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EDITORIAL

The clinical pharmacology of appetite – its relevance to psychiatry[1]

The effects of drugs on appetite and food intake are of potential interest to psychiatrists from both the practical and theoretical points of view. Of practical interest is the, by now well-recognized, observation that a number of drugs commonly used in the treatment of schizophrenia, such as chlorpromazine or fluphenazine, make patients feel very hungry (Robinson *et al.* 1975). As a consequence they increase their food intake and gain weight. This is not a rare occurrence: in a group of some 300 patients receiving regular depot injections of either fluphenazine or thioxanthene decanoate, we found that over a third were significantly obese (T. Silverstone & G. Smith, unpublished data). This has obvious implications for both compliance and rehabilitation. Young women patients are particularly reluctant to continue taking any medication which is likely to make them fat; and being fat often leads to a self-conscious avoidance of social interaction and may prejudice employment prospects.

Another area where the interaction of drugs and appetite is of relevance to psychiatrists is in the management of patients presenting with primary disorders of eating such as anorexia nervosa and bulimia nervosa. However, drugs appear to be of little benefit in these conditions (Goldberg *et al.* 1979), and have not thus far enhanced our understanding of the underlying pathogenesis or pathophysiology (Szmukler, 1982).

Where the clinical pharmacological approach to the study of appetite and its relationship to psychopathology has paid dividends is in the field of the major affective disorders. It has long been recognized that severe depressive illness is accompanied by a profound anorexia, severe enough at times to lead to serious malnutrition. As Lewis (1934) put it in his classical survey of melancholia: 'Depressive states are almost invariably characterised during the greater part of their course by disinclination for food.' Russell (1960) pointed out that improvement in appetite is one of the earliest and most reliable indications of recovery from this illness. Thus anorexia would appear to be inextricably bound up with depressive illness, and knowledge of the physiological mechanisms underlying this anorexia might well lead to a greater understanding of the pathophysiology of the illness itself.

Amphetamine is a drug which causes anorexia; because of this it was introduced as a treatment for obesity in the 1930s (Silverstone & Wells, 1980). It soon became apparent that, in addition to its anorectic properties, amphetamine was a potent central nervous system stimulant and euphoriant. While this proved to be a grave disadvantage from the clinical point of view, leading to its virtual elimination as a treatment for obesity, it has provided a useful pharmacological model for the study of mood and appetite. Unlike the situation obtaining in depressive illness, where anorexia accompanies a *lowering* of mood, with amphetamine the anorexia is associated with a *heightening* of mood (Smith & Davis, 1977). However, the dose–response relationship of amphetamine to changes in mood is not the same as that observed between amphetamine and changes in hunger (Silverstone *et al.* 1983). This finding raises the possibility that different neurochemical pathways might be involved in amphetamine-induced anorexia as compared with amphetamine-induced euphoria.

In laboratory animals amphetamine has been shown to act in the brain largely by releasing pre-formed dopamine (DA) and noradrenaline (NA) from pre-synaptic neurones (Carlsson, 1970). Given this dichotomy of neurochemical actions, it could be that the effect on one neurotransmitter might underlie the drug's anorectic effect, with its stimulant action being related to an action on the other neurotransmitter. We have examined this question in human subjects using neurotransmitter

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receptor blocking compounds. We found that pimozide, a relatively specific DA receptor blocker, attenuated the stimulant activity of amphetamine but was without effect on amphetamine-induced anorexia (Silverstone *et al.* 1980). Thymoxamine, on the other hand, a drug which blocks NA receptors, attenuated the anorectic but not the stimulant effect of amphetamine (D. Jacobs & T. Silverstone, unpublished data). These findings are consistent with the view that amphetamine-induced anorexia is mediated via NA pathways, while its stimulant and euphoriant activity is mediated via DA pathways.

Amphetamine can elevate mood transiently in a proportion of severely depressed patients (Fawcett & Siomopoulos, 1971; Kiloh *et al.* 1974). As already mentioned, remission of depressive illness is accompanied by an improvement in appetite. The question therefore arises: is amphetamine-induced improvement of mood also accompanied by a similar improvement in appetite, or does the drug's anorectic activity counterbalance any such improvement in appetite? Using visual analogue scales to follow changes in subjective mood and hunger, we compared the effects in depressed patients of a single intravenous injection of 10 mg methylamphetamine with those following an injection of sterile water in a double-blind crossover clinical trial. In the patients whose mood improved following amphetamine, appetite also improved (J. Cookson & T. Silverstone, unpublished data). Thus at least some depressed patients appear to be less sensitive to the anorectic action than to the stimulant action of amphetamine. If the stimulant effect is DA-mediated, and the anorectic effect is NA-mediated, the relative insensitivity to the anorectic action would imply that NA neurotransmission in depressive illness is reduced. This view is in keeping with other findings as, for example, that the cortisol response to amphetamine and the growth hormone response to clonidine are attenuated in depressive illness; both responses are generally thought to be NA-mediated (Checkley, 1980).

