A Neuroimmunological Model of Antisocial and Borderline Personality Disorders

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The neurobiology of the dramatic personality disorders (DSM-IV — Cluster B) has remained somewhat elusive, with the consequence that pharmacological treatment of these disorders is far from satisfactory. The clinical feature that characterizes the borderline personality disorder (BPD) is repeated acts of self-mutilation, whereas those with an antisocial personality disorder (ASPD) are disposed to repeated acts of criminality. While the antisocial group are inevitably incarcerated in penal institutions, the borderline patient, despite their acute psychological suffering, is often refused hospitalization primarily due to the absence of effective interventions. In this paper it will be hypothesized that both these disorders are due to a primary dysregulation of interferon-gamma (IFN-\(\gamma\)), neuropeptide Y (NPY), \(\beta\)-endorphin and insulin. A gender bias has also been observed in relation to these two conditions with females being predisposed to developing a BPD and males an ASPD — a gender bias that can be directly attributed to \(\beta\)-endorphin. Other perplexing features of these disorders are the self-injurious behaviour (SIB) and frequent amenorrhea of the BPD, a complete lack of morality often combined with heightened cognition and the ‘low serotonin syndrome’ (low serotonin, low LDL (low density lipoprotein) cholesterol and mild hypoglycaemia) of the ASPD. A neuroimmunological explanation of this curious constellation of symptoms will be advanced in this paper.

INTRODUCTION

An important prerequisite for understanding these disorders is the recognition of the important role insulin plays in brain neurophysiology. Although it has been widely accepted that the brain is an insulin-independent organ, an accumulated body of research over the last decade has effectively refuted this earlier held perception. For example, in vivo autoradiographic studies, using radio-labelled insulin injected intravenously, have shown that insulin enters the brain through the median eminence and the arcuate nucleus (ARC) of the hypothalamus (Baskin et al., 1983). Furthermore, in vitro studies have also established that certain neurons can synthesize insulin (Clarke et al., 1986), while insulin mRNA has been found in some brain areas, in particular, the periventricular region (Young, 1986). In addition, Craft et al. (1993) have demonstrated that the hypothalamus, hippocampus and olfactory bulb are densely populated with insulin receptors. Although the two brain glucose transporters, GLUT-1 and GLUT-3 function by facilitative diffusion, it is now known that GLUT-1 is insulin-responsive (Klip and Marette, 1992) and that both transporters are indirectly insulin-dependent in the brain (Holden and Mooney, 1994). This is due to the fact that insulin is involved in the conversion of the inactive form of p21ras.GDP (guanine diphosphate) to the active form of p21ras.GTP (guanine triphosphate) (Burgering et al., 1991), the latter of which controls

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both energy metabolism via the protein kinase C (PKC) signal transduction pathway, and neurotransmission via tetrahydrobiopterin (BH4) — the co-factor for tyrosine hydroxylase (TH) and tryptophan hydroxylase (TPH) (Ohue et al., 1991). Both PKC and p21ras.GTP influence the brain glucose transporters directly (Kozma et al., 1993; Holden and Mooney, 1994), while BH4 regulates the release of dopamine (DA), serotonin (5-HT), acetylcholine (ACh), and glutamate (Ohue et al., 1991; Matage et al., 1991). (For a detailed explication of the p21ras.GTP signalling pathway see Holden and Mooney (1994)).

