guildhall will bring the Stock Exchange to a halt', it would be incorrect to conclude that 'all share dealings take place under a manhole cover in Throgmorton Street'.

The development of highly specific histochemical methods utilizing fluorescence photomicrography has facilitated the delineation of many interconnecting neurons within the central nervous system. Identification of specific pathways with neurons rich in noradrenaline, dopamine and 5-hydroxytryptamine (5-HT) impinge on the hypothalamus from a number of other areas (Andén, Dahlström, Fuxe, Larsen, Olson & Ungerstedt, 1966). It is not surprising therefore that lesions in the amygdala, septum and temporal lobes also produce significant effects on feeding behaviour (Grossman, 1972). In general appetite increases modestly but lesioned animals will eat tainted food and attempt to consume non-food items. This evidence serves to emphasize the complexity of the regulation system. The most careful application of control procedures are necessary in such experiments. For example, animals accidentally deprived of water eat very little and unusual taste or smell may inhibit eating in rodents. In an experiment in which amphetamine had been incorporated in the diet, a group of six rats was observed to show profound weight loss with minimal food intake, until one animal died. The carcass was avidly eaten by the remaining rats indicating very little direct drug-induced appetite suppression. Provision of normal and medicated diets to such animals resulted in a rapid preference for the control diet (Barrett, unpublished).

Regional analysis of the brain has shown the hypothalamus to be particularly rich in noradrenaline, dopamine and 5-HT (Vogt, 1969; Cooper, Bloom & Roth, 1974). Pharmacological techniques have shown that the main criteria for acceptance as neurotransmitters are satisfied. It is generally accepted that impulse transmission is effected by these agents within the hypothalamus but not perhaps exclusively. The characteristics of synapses in which noradrenaline, dopamine and 5-HT are transmitter substances are well described by Moore (1971). Many sites of action are available for drug effects including post-synaptic receptor activation and blockade, release of transmitter, interference with biosynthesis or routes of elimination and metabolism or both. Principally from experimental evidence in peripheral tissues, the concept of drug–receptor interaction has evolved in which specific attachment sites exist responding only to the particular stimulant (agonist), the effects of which can be blocked by equally selective antagonists. Noradrenaline can act as either α- or β-adrenoceptors and its actions can be selectively inhibited by phentolamine and proprandol respectively. The actions of dopamine are blocked by pimozide or haloperidol and those of 5-HT by methysergide or cyproheptidine. Much evidence suggests that comparable effects occurs within the central nervous system.

Recent work suggests that other important receptor sites exist on the presynaptic terminals of peripheral noradrenergic nerves serving to regulate the efficiency of excitation secretion coupling (see Langer, 1977 for review). There is good evidence for an α-adrenoceptor which when stimulated, apparently by excess concentrations of noradrenaline in the synaptic cleft, decreases transmitter release. Less persuasive evidence supports the presence of a presynaptic β-adrenoceptor, activated by low concentrations of noradrenaline, or perhaps of more physiological importance by circulating adrenaline, which serves to enhance transmitter release. Preliminary studies suggest that these mechanisms also operate within the central nervous system and that they apply to neurons utilizing other transmitters.

In addition to these factors there are well established uptake processes whereby transmitter released into the synaptic cleft is actively recaptured by the nerve terminal (Iversen, 1967). Many drugs, notably the tricyclic anti-depressants block the uptake process whilst other drugs, being substrates for the active uptake process produce their effect by subsequent displacement of the active transmitter (e.g. amphetamine).

The biosynthetic pathway for catecholamines can be disrupted in several ways. The conversion of tyrosine to dihydroxyphenylalanine can be blocked by α-methyltyrosine and its administration is followed by a decrease in brain noradrenaline content. Alternatively, intracerebroventricular injection of 6-hydroxydopamine produces selective degeneration of noradrenergic and dopaminergic pathways, without affecting 5-HT neurons (Ungerstedt, 1971). The biosynthesis of 5-HT from tryptophan may be inhibited by p-chlorophenylalanine at the tryptophan hydroxylase step, reducing the brain content of 5-HT (Koe & Weissmann, 1966). The selective degeneration of 5-HT containing neurons may be produced by intraventricular injection of 5,6-dihydroxytryptamine (Victor, Baumgarten & Lovenberg, 1974). A number of agents including chlorimipramine (Carlsson, Corrodi, Fuxe & Hokfelt, 1969), fluoxetine (Lilly 110140; Fuller, Perry, Snoddy & Molloy, 1974) and ORG–6582 (Goodlet, Mireylees & Sugrue, 1976) appear to produce a selective inhibition of the neuronal uptake of 5-HT.

