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Review

Antidepressant treatments and human aggression

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Abstract

Aggressive behaviour is associated with negative mood and poor impulse control. Serotonin has been specifically associated with impulse regulation and deficiencies in serotonin have been linked to impulsive aggression. However, aggression occurs in a social context and noradrenaline has been implicated in social motivation. Both serotonergic and noradrenergic antidepressants may therefore be effective in reducing aggression. The evidence for the effects of antidepressants on aggression comes from a wide range of sources but there are few controlled trials or experimental studies. Current findings point to decreases in negative mood and anger attacks and positive changes in personality traits after antidepressant treatment. Clinical studies in personality disorder patients have shown some efficacy for serotonergic antidepressants in reducing irritability and impulsive aggression. Experimental work in healthy volunteers has shown both serotonergic and noradrenergic antidepressants to increase assertiveness and affiliative behaviour. Both may therefore decrease aggression through different routes.

Keywords: Aggression; Antidepressant; Negative affect; Impulse regulation; Personality trait; Dominance; Affiliative behaviour

Contents

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1. Introduction

Aggressive behaviour can be a feature of many different psychiatric disorders (Posternak and Zimmerman, 2002). It can be associated with the manic state in bipolar disorder, with confusion and agitation in dementia, with paranoid ideation in schizophrenia, with intrusive memories in posttraumatic stress disorder, with extreme fear in panic disorder, with anger and irritability in depression and premenstrual dysphoric disorder and with substance abuse. Pharmacological treatment should not be used to control behaviour per se but should be targeted at the underlying disorder. Aggressive behaviour is perhaps more commonly associated with certain personality characteristics in the general population and is therefore more typical of Axis II cluster B disorders such as antisocial, borderline and narcissistic personality disorders.

Negative affect has been shown to be important in the genesis of aggression and Berkowitz (1990) hypothesises that anger and aggression are parallel processes generated by negative affect. Negative moods like sadness, dysphoria or feeling low are cardinal symptoms of depression and dysthymia at which antidepressant treatment is targeted. Accompanying mood changes of guilt and anxiety are common. However, increased experience of other emotions such as anger and irritability are also reported and their incidence may be underestimated. A symptom cluster including anger, irritability, aggressiveness and hostility was identified in 23% patients with a diagnosis of major depressive disorder but no other comorbid Diagnostic and Statistical Manual of Mental Disorders-IV axis I or II disorder (Pasquini et al., 2004).

There are now many different antidepressant drugs with a range of pharmacological actions. The tricyclic antidepressants have widespread actions on many different neurotransmitters and are often divided into sedative and non-sedative compounds. The monoamine-oxidase inhibitors have been reserved for patients failing to respond to other treatments because of the danger of toxicity caused by dietary and drug interactions. The second generation antidepressants still have multiple actions but were manufactured to increase safety and reduce side effects. The reversible inhibitors of monoamine-oxidase were also developed primarily to increase safety. More recently more specific pharmacological compounds have been developed. The selective serotonin reuptake inhibitors (SSRIs) are specific to serotonin, the noradrenaline reuptake inhibitors are specific to noradrenaline and the serotonin and noradrenaline reuptake inhibitors are specific to both serotonin and noradrenaline.

Despite the wide variety of antidepressant treatments now available, few of them have been systematically tested in aggression either clinically or in human volunteers. Claims have been made for both increased and decreased aggression in humans. However, reports of increased aggression are generally found in case reports, often after high doses or in combination with other substances e.g. alcohol, and may be related to disinhibition (Bond, 1998). A recent review found no satisfactory evidence to link SSRIs causally to violence (Walsh and Dinan, 2001). Aggressive behaviour often results from increases in negative affect and clinical studies tend to report changes in affect rather than behaviour after antidepressant treatment although some have examined impulsive aggressive acts. A few experimental studies have been carried out in healthy volunteers. This review will examine the evidence for anti-aggressive effects of antidepressants in patients and volunteers, will evaluate differences between compounds and look at the possible mechanisms involved.