A good case has also been made out for an involvement of serotonergic (5HT) pathways in the pathogenesis of depression, particularly in patients who manifest suicidal behaviour (Åsberg *et al.* 1976). The non-stimulant anorectic drug, fenfluramine, is believed to suppress hunger by increasing the release of 5HT from pre-synaptic neurones, rather than through any action on DA or NA neurotransmission (Garattini *et al.* 1975). It is therefore of interest that fenfluramine, in contrast to amphetamine, causes a lowering of mood in normal subjects (Holmstrand & Jonsson, 1975), and an exacerbation of symptoms in already depressed patients (Gaind, 1969).

Furthermore, frank depressive symptoms may appear on sudden withdrawal of fenfluramine (Steel & Briggs, 1972). Such findings confirm a role for 5HT in the pathogenesis of depressive symptoms.

Zimelidine, a recently introduced antidepressant drug which is believed to act by blocking the re-uptake of 5HT into pre-synaptic neurones, has been noted to decrease appetite and food intake in non-depressed subjects, and to cause weight loss in depressed patients (Gottfries, 1981). This finding is consistent with the view that an increase in central 5HT neurotransmission (whether by an increase in 5HT release as with fenfluramine, or by a blockade of re-uptake as with zimelidine) suppresses appetite. The fact that amitriptyline, another antidepressant compound which blocks the re-uptake of 5HT, causes an increase in appetite and weight in euthymic patients (Paykel *et al.* 1973) would appear to contradict that view. However, amitriptyline has also been reported to have a pronounced blocking action in post-synaptic 5HT receptors (Maj *et al.* 1979), which could explain its appetite stimulating properties.

Looking at the other end of the manic-depressive spectrum – that is, at mania – amphetamine, when given to bipolar depressed patients (but not those with unipolar depression), frequently precipitates an attack of mania (Van Kammen & Murphy, 1975). Such manic symptoms, and indeed manic symptoms generally, can be rapidly ameliorated by the DA receptor blocking drug, pimozide (Cookson & Silverstone, 1981). Therefore, the likelihood is that manic states are a reflection of an increased activity in central DA pathways (Silverstone, 1979). In fact, amphetamine-induced arousal which, as we have already seen, is DA-mediated, might be a heuristically useful model for studying mania; certainly some of the subjective changes produced by a single oral dose of 20 mg dextroamphetamine in normal subjects closely resemble, albeit in a muted form, those seen in manic illness (D. Jacobs & T. Silverstone, unpublished data).

Another drug which improves mania, and is even more effective in preventing relapse, is lithium. Here too there is a supra-added effect on body weight, long-term administration of lithium frequently being accompanied by weight gain (Vendsborg *et al.* 1976). It is as yet uncertain whether this weight gain is in fact due to an increase in appetite or whether it is secondary to an increase in thirst leading to a high intake of sugar-containing drinks. Whatever the mechanism, the resulting obesity is not only undesirable in itself but, as with phenothiazine-induced obesity in schizophrenic patients, it can prejudice compliance and thereby increase the risk of relapse.

Thus, as stated at the outset, the clinical pharmacology of appetite has both practical and theoretical implications for psychiatrists. Of practical importance is the observation that many of the drugs used in psychiatry have pronounced effects on appetite and body weight over and above the psychotropic actions for which they are primarily prescribed. Of more theoretical interest are the findings relating to the interactions of drugs such as amphetamine and fenfluramine on mood and appetite in normal subjects and in depressed patients. The study of these matters, using the techniques of clinical pharmacology, has already yielded valuable information concerning the possible pathophysiology of the major affective disorders. Further investigation along these lines is likely to prove even more fruitful.

Indeed if, as it has been said, 'The way to a man's heart is through his stomach', then perhaps the way to his central nervous system is through his appetite.

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REFERENCES

Åsberg, M., Thoren, P., Träskman, L. & Bertilsson, L. (1976). 'Serotonin depression' – a biochemical subgroup within the affective disorders. *Science* **191**, 478–481.

