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5-HT and physical illness

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The discovery and clinical evolution of 5-HT re-uptake inhibiting drugs are reviewed. From the widespread distribution of 5-HT in bodily systems and the range of effects and side effects reported, it is concluded that these and other drugs active on the 5-HT system are likely to have beneficial effects on a range of other physical conditions coincident and co-morbid with the affective disorders. Clinical vigilance may therefore be repaid with serendipitous discoveries.

Key words: 5-HT; SSRI; physical illness, review

The 5-HT re-uptake inhibitors and physical illness

5-Hydroxytryptamine (5-HT) has been a multiply discovered neurotransmitter. It was first discovered in 1939 by Erpsamer and colleagues in the gastrointestinal tract and accordingly named enteramine (Vialli and Erpsamer, 1939). In 1947 it was rediscovered in blood and platelets by Page and Rapoport and colleagues and noted to have a tonic effect on blood vessels, which led to the name serotonin (Rapoport, Green and Page, 1947). These early discoveries give some indication of its widespread distribution in the body and, accordingly, of the potential impact that drugs acting on the 5-HT system might have on a range of physical conditions.

Subsequently in 1949 the chemical structure of serotonin was established as being that of 5-hydroxytryptamine (Rapoport, 1949). With the establishment of the structure of serotonin, and its subsequent isolation in the brain (Twarog and Page, 1953), it was noted that there was a structural similarity between this and the recently discovered LSD. This led to early speculation that serotonin might have a place in the economy of mental functions and that derangements in its metabolism of functioning might lead to mental derangement (Carlsson, 1990a).

The first physiological or biochemical observations on antidepressants involved 5-HT and not catecholamines. Pletscher noted that the monoamine oxidase inhibitors increased blood 5-HT levels (Pletscher and Bernstein, 1958). Subsequently in 1960, Todrick and colleagues, much to their surprise, established that imipramine, the first tricyclic antidepressant, led to a decrease in blood and platelet 5-HT levels (Marshall *et al.*, 1960; Todrick, 1991). This posed a conundrum given that both groups of drugs apparently had the same clinical action. The difficulty was resolved by Axelrod's proposal that tricyclic antidepressants could block the re-uptake of neurotransmitters such as the catecholamines and indoleamines (Axelrod, Whitby and Hertting, 1961; Axelrod and Inscoe, 1963). This proposal not only potentially resolved the discrepancies between the actions of the two major classes of antidepressants but it involved a first demonstration of the existence of a re-uptake mechanism (Todrick, 1991). As Axelrod himself was later to say (Axelrod, 1972), part of the reason perhaps for making claims such as these was that being new to the field he was not as inhibited by received wisdom as he might otherwise have been.

The monoamine hypotheses

Axelrod's initial formulations of the mechanism of action of tricyclic antidepressants applied equally well to both catecholamine and indoleamines. Yet only a few years later Schildkraut (1965) and Bunney and Davis (1965) were to propose catecholamine hypotheses of depression. After that, for almost 20 years, serotonin was the poor relation of neurotransmitters. Why?

One reason for this was that it had been shown that the early tricyclics—amitriptyline and imipramine—broke down to nortriptyline and desipramine in the body. It had also been demonstrated that these were effective antidepressants in their own right. This demonstration tilted the balance in favour of the catecholamines being the pertinent neurotransmitters involved in depression as nortriptyline and desipramine were quite potent inhibitors of catecholamine re-uptake but only acted very weakly on 5-HT systems (Healy, 1991a).

Despite this and the natural conclusion that catecholamines were the relevant neurotransmitters, Arvid Carlsson

suggested that it would be useful to synthesize specific 5-HT re-uptake inhibitors (Carlsson, 1990a). The rationale for this was that clinicans appeared to prefer imipramine and amitriptyline to desipramine and nortriptyline. Of course, the thing that imipramine and amitriptyline did that desipramine and nortriptyline did not do particularly well was to inhibit the re-uptake of serotonin. This led to the development of zimelidine and subsequently the range of 5-HT re-uptake inhibitors we now have.

These agents appear to be effective in the treatment of depression. They also appear to be significantly anxiolytic (Healy, 1991a). Awareness of their effects on anxiety grew with indications that clomipramine, the first potent 5-HT re-uptake inhibitor, had both anti-obsessional and anti-phobic activity (Healy, 1990). Whether their effects in obsessive–compulsive disorder (OCD) come about by virtue of correcting a serotonergic deficit in OCD (Lucey *et al.*, 1992) or by virtue of a more general anxiolytic effect (Healy, 1991b) at present is unclear.

Both theoretical and experimental developments, therefore, led during the 1980s to increased interest in 5-HT. This in turn has led to a mapping out of the 5-HT system, with upwards of eight receptor subtypes now identified and the availability of a range of compounds with potential agonist or antagonist activity (Healy, 1991a; Leonard, 1992).

Increased or decreased 5-HT?