2. Clinical evidence

2.1. Irritability and anger attacks

Mood changes in symptoms such as anger and irritability are not always examined in clinical trials of antidepressants but where they have been, improvement has been shown (Andrews et al., 1998). In addition, a novel study looked at subthreshold symptoms of irritability and anxiety in symptomatic volunteers and found improvement after 5 weeks of low dose clomipramine compared to active placebo (Gorenstein et al., 1998).

Anger attacks occurring as part of major depressive disorder have been described comprehensively (Fava et al., 1993; Rosenbaum et al., 1993). These attacks are very similar to panic attacks. They are accompanied by symptoms of autonomic activation such as tachycardia, sweating, flushing, and tightness of the chest but the overriding emotion is anger rather than fear or anxiety. The attacks are experienced as ego-dystonic and inappropriate to the situations in which they occur. Fava and Rosenbaum (1998) have estimated that approximately one-third of patients with unipolar depression present with anger attacks. They posit that unipolar depression with anger attacks thus constitutes a subtype of depression. However, it should be noted that these patients are also more likely to meet criteria for Axis II personality disorders than depressed patients without anger attacks (Fava and Rosenbaum, 1998). Patients with anger attacks show similar response rates to antidepressant treatments as patients without them and anger attacks also subside after treatment with both SSRIs and tricyclic antidepressants in 53–71%. Therefore antidepressants with both noradrenergic and serotonergic actions have been shown to decrease this form of aggression.

2.2. Impulsive aggression and personality disorder

Impulsive aggression is a common feature of Axis II cluster B personality disorders which can be difficult to treat. Various drug treatments including tricyclic and MAO inhibitor antidepressants have been tried in older trials but the results were equivocal (Stein, 1994; Tuinier and Verhoeven, 1995). More recently, several open studies have suggested that antidepressants with serotonergic actions may be effective (e.g. Cornelius et al., 1991; Markovitz et al., 1991; Markovitz and Wagner, 1995; Reist et al., 2003). In a trial in which patients with major depressive disorder were randomised to receive treatment with either fluoxetine or nortriptyline for 6 weeks, patients with an additional cluster B personality disorder did

poorly on nortriptiline compared to fluoxetine (Mulder et al., 2003). However very few controlled clinical trials have been done (Table 1) and SSRIs have not been compared to antidepressants with other pharmacological actions. One study examined the effects of fluoxetine versus placebo in 22 symptomatic volunteers with borderline personality disorder and found an improvement on anger and aggression after fluoxetine but only after controlling for a large placebo effect (Salzman et al., 1995). Another larger study looked at the effects of fluoxetine in 40 patients with mixed personality disorders and a current history of impulsive aggression and found an improvement in both irritability and aggression measured on the Overt Aggression Scale (Coccaro and Kavoussi, 1997). In these two studies, patients with comorbid Axis I depressive disorders were excluded. A third study examined the effects of a different SSRI, fluvoxamine, in female patients with borderline personality disorder (Rhinne et al., 2002). They did not exclude depression but used statistical procedures to control for axis I disorders. The outcome measure consisted of 3 subscales of the Borderline Personality Disorder Index, brief mood shifts, anger and impulsivity. Although mood shifts were significantly reduced by fluvoxamine both during the first 6-week double blind phase and at the end of treatment, the effects on anger and impulsivity were not significant. However, the levels of anger and impulsivity reported by these women were low and were reduced by both fluvoxamine and placebo, which may have made it difficult to obtain significant effects. The results of these studies seem promising, if not definitive. However, it is clear from the authors' accounts that these studies are very difficult to do and suffer from both high placebo response and drop-out rates which casts doubts on the results from uncontrolled studies.

Table 1
Double-blind controlled trials of antidepressants in impulsive aggression

Study	Patients (*N*)	Treatment	Aggression-related measure	Outcome
Salzman et al., 1995	Borderline personality disorder: 14F 8M (22)	Fluoxetine 20–60 mg Placebo 12 weeks	Overt Aggression Symptom Checklist POMS[a]-Anger	Significant improvement on anger
Coccaro and Kavoussi, 1997	Mixed personality disorders with impulsive aggression: 12F 28M (40)	Fluoxetine 20–60 mg Placebo 3 months	Overt Aggression Scale—Modified Irritability and Aggression	Significant improvement
Rhinne et al., 2002	Borderline personality disorder: females (38)	Fluvoxamine 150 mg/day Placebo 6 weeks DB[b] 6 weeks SB[c] 12 weeks Open	BPD[d] Severity Index Brief mood shifts Anger/Aggression Impulsivity	Significant improvement only on mood shifts

[a]Profile of Mood States, [b]double blind, [c]single blind, [d]Borderline Personality Disorder.