Among the many anorexic drugs, the most frequently reported in neuropharmacological studies are amphetamine, fenfluramine and mazindol. Structural analogies may be drawn with the putative neurotransmitters but no simple relationship emerges. Maickel & Zabik (1977) have reviewed the general pharmacology, including chemical structures. The original observation, some 40 years ago, of the capacity of amphetamine to decrease voluntary eating behaviour in man was co-incidental (Lesses & Meyerson, 1938). Evaluation in animals rapidly confirmed the clinical impression but, as is well recognized, the concomitant stimulation of the central nervous system and the potential for non-medical abuse render the substance unacceptable as a routine anti-suppressant. Most of the subsequent new drug introductions have come from selective chemical manipulation of the amphetamine molecule with the claim of dissociation of anorexic and stimulant properties. Time has proved most such claims to be ill-

founded but an important exception is fenfluramine which, despite its chemical similarity to amphetamine, is generally recognized as a depressant of the nervous system.

The chemical relationship between amphetamine and noradrenaline, the richness of the hypothalamus in noradrenaline content and the knowledge that transmitters are influenced by compounds that alter both monoamine stores and feeding behaviour, all contributed to the assumption of catecholamine involvement *in* anorexic activity. The involvement of 5-HT has been implied similarly from experimental studies but also from clinical observation. For example the partially-selective 5-HT antagonist cyproheptidine, was found to stimulate eating behaviour and to induce weight gain in asthmatic children (Lavenstein, Dacaney, Lasagna & Van Metre, 1962). The treatment of migraine often involves the use of 5-HT antagonists such as methysergide and pizotifen and careful inspection of the clinical information often suggests weight gain as 'adverse' response (Graham, 1967; Speight & Avery, 1972). The possible role of dopamine has been put forward almost entirely from experimental evidence.

It is pertinent to consider the methods employed by pharmacologists in the detection and quantification of anorexic activity. Rats are the most commonly employed experimental species and the index is usually the weight of food removed by individual, or grouped rats, from a preweighed container in a specified time. Many workers use animals made artificially hungry by a 24 h fast before food exposure or alternatively 'train' their rats to consume their daily ration within a preset period time e.g. 4 h/d. Almost always the animals are non-obese and perfectly healthy and the diet is usually standard laboratory chow. This artificial model is remote from the situation of clinical obesity and it is perhaps not surprising that the results of its use have generally failed to produce a specific and effective remedy. It is true, however, that amphetamine and many of its analogues and derivatives do produce a statistically significant reduction in food intake in the biological model described. Laboratory tests are most often short term lasting 2–6 h, drugs are usually administered intraperitoneally and the index is food intake. Clinical assessment is usually over 2–6 weeks, drugs are given by the oral route and the index is invariably weight loss. In many cases the effective animal dose (mg/kg) is applied to man as mg/70 kg. It seems fair to question the relevance and relationship of the two types of study to each other. A reasonable neuropharmacological account of anorexic drug action in healthy non-obese rodents may be forthcoming but there is no guarantee that such mechanisms are important in obese man. Recent developments in methodology promise a new dimension to animal experiments with the introduction of the 'rat eatometer' (Blundell, Latham & Leshem, 1976). The equipment permits the size and frequency of individual meals to be monitored continuously for indefinite periods. The technique affords a significant improvement in sensitivity and precision in the evaluation of anorexic drugs. Clearly much of the investigation of the last three decades is too crude and imprecise to be of real prospective value.

The remaining material is therefore restricted to the pharmacological analysis of

short-term inhibition of food consumption in laboratory animals. Depletion of brain noradrenaline is usually associated with decreased eating behaviour and pre-treatment of animals with α-methyltyrosine antagonizes the anorexic action of amphetamine (Clineschmidt, McGuffin & Werner, 1974). In contrast, pre-treatment with 6-hydroxydopamine was relatively ineffective in preventing amphetamine anorexia (Samanin, Ghezzi, Valzelli & Garattini, 1972). A careful review of the literature leaves little doubt that noradrenergic or dopaminergic mechanisms are directly influenced by amphetamine and its congeners (Kruk & Zarrindast, 1976*a*,*b*). There is little evidence to suggest that the anorexic activity is dissociable from stimulation of the central nervous system. Amphetamine displaces noradrenaline from intraneuronal stores and also prevents neuronal re-uptake of the transmitter after release from nerve terminals. It therefore serves to increase noradrenaline availability at receptor levels. Tricyclic anti-depressants are more effective inhibitors of neuronal uptake but do not demonstrate anorexic activity under comparable conditions. Lesions of the lateral hypothalamus interrupt dopamine-mediated pathways of the nigro-striatal tract (Ungerstedt, 1971) and are associated with aphagia (Anand & Brobeck, 1951). The fact that 6-hydroxydopamine treatment produces neither extensive depletion of brain dopamine nor abolishes the anorexic effect of amphetamine (Samanin *et al.* 1972) whereas α-methyltyrosine does both (Clineschmidt *et al.* 1974) supports the view that amphetamine action is more related to modulation of dopaminergic pathways. Some evidence implies a similar mechanism for mazindol (Kruk & Zarrindast, 1976*b*).