Carlsson, A. (1970). Amphetamine and brain catecholamines. In *Amphetamines and Related Compounds* (ed. E. Costa and S. Garattini), pp. 289–300. Raven Press: New York.

Checkley, S. A. (1980). Neuroendocrine tests of monoamine function in man: a review of basic theory and its application to the study of depressive illness. *Psychological Medicine* **10**, 35–53.

Cookson, J. & Silverstone, T. (1981). A double-blind comparative clinical trial of pimozide and chlorpromazine in mania: a test of the dopamine hypothesis. *Acta Psychiatrica Scandinavica* **64**, 381–392.

Fawcett, J. & Siomopoulos, V. (1971). Dextroamphetamine response as a possible predictor of improvement with tricyclic therapy in depression. *Archives of General Psychiatry* **25**, 247–253.

Gaind, R. (1969). Fenfluramine (Ponderax) in the treatment of obese psychiatric outpatients. *British Journal of Psychiatry* **115**, 963–964.

Garattini, S., Buczko, W., Jori, A. & Samanin, R. (1975). The mechanism of action of fenfluramine. *Postgraduate Medical Journal* **51**, 27–35.

Goldberg, S., Halmi, K., Eckert, E., Casper, R. & Davis, J. (1979). Cyproheptadine in anorexia nervosa. *British Journal of Psychiatry* **134**, 67–70.

Gottfries, C. G. (1981). Influence of depression and antidepressants on weight. *Acta Psychiatrica Scandinavica* **63** (Supplement 290), 353–356.

Holmstrand, J. & Jonsson, J. (1975). Subjective effects of two anorexigenic agents – fenfluramine and AN 488 – in normal subjects. *Postgraduate Medical Journal* **51**, 183–186.

Kiloh, L., Neilson, M. & Andrews, G. (1974). Response of depressed patients to methylamphetamine. *British Journal of Psychiatry* **125**, 469–499.

Lewis, A. (1934). Melancholia: a clinical survey of depressive states. *Journal of Mental Science* **80**, 277–378.

Maj, A., Lewandowska, A. & Rawton, A. (1979). Central serotonin action of amitriptyline. *Pharmakopsychiatry* **12**, 281–285.

Paykel, E., Muller, P. & de la Vergue, P. (1973). Amitriptyline, weight gain and carbohydrate craving: a side effect. *British Journal of Psychiatry* **123**, 501–502.

Robinson, R., McHugh, P. & Folstein, M. (1975). Measurement of appetite disturbance in psychiatric disorders. *Journal of Psychiatric Research* **12**, 59–68.

Russell, G. (1960). Body weight and balance of water, sodium and potassium in depressed patients given ECT. *Clinical Science* **19**, 327–336.

Silverstone, T. (1979). Psychopharmacology of manic-depressive illness. In *Current Themes in Psychiatry*, Vol. 2 (ed. R. Gaind and B. Hudson), pp. 271–282. Macmillan: London.

Silverstone, T. & Wells, B. (1980). Clinical psychopharmacology of amphetamine and related compounds. In *Amphetamine and Related Compounds* (ed. J. Caldwell), pp. 148–159. CRC Press: New York.

Silverstone, T., Fincham, J., Wells, B. & Kyriakides, M. (1980). The effect of the dopamine receptor blocking drug pimozide on the stimulant and anorectic actions of dextroamphetamine in man. *Neuropharmacology* **19**, 1235–1237.

Silverstone, T., Wells, B. & Trenchard, E. (1983). Differential dose–response effects of dexamphetamine sulphate on hunger, mood and arousal in human volunteers. *Psychopharmacology* (in the press).

Smith, R. & Davis, J. (1977). Comparative effects of *d*-amphetamine, *l*-amphetamine and methylphenidate in mood in man. *Psychopharmacology* **53**, 1–10.

Steel, J. & Briggs, M. (1972). Withdrawal depression in obese patients after fenfluramine treatment. *British Medical Journal* iii, 26–27.

Szmukler, G. (1982). Drug treatment and anorexic states. In *Drugs and Appetite* (ed. T. Silverstone), pp. 159–181. Academic Press: London.

Van Kammen, D. & Murphy, D. (1975). Attenuation of the euphoriant and activating effects of *d*- and *l*-amphetamine by lithium carbonate treatment. *Psychopharmacology* **44**, 215–225.

Vendsborg, P. B., Bech, P. & Rafaelsen, O. J. (1976). Lithium treatment and weight gain. *Acta Psychiatrica Scandinavica* **53**, 139–147.