3. Personality traits related to aggression

3.1. Depressed patients

Although aggressive behaviour is associated with particular personality disorders, the classification of personality disorder has been described as one of the least satisfactory of all contemporary psychiatric diagnoses (Livesley, 1998). It relies on a clinician assigning patients to discrete categories according to symptoms and thus overlooks the dimensional nature of personality traits (Bond, 2001; Tuinier and Verhoeven, 1995). Some studies have investigated the effects of antidepressants on personality traits using the NEO personality inventory (NEO-PI: Costa and McCrae, 1990) or the Temperament and Character Inventory (TCI: Cloninger et al., 1993). Most of the traits that have been examined are not directly related to aggression and much of the improvement on traits such as TCI harm avoidance or NEO neuroticism is related to clinical improvement (Bond, 2001). However, a few studies have found antidepressant effects on traits related to aggression. Bagby et al. (1999) compared a tricyclic antidepressant, desipramine, with two SSRIs, paroxetine and sertraline on NEO traits. They found decreases in the subscale anger–hostility and increases in the subscale gregariouness following treatment with all three antidepressants. These changes were not significantly correlated with change in depression severity. The changes in aggression-related traits were therefore independent of illness status but were not related to a particular type of antidepressant in this study.

Other studies have found that antidepressant treatment can also affect the character factors of the TCI, especially self-directedness and cooperativeness. Self-directedness represents the ability of the individual to regulate their behaviour and commit to chosen goals and cooperativeness represents the ability to identify with and accept other people. Therefore both are likely to be related to aggressive behaviour. Allgulander et al. (1998) reported that symptomatic volunteers diagnosed with generalised anxiety disorder showed increases in self-directedness and cooperativeness after paroxetine treatment for 4–6 months. Similar results were found in patients with unipolar depression who received treatment with a serotonergic antidepressant (paroxetine, fluoxetine, fluvoxamine or amesergide) (Black and Sheline, 1997). These patients not only had increased self-directedness and cooperativeness scores but were also less likely to meet the criteria for a PD after 6–10 weeks' treatment.

Positive effects have also been found on other measures of personality after SSRI treatment. The Karolinska Scales of Personality were used to measure personality traits in patients with major depressive disorder before and after 24 weeks' treatment with one of two SSRIs, sertraline or citalopram (Ekselius and Von Knorring, 1999). Significant positive changes were seen on all except one scale and 3 of the scales specifically measured aggressive traits; indirect aggression, verbal aggression and irritability. Improvements in depressive symptoms only accounted for up to 8.4% of the variance on the personality dimensions. The Cattell 16 Personality Factor Inventory (16PF)

was used in a study of patients with major depressive disorder or obsessive compulsive disorder before and after 8–12 weeks' treatment with paroxetine (Brody et al., 2000). Six of the seven 16PF factors changed in the predicted direction after treatment. The two social dominance factors and one of the two social affiliation factors showed positive change which was independent of clinical improvement. These factors may then be more like the TCI character factors and are likely to relate to aggressive behaviour.

3.2. Healthy volunteers

These studies were all conducted in clinical populations. It is possible that because depressed patients are reported to have lower self-directedness and cooperativeness scores generally (Hansenne and Ansseau, 1999; Richter et al., 2000), these dimensions might also be related to illness as well as personality variables and therefore might be responsive to antidepressant treatment. To test whether antidepressant drugs have independent effects on personality, it is possible to use healthy controls in whom personality variables such as self-directedness and cooperativeness would be expected to be stable and not to change after drug administration. Very few studies have examined the effects of drug treatment on the personality of healthy volunteers. One study looked at changes in the TCI in 20 healthy male volunteers pre and post 2 weeks of citalopram or placebo (Tse and Bond, 2001). No changes were shown on the temperament factors but an increase in S.D. was found after citalopram compared to placebo. These preliminary results indicate that the effects of antidepressants, specifically those with serotonergic actions, are not confined to those with psychiatric illness. Positive character changes, which may reduce aggressive behaviour, can also occur in normal healthy volunteers.

