THE SEROTONERGIC APPETITE SUPPRESSANT FENFLURAMINE

Reappraisal and Rejection

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ABSTRACT

Medical and social pressures have led to increased emphasis on dieting. However, there has been a concurrent world wide increase of obesity. Therefore, much attention has been paid to the development of drugs which decrease appetite. The most extensively used drug of this type over the past three decades has been the serotonergic compound fenfluramine. Recent findings have cast doubt on the previously accepted view that its action requires the release of central 5-HT. Instead, it seems likely that action on specific 5-HT receptors independently of 5-HT stores is involved. It is ironic that these new developments in understanding its mechanism of action have coincided with the recognition of its cardiovascular side-effect apparent especially in patients treated with d-fenfluramine combined with phentermine. This has forced the withdrawal of fenfluramine (both as racemate and d-isomer) from clinical use. The implications of these developments are commented upon.

1. INTRODUCTION

Obesity is a chronic pathological condition due to complex interactions between cultural, psychological and genetic factors. During the past 30–40 years, a markedly increased emphasis on its control has been encouraged by evidence of risks to the health of the obese by numerous metabolic disorders, including non-insulin dependent diabetes...
mellitus, hypercholesterolaemia, cardiovascular and gall bladder disease and arthritis (Kissebah and Krakower, 1994). Obesity also causes social stigmatization and poor self-image. Associated pressures towards dieting have increased as a result of social changes: for example, the increasing divergence between reality and image as revealed by a comparison of Playboy centre-folds and US average weight for women of the same ages and heights (Wiseman, Gray, Mosimann, and Ahrens, 1992). According to Snow and Harris (1986) "with the demise of the girdle and corset... a new way of controlling the size and shape of the female body evolved: the diet" as illustrated by numerical analysis of the changing contents of women's magazines.

Despite the above influences, more people are becoming overweight or obese. A recent W.H.O. report (1998) states that obesity, defined as a body mass index (BMI = weight in kg/height in m² of ≥30) is (with the exception of hunter-gatherer societies), increasing world-wide. Thus, in the US obesity rose from 10% (men) and 15% (women) in 1960 to 19.7% (men) and 24.7% (women) in 1991. In England it rose from 6% (men) and 8% (women) in 1980 to 15% (men) and 16.5% (women) in 1995. A strong demand has therefore developed for treatments resulting in long-term weight loss. However, as both exhortations and non-pharmacological treatments (e.g. dietary restriction, nutritional education and psychological support) usually lead to no more than limited loss of weight, their supplementation by anorectic drugs is receiving much attention (National Task Force on the Prevention and Treatment of Obesity, 1996).

Tryptophan decreases feeding in both rats (White, Cybulski, Primus, Johnson, Collier, and Wagner 1988) and humans (Blundell and Hill, 1987) which presumably results, at least in part, from an increased availability of its metabolite 5-hydroxytryptamine (5-HT). Many compounds which either increase the availability of 5-HT or directly activate postsynaptic 5-HT receptors suppress feeding (rev. Curzon, 1995). One of these substances, fenfluramine racemate (DLFN), for many years the most commonly used clinical appetite suppressant, was recently replaced by the more potent D-isomer, dexfenfluramine (DFN). In the USA, DLFN with phentermine, the so-called fen-phen combination, has been widely prescribed. These drugs are all structurally related to amphetamine but lack its stimulant and abuse properties.

This chapter will review new findings on how DFN acts and will comment on the side effects which precipitated its withdrawal in 1997 as a clinical hypophagic agent.

2. MECHANISM OF ACTION OF DFN

Microdialysis reveals that extracellular brain 5-HT is increased in rats given DFN at hypophagic dosages (Oluyomi, Gibson, Barnfield, and Curzon 1994a). It has usually been assumed that the hypophagia requires action of this 5-HT at receptors thought to be mainly in the hypothalamus, in particular in the paraventricular nucleus (PVN) and adjacent regions. Indeed, injection of DFN, its metabolite d-norfenfluramine (DNFN) or 5-HT into the PVN all suppressed noradrenaline-induced feeding (Leibowitz, Weiss, and Shor-Posner, 1988). However, rat experiments now strongly indicate that increased 5-HT availability is not necessary for the hypophagic response (Curzon, Gibson, and Oluyomi, 1997). For example, although DFN (2.5 mg/kg) was markedly hypophagic and significantly increased medial hypothalamic extracellular 5-HT, only the hypophagia resisted pretreatment with the inhibitor of 5-HT synthesis p-chlorophenylalanine (PCPA) sufficient to reduce extra-raphe 5-HT to about 10% of control values (Gibson, Kennedy, and Curzon, 1993; Oluyomi et al., 1994a). In the case of DNFN (Gibson et al., 1993),