Whilst there is much evidence supporting the inverse relationship between aggression and central serotonergic activity, much is of cross-sectional nature. Studies using the tryptophan depletion and/or enhancement paradigm have provided evidence of a causal relationship: lowering brain serotonin provokes an increase and increasing brain serotonin provokes a reduction in aggressive behaviour in susceptible individuals (e.g. Cleare and Bond 1995). A different line of work using neuropharmacological challenge paradigms has provided some support that, specifically, blunted 5-HT$_{1A}$ receptor function is associated with aggression (e.g. Coccaro et al. 1995). What has remained unclear is the extent to which the effect of tryptophan manipulations on aggression and this blunting of the 5-HT$_{1A}$ receptor are linked. We used data from two previous studies to investigate the presence of possible links.

We identified 12 subjects who had participated in two studies: a) a study of tryptophan depletion and enhancement on aggression (Cleare and Bond 1995); and b) a study using the neuroendocrine responses to ipsapirone (20 mg orally) as an index of 5-HT$_{1A}$ receptor sensitivity (Cleare and Bond 1999). All subjects had been selected to have high scores on trait measures of aggression [40 or more out of 75 on the Buss-Durkee Hostility Inventory (Buss and Durkee 1957)] but had no history of mental illness or alcohol/substance abuse. Detailed protocols for the tryptophan manipulations (Cleare and Bond 1995) and ipsapirone challenge tests are published elsewhere (Cleare and Bond 2000).

For the present analysis, our purpose was to discover whether the response to ipsapirone challenge was related in any way to the response seen during tryptophan manipulations. We had previously shown an equal and opposite response to tryptophan manipulation in aggressive subjects: tryptophan depletion produced an increase of approximately 7 points on the Aggression Rating Scale (ARS) mean (Bond and Lader 1974) while tryptophan enhancement produced a reduction of approximately 7 points (Cleare and Bond 1995). Therefore, the subjects presented now were rated as “responders” if they experienced a change of 7 points or more on the ARS in the expected direction, and “non-responders” if the change was less than this, or in the opposite direction.

For the ipsapirone challenge, each subject had undergone an active and a placebo challenge. The response to each challenge was calculated by determining the Δ hormone value (peak-baseline) and the hypothermic response. The placebo response was then subtracted from the active response to give a final ΔΔ response. We used an independent group t-test to compare the ΔΔ responses to ipsapirone between tryptophan responders and non-responders.

Six patients were rated as responders and six as non-responders to the tryptophan manipulation. Those who were tryptophan responders had significantly blunted temperature responses to the ipsapirone challenge. Mean values were –0.78°C in tryptophan non-responders and –0.38°C in tryptophan ignore responders (t = –3.18, P = 0.01, 95% CI for difference –0.69 to –0.11). Figure 1 shows the individual responses. There were no significant differences seen in the ACTH, cortisol, growth hormone or prolactin responses. Comparison of peak ipsapirone levels during the ipsapirone challenge revealed no significant difference (tryptophan responders 105.4, non-responders 124.7 µg/l; t = 0.5, P = 0.63).

Thus, our main finding is that subjects in whom aggression can be provoked or inhibited by tryptophan depletion or enhancement, respectively, show a blunted hypothermic response to ipsapirone. Since ipsapirone acts specifically to stimulate 5-HT$_{1A}$ receptors, and the hypothermic effects are inhibited by pindolol (Lesch et al. 1990b), the blunted hypothermic response is likely to
5-HT1A receptor dysfunction may be specifically linked to criminality (O’Keane et al. 1992) and other unpremeditated aggressive acts (Coccaro et al. 1995). However, another possibility is that the hypothermic response is a measure specifically of presynaptic 5-HT1A receptor function (Hillegaart 1991).

There are several possible interpretations of this finding. First, it is possible that the 5-HT1A receptor blunting is a biological marker of a tendency to respond to many types of situations by becoming angry and feeling aggressive. This is supported by previous research linking 5-HT function to a past history of criminality (O’Keane et al. 1992), fire setting (Virkkunen et al. 1990a), and other unpremeditated aggressive acts (Coccaro et al. 1995). However, another possibility is that the 5-HT1A receptor dysfunction may be specifically linked to the mechanism by which tryptophan manipulations exert their effect. Thus, during tryptophan depletion there is a reduction, and during tryptophan enhancement an increase, in the synaptic synthesis and release of 5-HT (evidence cited in Cleare and Bond 1995). A normally functioning presynaptic 5-HT1A autoreceptor could be expected to work in a homeostatic way, i.e. to normalise these changes in synaptic concentrations. Accordingly, in those subjects with a normally responsive 5-HT1A receptor, tryptophan manipulations should be rapidly attenuated. However, in those subjects who have an under-functioning 5-HT1A receptor, these changes in serotonin synaptic levels would be more prolonged. In a group of subjects specifically chosen to have high aggression levels, this would allow the effects of synaptic 5-HT to be expressed as increased or decreased aggression, respectively.

In low aggressive populations, subjects do not experience changes in aggression during tryptophan manipulation (Cleare and Bond 1995), despite showing the same inverse correlation between aggression and 5-HT function as in high aggressive populations (e.g. Cleare and Bond 1997). This is consistent with the theory that 5-HT1A autoreceptor changes may allow expression of an underlying vulnerability during tryptophan depletion. This theory is also consistent with the effects of tryptophan manipulations in other conditions, where serotonergic changes are expressed in ways relevant to the underlying vulnerability. Thus, tryptophan depletion provokes depressive symptoms in subjects at high risk of depression such as those with a personal (Smith et al. 1997) or family (Benkelfat et al. 1994) history of depression. Similar results have been obtained in pre-menstrual syndrome (Menkes et al. 1994) and bulimia nervosa (Weltzin et al. 1995). Whilst there is also evidence that aspects of depression are also linked to impaired function of the presynaptic 5-HT1A receptor (Lesch et al. 1990a), there is not as yet evidence linking this to the responses to tryptophan manipulations.

It is important to acknowledge some shortcomings with this study. First, the number of subjects was relatively small. Second, we are assuming that the mechanism underlying tryptophan enhancement and tryptophan depletion is the same, based upon our previous findings. However, it is conceivable that different mechanisms may be relevant in these two situations. This possibility could be untangled by looking separately at tryptophan enhancement and tryptophan depletion in a crossover design within the same subjects. Finally, the second study was undertaken approximately 12 months after the completion of the first, and there has been little work on the stability over time of 5-HT mediated responses. Nonetheless, our study provides preliminary evidence that reduced 5-HT1A receptor function may underlie the effect of tryptophan manipulations on aggression in predisposed subjects, and should stimulate research assessing this link more directly.

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References


Fig. 1 Change in oral temperature in response to ipsapirone challenge in men who had previously shown an effect of tryptophan manipulation on aggression in the expected direction (responders to TRP) or who did not show this effect (non-responders to TRP).