4. Experimental studies

4.1. Tryptophan manipulation

Serotonin has been shown to have a major role in the modulation of aggressive behaviour in humans as well as animals. An inverse relationship between indices of serotonergic function and impulsive aggressive behaviour has been repeatedly displayed (Coccaro et al., 1989) but much of the evidence is correlational. An experimental procedure for investigating the effects of serotonin involves tryptophan depletion and enhancement.

Tryptophan is the precursor of serotonin and tryptophan depletion has been shown to be an effective procedure for lowering brain serotonin (Nishizawa et al., 1997). A review of studies using this procedure specifically to examine effects on anger and aggression (Bond and Wingrove, 2001) identified 11 studies, 9 of which found evidence of increased negative affect or aggression. However the conditions for this increase appeared to be critical. Firstly, it was much more likely to occur in subjects with a predisposition or underlying vulnerability e.g. those with high levels of trait hostility. Secondly, the effects on mood were not confined to anger but represented a general increase in negative affect, which may have increased the likelihood of aggressive behaviour occurring. Thirdly, the effects were greater when contrasted with tryptophan enhancement rather than a control condition. These factors may have implications for treatment; increasing serotonin synthesis in vulnerable individuals may decrease the risk of aggression.

The subjects in these 9 studies were all male but since the review, a further two studies have been published, both in women and both using a balanced drink as the control (Bond et al., 2001; Marsh et al., 2002). Neither of these studies preselected women on a trait measure of aggression but Bond et al. (2001) chose to test women in the premenstrual phase of their cycle in an attempt to increase their emotional vulnerability. This may have accounted for no differences in mood changes between the depleted and balanced conditions but they found increased aggressive responding on a laboratory task, the competitive reaction time task, in the depleted group. This result was similar to previous studies using this technique in males (Cleare and Bond, 1995; Pihl et al., 1995). Marsh et al. (2002) used a different laboratory task, the point subtraction aggression paradigm, which has also shown increased aggressive responding after tryptophan depletion in men (Moeller et al., 1996; Bjork et al., 2000) and found a trend for increased aggressive responding over the day in the depleted condition compared to decreased aggressive responding in the balanced drink condition.

These studies then indicate that lowering serotonin can increase aggression and possibly enhancing serotonin can decrease it. So what do studies specifically looking at administration of the drugs tell us?

4.2. Acute doses of antidepressants

There is some evidence which suggests that the action of SSRIs on feelings of irritability and anger differs from their action in depression. Patients with premenstrual dysphoric disorder without comorbid depression respond as well to intermittent as to continuous treatment (Dimmock et al., 2000). SSRIs need only be administered premenstrually while symptoms are present which may only be for a few days in some patients. Therefore acute administration might be predicted to decrease negative affect related to aggression in some individuals.

No studies were found which examined the acute administration of antidepressants on aggression specifically. However, one study has compared the effects of an acute dose of a noradrenergic and a serotonergic antidepressant on social behaviour in the laboratory (Tse and Bond, 2002a). Participants were randomly allocated to receive a single dose of an SSRI (citalopram 10 mg), a Noradrenaline Reuptake Inhibitor (reboxetine 4 mg) or placebo. They socially interacted with a confederate trained to behave in an unresponsive, non-sociable manner in a stranger–dyadic social interaction paradigm 1.5 h post drug. Social behaviour during the interaction was video recorded by a hidden camera and subsequently analysed. After the interaction, volunteers played the Mixed Motive game with

the confederate. This game has been shown to measure cooperative behaviour and communication. Participants rated their mood on the Positive and Negative Affect Scale (PANAS) pre drug and before and after the interaction. Neither drug affected mood. An acute dose of reboxetine led to an increase in both cooperative communication during the game and cooperative behaviour on the game. Citalopram had no effects on behaviour during either the interaction or the game. The results suggest that acute elevation of noradrenaline can increase engagement and cooperation with others whereas an acute increase in 5-hydroxytryptophan (5-HT) induced by citalopram had little effect. Noradrenaline may therefore be important for social behaviours which are generally understood to represent the opposite of aggression.