Neuropharmacological studies with fenfluramine have emphasized the potential importance of 5-HT-mediated pathways in the control of feeding. Blundell (1977) has comprehensively reviewed the evidence concerning 5-HT. Despite similarity in chemical structure, the pharmacological profiles of amphetamine and fenfluramine differ significantly. Fenfluramine does not exhibit the central and cardiac stimulant properties of amphetamine, it releases 5-HT from central neurons and inhibits its re-uptake. Electrolytic lesions in the mid-brain raphe nuclei produce a selective decrease of 5-HT in the brain and abolish the anorexic effect of fenfluramine but not that of amphetamine (Samanin *et al.* 1972). Fenfluramine dependence on 5-HT stores for anorexic effect was not confirmed by Sugrue, Goodlet & McIndewar (1975) although the extent of depletion may be too small for unequivocal results.

Direct placement of 5-HT intraventricularly depressed food intake, an effect blocked by cyproheptidine but not by pimozide, an antagonist of dopamine (Kruk, 1973). The effect was only partial and from several studies appears dependent on using hungry animals, little effect being demonstrable in satiated rats. Indirect increase in brain 5-HT by feeding precursors (5-hydroxytryptophan, tryptophan) also results in reduced eating behaviour but in general dietary manipulation does not yield convincing evidence (see Blundell, 1977 for references).

The inactivation of tryptophan hydroxylase by p-chlorophenylalanine depletes brain 5-HT as a result of reduced synthesis (Koe & Weissmann, 1966). When administered intraventricularly, clear evidence of hyperphagia and weight gain has

been obtained (Breisch & Hoebel, 1975). Results of peripheral injections and oral adminstration are less definite and may be secondary to severe gastrointestinal irritation (Funderburk, Hazelwood, Ruckart & Ward, 1971). Long-lasting depletion of neuronal 5-HT follows administration of 5,6-dihydroxytryptamine and both qualitative and quantitative variation in food intake have been observed. Lesions of mid-brain raphe nuclei do not *per se* produce profound changes in eating pattern. As brain 5-HT decreases there may be an increase in food consumption and larger but less frequent eating periods (Blundell, 1977).

The relatively specific antagonists of 5-HT, methysergide, cyproheptidine and pizotifen have all been shown to block the anorexic activity of fenfluramine but agreement is not universal (Blundell, 1977). Endogenous brain 5-HT can be increased by pretreatment with L-tryptophan and a monoamine oxidase inhibitor. This results in anorexia and, choosing comparable doses of fenfluramine and mazindol, all three anorexic effects are dose-dependently blocked by methysergide (Barrett & McSharry, 1975). The linearity of response and parallelism between the curves, argue strongly for a common mode of action. Another study showing functional blockade of 5-HT depletion by mazindol is additional evidence against the view that this drug acts only via a catecholaminergic mechanism (Carruba, Picotti, Zambotti & Mantegazza, 1977).

Selective inhibition of 5-HT uptake into nerve terminals has been demonstrated for chlorimipramine, fluoxetine and ORG-6582 (Goodlet, Mireyless & Sugrue, 1976, 1977). Chlorimipramine (J. E. Blundell, unpublished results), fluoxetine (Goudie, Thornton & Wheeler, 1976) and ORG-6582 (Barrett, unpublished; M. F. Sugrue, unpublished results) have all been shown to produce anorexia and thereby imply that facilitation of synaptic 5-HT represents a sufficient condition for reduced eating behaviour. Quipazine, for example, a selective 5-HT agonist also produces a dose-dependent anorexia (Samanin, Bendotti, Miranda & Garattini, 1977). Such results are indicative of the importance of 5-HT as a satiety mediator. Blundell *et al.* (1976) suggest that increased availability of 5-HT leads to reduced eating via premature recognition of satiety. Decreased availability leads to over-eating associated with failure to recognize satiety. From their 'eatometer' experiments they suggest that whereas amphetamine delays the onset of feeding fenfluramine hastens termination of the initial bout of eating activity.

This brief review gives some indication of the kind of evidence being obtained regarding the neuropharmacology of appetite reulgation. A coherent hypothesis of unitary explanation of drug-induced anorexia is not yet possible. There are many difficulties in extrapolating the animal information to human obesity but perhaps the biggest deficiency is the absence of a truly-reliable animal model. It seems hard to dispute, however, the growing body of evidence implying a physiological role of 5-HT in the control of feeding.

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