At present the catecholamine hypothesis appears to remain only as a lingering afterglow. However, it has left a grin behind. The original hypothesis was predicated on the notion that in some way the inhibition of monoamine re-uptake must lead to an increase of monoamines in the brain. The increase in catecholamines or 5-HT in synaptic clefts would be equivalent, it was argued, to a functional increase in monoamines. This idea was required in order to mirror the understanding of how monoamine oxidase inhibitors worked and findings such as those of Pletscher and Bernstein (1958). It seemed to follow that the re-uptake inhibiting antidepressants must also in some way increase monoamine levels. However, the purpose of a re-uptake mechanism is to conserve the levels of neurotransmitters. A blockage of re-uptake would therefore, on the face of it, appear liable to lead to decreases in monoamine levels. There is a substantial amount of evidence that in the brains of animals chronically taking antidepressants there are decreases in the levels of monoamines (Healy, 1987).

There is, furthermore, a considerable amount of evidence from the use of 5-HT re-uptake inhibitors that they are more likely to have effects in common with 5-HT receptor antagonists than with 5-HT receptor agonists. For example, 5-HT antagonists are anxiolytic as are the 5-HT re-uptake inhibiting antidepressants (Healy, 1991a). A number of observations indicate that both the 5-HT re-uptake inhibitors and antagonists at 5-HT_2 and 5-HT_3 receptors may have cognitive enhancing effects (McEntee and Crook, 1991). Empirically, therefore, as good a case can be made that these drugs act to produce their therapeutic actions by depleting or blocking 5-HT as can be made for any action to increase its level or facilitate serotonergic neurotransmission. In fact, however, a consideration of the multiple effects of 5-HT re-uptake inhibitors, outlined below, should indicate it is not possible to explain the effects of these compounds simplistically in terms of either an increase or decrease in 5-HT levels.

5-HT and other systems

5-HT, appetite and feeding

One of the striking effects of the 5-HT re-uptake inhibitors is their propensity to produce nausea. They may also produce other elements of a non-ulcer dyspepsia syndrome (Dinan *et al.*, this volume). Whether these effects arise as a consequence of there being a substantial amount of 5-HT in the gut or whether the effects are mediated by the central mechanisms or a combination of both of these actions is at present uncertain.

A number of other agents active on the 5-HT system also affect appetite and weight. In the case of 5-HT_2 receptor antagonists, such as cyproheptadine, clozapine, chlorpromazine or mianserin, a consequence of the use of all agents is weight gain. So much so that cyproheptadine in particular has, in the past, been prescribed by a number of general practitioners as a 'tonic' (Healy, personal observation).

The more recently released 5-HT_3 receptor antagonists, ondansetron and granisetron have anti-emetic and anti-nausea activity. These appear to be mediated more by central mechanisms in the brain stem than through local gastrointestinal effects.

There appear to be two clinical indications emerging for the use of 5-HT re-uptake inhibitors from these findings. One is a use in appetite regulation. At present, fluoxetine appears helpful in the management of bulimia nervosa (Walsh, 1991). It also seems that drugs active on the 5-HT system, including the 5-HT re-uptake inhibitors, may help in the management of the functional bowel disorders such as irritable bowel syndrome or non-ulcer dyspepsia (Dinan *et al.*, this volume).

5-HT and sex

The most important neurotransmitter in the economy of sexual functions appears to be noradrenaline which by

virtue of a vasodilator action in the sexual vasculature enhances potency in males certainly and possibly also in females (Segraves, 1989).

Two of the most potent pharmacological aids to sexual functioning are trazodone and yohimbine (Sullivan and Lukoff, 1990; Riley *et al.*, 1989; Healy, 1993). Both of these have pronounced alpha-2 antagonist properties and one can presume that a greater part of their effects on potency stem from these actions. However, they also have significant 5-HT receptor blocking effects and, in particular, 5-HT_2 antagonist properties. While there is not a profusion of 5-HT terminals in the sexual vasculature, it has been known for some time that giving 5-HT antagonists such as cyproheptadine can have beneficial effects on sexual interest as well as on sexual performance (Segraves, 1989).

In this regard the effects of the 5-HT re-uptake inhibitors are also significant. In some cases they appear to lead to an interference with sexual functioning, notably anorgasmia and retarded ejaculation (Beaumont, 1977). This appears to be dose dependent. Observations such as these have led to more systematic work in recent years and it is clear that 5-HT has a clear role in sexual behaviour and that this effect is mediated centrally (Wilson, 1992). In general, 5-HT re-uptake inhibitors delay orgasm. This may be a problem for women but, with recent reports that up to one third of younger males have premature ejaculation, it may be a significant benefit for males. In contrast, 5-HT_1 agonists and 5-HT_2 antagonists appear to reduce ejaculatory latency and these agents may therefore be of benefit in conditions where orgasms are inhibited.