4.3. Repeated dose studies

In contrast to the effects of SSRIs in premenstrual dysphoric disorder, studies of SSRI treatment in impulsive aggression have indicated that clinical effects on aggression are not usually apparent until 4 weeks, partly due to the high placebo response. There are five studies which have looked at the effects of repeated doses of antidepressants on negative affect or behaviour related to aggression (Table 2). Three have examined SSRIs, one tryptophan and one reboxetine. Various techniques have been used to measure both mood and aggression. Knutson et al. (1998) administered an SSRI (paroxetine 20 mg/day) or placebo to 46 healthy volunteers for 4 weeks. They assessed effects on two subscales (assault and irritability) of the Buss Durkee Hostility Inventory, the PANAS and on a collaborative dyadic puzzle task at baseline and after 1 and 4 weeks. They found that ratings of assault and negative affect decreased significantly after both 1 and 4 weeks of paroxetine compared to placebo. Affiliative behaviour on the puzzle task increased after 1 week of paroxetine compared to placebo but there was no difference at 4 weeks. Changes in assault, irritability, negative affect and affiliative behaviour were related to plasma levels of paroxetine at the end of the study.

Paroxetine was also used in another study (Cherek et al., 2002) which lasted for 8 weeks. The participants were 12 male subjects with a history of criminal behaviour. No tablets were administered for the first week, which was used to establish baseline responding and placebo was administered to all subjects for the following 2 weeks. Then subjects were randomly allocated to receive paroxetine (20 mg/day) or placebo for 3 weeks and all subjects returned to placebo for the final 2 weeks. The effects were assessed on the point subtraction aggression paradigm and on a separate impulsivity task measuring delay of gratification on 2 days each week. Aggressive responding declined steadily in the paroxetine group with a significant within group effect between the initial placebo phase and the end of treatment which was not present in the placebo group, in whom responding remained stable. In addition paroxetine progressively reduced impulsive responses.

The social behaviour paradigm described earlier was used to examine the effects of citalopram, another SSRI (Tse and Bond, 2002b). Participants socially interacted with a confederate trained to behave in a responsive, sociable manner in a stranger–dyadic social interaction. After the interaction, volunteers played the Mixed Motive game with the confederate. Citalopram 20 mg/day and placebo were administered for 2 weeks each in a double-blind, crossover trial. Ten pairs of same sex healthy volunteers took part. In each pair, one (subject) took the tablets while the other (flatmate) received no treatment. The social interaction took place on the final day of treatment and the flatmate evaluated the social behaviour of the subject before and at the end of treatment. Subjects showed a dominant pattern of eye contact during the interaction, reduced the number of points they awarded themselves on the game and sent more cooperative messages during the game when on citalopram. They were also rated as less submissive by their flatmates.

Moskowitz et al. (2001) administered tryptophan to study the effects of increasing serotonin on behaviours denoting agreeableness–quarrelsomeness and dominance–submission during daily social interactions recorded by 98 healthy volunteers. They administered tryptophan (1 g three times a day) and placebo for 12 days each in a crossover design. Tryptophan increased self-

Table 2
Experimental studies with double-blind repeated dose administration

Study	Subjects	Drug	Measures	Result
Knutson et al., 1998	46 HVs[a]	Paroxetine 20 mg/day 4 weeks	BDHI[b] Assault BDHI[b] Irritability PANAS[c] Dyadic puzzle task	Decreased Assault Decreased negative mood Increased affiliative behaviour
Cherek et al., 2002	12M with criminal record	Paroxetine 20 mg/day Placebo 3 weeks	PSAP[d] Impulsivity task	Decreased aggressive and impulsive responding
Tse and Bond, 2002b	10 HVs[a]	Citalopram 20 mg/day Placebo 2 weeks crossover	PANAS[c] Impact Message Inventory Social Interaction Mixed Motive Game Communication Checklist	Less submissive Dominant eye contact Reduced points to self Sent more cooperative messages
Moskowitz et al., 2001	98 HVs[a]	Tryptophan 1g TID[e] Placebo 12 days crossover	Dominance Quarrelsomeness	Increased dominance Decreased quarrelsomeness (when administered after placebo)
Tse and Bond, 2003	10 HVs	Reboxetine 8 mg/day Placebo 2 weeks crossover	PANAS[c] Impact Message Inventory Social Interaction Mixed Motive Game Communication Checklist	Less submissive Less eye contact More agreeable Sent fewer helplessness messages

[a]Healthy volunteers, [b]Buss Durkee Hostility Inventory, [c]Positive and Negative Affect Scales, [d]Point Subtraction Aggression Paradigm, [e]three times a day.

reported dominance but only decreased quarrelsomeness when it was given after placebo. The authors explain this as a carryover effect which may have occurred because when given first, tryptophan initiated change in the interaction cycles of participants with others which then persisted. It should also be noted that the washout period between treatment periods was only 2 days. This study indicates that serotonin may have effects on social behaviour related to aggression which are not associated with any mood effects. The event-contingent recording method which they used is more naturalistic than laboratory work but all the data is dependent on self-report and there is no objective verification.

Reboxetine, a selective noradrenaline reuptake inhibitor, has been looked at in one study using the aforementioned social behaviour paradigm (Tse and Bond, 2003). The design was similar to the previous study. Reboxetine 8 mg/day and placebo were administered for 2 weeks each in a double-blind, crossover trial. Ten pairs of same sex healthy volunteers took part. In each pair, one (subject) took the tablets while the other (flatmate) received no treatment. The social interaction took place on the final day of treatment and the flatmate evaluated the social behaviour of the subject before and at the end of treatment. Subjects showed less eye contact and were rated as more agreeable and cooperative during the interaction by an independent observer when on reboxetine. They also gave fewer helplessness messages during the game. They were rated as less submissive by their flatmates.

There are too few experimental studies to draw firm conclusions but it seems that antidepressants generally increase assertiveness, SSRIs reduce aggressive behaviour and increase affiliative responses, and reboxetine has some prosocial effects. It is also possible to propose some mechanisms when considering the data from different sources.

5. Mechanisms involved in reducing aggression

5.1. Negative affect

Negative affect is an important factor in generating anger and aggression. Antidepressant treatments are primarily targeted at alleviating negative affect. The evidence presented here shows that they are effective in improving not only sadness and dysphoria but also irritability and anger where these are features of depression. This effect would decrease the likelihood of aggressive behaviour. In confirmation, in one of the experimental studies, the reduction in negative affect accounted for the reduction in assaultiveness (Knutson et al., 1998). There is some evidence that in premenstrual dysphoric disorder, premenstrual symptoms of irritability and aggression may respond preferentially to SSRIs (Eriksson et al., 1985).

5.2. Impulse regulation

Serotonin has been implicated in impulse regulation (Spoont, 1992). Soubrié (1986) suggested that increasing serotonergic neurotransmission results in inhibition of behaviour by increasing the ability of the organism to tolerate delay. In an experimental study cited earlier, an SSRI was found to reduce impulsive responses on a task measuring delay of gratification in subjects with a history of criminal behaviour (Cherek et al., 2002). People with deficient levels of serotonin as reflected by low levels of 5-hydroxyindoleacetic acid or blunted responses to serotonergic drugs such as D-fenfluramine may be unable to restrain their behaviour and therefore at risk of acting out aggressively. This best describes patients with impulse control disorders or cluster B personality disorders and preliminary evidence presented here suggests that SSRIs may help to regulate the impulse to act out aggressively in these patients. In confirmation, in a recent study, impulsive aggressive patients with borderline personality disorder had a Positron Emission Tomography scan before and 12 weeks after treatment with fluoxetine. Fluoxetine was found to decrease aggression and increase relative metabolic rate in the orbitofrontal cortex, an area associated with impulse control (New et al., 2004). The association of serotonin with impulse regulation has led to much more work using serotonergic drugs in the treatment of patients with primary impulse control disorders. However, depressed patients who experience anger attacks may also be displaying problems with restraining their behaviour and although SSRIs have been studied more often and are often recommended, there is evidence that tricyclic antidepressants are also effective (Fava and Rosenbaum, 1998).