5-HT and salivary secretions

With the lack of anticholinergic effects of the serotonin re-uptake inhibitors (SSRIs) it was predicted that many of the side effects of the tricyclic antidepressants such as dry mouth, blurred vision, etc. would not occur. This has not been the case. The SSRIs quite clearly can cause blurring of vision although this is less marked than with anticholinergic compounds (Healy, personal observation). They may also cause a dry mouth. In contrast both 5-HT_2 receptor antagonists such as clozapine and cyproheptadine as well as 5-HT_3 receptor antagonists are liable to cause an increased production of saliva secretions. This can reach a very noticeable level, in some instances causing drooling (Adams and Essali, 1990).

5-HT and dyskinesia

At present the literature as regards possible dyskinesia induced by drugs active on the 5-HT system is somewhat scanty. In favour of the possibility that there might be such side effects are the following scattered observations: clozapine has been reported in a number of incidences to cause a jaw dyskinesia that differs from that produced by neuroleptics (de Leon *et al.*, 1991). Fluoxetine has also been reported to cause yawning without drowsiness (Modell, 1989). This particular finding is one that the author has noted happening not infrequently with all current 5-HT re-uptake inhibitors.

There have been a number of reports also that fluoxetine, in particular and especially in combination with neuroleptics, is liable to cause dyskinesias, akathisia and a number of other neuroleptic-associated adverse events (Meltzer *et al.*, 1979; Lipinski *et al.*, 1989; Halman and Goldbloom, 1990; Baldwin, Fineberg and Montgomery, 1991; Teicher, Glod and Cole, 1990; Rothschild and Locke, 1991; Creaney, Murray and Healy, 1991). The extent of such reactions is at present undetermined as is their association with 5-HT re-uptake inhibitors or with fluoxetine in particular. The author has had three patients present with tooth grinding while on selective 5-HT re-uptake inhibitors. This appeared to be present with all of the currently available selective re-uptake inhibitors, each of which was tried in each of these patients.

There appears to be a possible basis for such reactions in that there is an interaction between the 5-HT and dopamine systems in the basal ganglia and other areas such that iontophoresis of 5-HT into regions of dopamine nerve terminals leads to a modulation of dopamine release (Tricklebank, 1989).

5-HT and the cardiovascular system

Given the presence of 5-HT receptors in the vasculature and of 5-HT in platelets, one might expect that drugs active on the 5-HT system would have significant cardiovascular effects. A number of 5-HT_1 agonists and 5-HT_2 antagonists in particular have undergone clinical trials with a view to assessing their antihypertensive effects. To date, however, in contrast to their effects in animals and in particular in rats, there appears to be no dramatic effect in humans (Leonard, 1992).

Nevertheless, given the role of 5-HT in the vascular system, it seems likely that many of the drugs emerging for use in psychiatry will find applications also in the treatment of conditions such as Raynaud's disease or other peripheral vascular disorders.

5-HT and arousal

Early observations on clomipramine suggested that it abolished REM sleep (Passouant *et al.*, 1973). This led to interest in its use in disorders of arousal such as the narcoleptic syndrome. Somewhat surprisingly it does not appear to abolish narcoleptic attacks but it does appear to be beneficial in alleviating the cataplexy associated

with this condition (Guilleminault *et al.*, 1976). It seems probable that the newer 5-HT re-uptake inhibitors will be similarly helpful.

In most cases, unlike the majority of tricyclics, the 5-HT re-uptake inhibitors are not clearly sedative. However, a proportion of individuals complain of drowsiness. Surprisingly, even in the presence of complaints of drowsiness, indicators of arousal or alertness, such as reaction times or critical flicker fusion thresholds, indicate that subjects are not sedated, indeed they seem more, rather than less, alert (Kerr, Sherwood and Hindmarch, 1991). Thus there appears to be some dissociation between subjective and objective indices of sedation.

Discussion

In evolutionary terms 5-HT appears to be the oldest of the classical neurotransmitters (Kandel *et al.*, 1986; Carlsson, 1990b). Not surprisingly, therefore, it is distributed widely in the body, as the story of its multiple discovery bears out. Equally it should come as no surprise that manipulations of the 5-HT system lead to effects on a wide range of physiological functions and behaviours.

It would seem highly likely, therefore, that there are a number of other significant effects of drugs active on the 5-HT system waiting to be discovered. The position is perhaps comparable to the effects of aspirin on prostaglandins. During the course of almost a century of use, the effects of aspirin on cardiovascular conditions were unsuspected (Mann and Plummer, 1991). An initial trickle of observations from primary care physicians supplemented by developments in establishing the mode of action of aspirin led to a recognition of the beneficial effects of aspirin in the prevention of stroke, heart attacks and possibly a number of cancers also (Mann and Plummer, 1991).

In the case of drugs active on the 5-HT system, and the 5-HT re-uptake inhibitors in particular, there would appear to be a good case for suggesting that clinical use of these compounds, especially when the depression being treated occurs in the presence of a concomitant physical illness, should take place against a background of awareness that observations of the effects produced may serendipitously yield clues on the future treatment of other disorders. In this way psychopharmacology may, in due course, repay the debt it owes to medical pharmacology, from where most of its compounds have serendipitously derived.

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