5.3. Individual characteristics

Personality characteristics may determine response to different antidepressant treatments but there is currently little work on this relating to aggression. However evidence has been presented that antidepressants with predominant actions on either the serotonergic or the noradrenergic systems had positive effects on traits related to aggression. They improved anger and hostility and increased gregariousness (Bagby et al., 1999). Certain characteristics have only been investigated using SSRIs and these antidepressants have shown positive effects on the ability of both depressed and healthy individuals to both regulate their behaviour and commit to chosen goals and to identify with and accept other people (Allgulander et al., 1998; Black and Sheline, 1997; Tse and Bond, 2001).

5.4. Dominance–submission

Preclinical work has emphasised the role of dominant–submissive behaviour in aggression and submissive behaviour has been linked to depression (Willner, 1995). Some effects of antidepressant treatment on this dimension have been shown in this review. Traits related to social dominance were shown to improve after SSRI treatment (Brody et al., 2000). In the experimental studies, self-rated dominance during daily social interactions was increased after tryptophan (Moskowitz et al., 2001) and observer-rated submissiveness was reduced after both citalopram and reboxetine (Tse and Bond, 2002b, 2003). Administration of antidepressants can therefore increase assertiveness and

independence even in healthy volunteers. In addition, a dominant pattern of eye gaze was shown in the interaction with a stranger after citalopram compared to placebo. The function of dominance is to gain social status within an interaction. These results are consistent with primate research showing that when tryptophan or fluoxetine are administered to subordinate male vervet monkeys, they achieve dominance status (Raleigh et al., 1991). Baumeister et al. (1996) have suggested that aggression stems from high but unstable self-esteem and so an increase in self-efficacy and social status might make aggression less likely.

5.5. Prosocial or affiliative behaviour

Affiliative behaviour can be seen as the opposite of aggression and some evidence has been presented here that antidepressants can increase this aspect of social interaction. Traits related to social affiliation were increased by SSRI treatment (Brody et al., 2000). In the experimental studies, tryptophan decreased self-rated quarrelsomeness (Moskowitz et al., 2001) and SSRIs increased affiliative and cooperative behaviour in different types of dyadic interaction (Knutson et al., 1998; Tse and Bond, 2002b). In addition, reboxetine showed evidence of more cooperative communication after an acute dose as well as after repeated administration (Tse and Bond, 2002a, 2003). This work confirms the findings of a clinical study in which both fluoxetine and reboxetine lead to higher reported social functioning after 8 weeks' treatment (Dubini et al., 1997). In fact, in the latter study, reboxetine produced significantly greater effects than fluoxetine. Therefore antidepressants with serotonergic and noradrenergic actions may reduce aggression by different routes. Both decrease negative affect and increase assertiveness but serotonin reduces impulsivity whereas noradrenaline increases social drive.

6. Conclusions

The evidence for the effects of antidepressants on human aggression is not well developed but comes from a wide range of sources. Some case studies have reported increased aggression but these effects do not emerge in controlled trials and are therefore probably idiosyncratic. For example, the emergence of anger attacks after treatment is greater after placebo than after antidepressant treatment (Fava and Rosenbaum, 1998). Few experimental investigations have been carried out but coupled with other data sources such as clinical trials, studies of personality factors and tryptophan manipulation, the overall picture is of reduced aggression related to a number of different mechanisms. There is insufficient work at present comparing drugs acting on different neurotransmitters but antidepressants with serotonergic and noradrenergic actions may reduce aggression by different routes. Both decrease negative affect and increase assertiveness but serotonin reduces impulsivity, allowing time to reflect, which may result in reduced perception of threat and therefore less need for action whereas noradrenaline increases social drive, encouraging people to mix more, which may result in increased social competence.

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