Understanding that brain insulin plays a critical role in both energy metabolism and neurotransmission is an important prerequisite for understanding the significance of the inflammatory cytokines when they become dysregulated. Studies have shown that interleukin-1 beta (IL-1β), tumour necrosis factor-alpha (TNF-α) and IFN-γ all influence insulin secretion both independently and synergistically (Eizirik et al., 1994). When these cytokines are mildly elevated they increase insulin secretion, and when moderately elevated they inhibit insulin secretion (Mehta et al., 1994; Jhala et al., 1994). This means that either mild or moderate elevation of these cytokines will indirectly influence both energy metabolism and neurotransmission via their individual and/or collective influence on insulin secretion. In addition, IL-1β can influence neurotransmission directly since this cytokine augments the release of DA, 5-HT, norepinephrine (NE) and the DA and 5-HT metabolites, dihydroxyphenylacetic acid (DOPAC) and 5-hydroxyindoleacetic acid (5-HIAA) from the hypothalamus (Shintani et al., 1993; Mohankumar et al., 1993). Consequently, if IL-1β is either up-regulated or downregulated this can have a direct effect on hypothalamic secretion of these neurotransmitters. However, IFN-γ also influences the relative expression of 5-HT. Studies have shown that when IFN-γ is elevated it downregulates 5-HT (Coleman et al., 1991; Pihl et al., 1993a; Holliday et al., 1994) — a factor that has an important bearing on ASPD given that the ‘low serotonin syndrome’ (Linnoila and Virkkunen, 1992a) is a biological marker for this condition. The main features of the ‘low serotonin syndrome’ are low serotonin, low LDL cholesterol (Virkkunen, 1979) and mild hypoglycaemia (Linnoila and Virkkunen, 1992a) all of which are induced by elevated IFN-γ. Elevated IFN-γ downregulates LDL cholesterol (Hansson, 1994) and induces hypoinsulinaemia (Sjöholm, 1991; Suarez-Pinzon et al., 1994). It has recently been found that IFN-γ lowers LDL cholesterol by inhibiting foam cell formation through the downregulation of the macrophage receptor (Hansson, 1994); and induces hypoinsulinaemia (Sjöholm, 1991; Suarez-Pinzon et al., 1994) which, in the brain causes hypoglycaemia of the cells. This is because (i) some glucose transporters in the brain are insulin sensitive; and (ii) the rate and/or extent of conversion of p21ras.GDP to p21ras.GTP is reduced. When the active form of p21ras — p21ras.GTP — is downregulated then energy metabolism and neurotransmission are both inhibited, and such inhibition of energy metabolism induces hypoglycaemia of the cells. Consequently, the ‘low serotonin syndrome’, first identified by Linnoila and Virkkunen (1992a), may be caused by elevated IFN-γ which is known to be elevated in the Cluster B personality disorders (Naidenova et al., 1994). A recent Russian study investigated 94 patients with borderline and hysterical personality disorders and found that serum interferon levels were significantly higher in patients with aggressive personalities than those with more submissive features (Naidenova et al., 1994). This finding concurs with the many studies conducted by a group of researchers from Finland who repeatedly found evidence of the residual effects of elevated IFN-γ they referred to as the ‘low serotonin syndrome’ which, apart from low 5-HT, LDL cholesterol and mild hypoglycaemia, also includes low CSF 5-HIAA concentrations, early-onset alcohol and substance abuse, a family history of alcohol abuse, and circadian rhythm disturbances (Virkkunen, 1979; Linnoila et al., 1983; Linnoila and Virkkunen, 1992a,b, 1993).

THE ANTISOCIAL PERSONALITY DISORDER

Although the term ‘antisocial personality disorder’ has replaced the term ‘psychopath’ in the Diagnostic and Statistical Manuals of Mental Disorders (DSM I-IV), Schlesinger (1980) has re-employed the original terms ‘psychopath’ and ‘sociopath’ in an effort to clearly distinguish between three types of ASPDs. Schlesinger reserves the term ‘psychopath’ to refer to the middle-class con man who rarely excites psychiatric attention and equally rarely invites penal incarceration. Schlesinger characterizes the ‘psychopath’ as a person in possession of ‘good intelligence, loyalty to one’s self, and a lack of emotional depth’. By way of
contrast, ‘sociopath’ is reserved for those who are substance abusers and engage in substance abuse-related crime, while ‘antisocial personality disorder’ refers to the criminal underclass, congregating in correctional institutions who are predisposed to commit crimes of violence.

In contradistinction to Schlesinger, Karpman (1961), Cleckley (1988) and Wells (1988) draw a distinction between the primary and secondary psychopath. For Karpman (1961), the primary psychopath is resistive to all forms training, including early toilet training and enjoys a relative freedom from neurosis; while the secondary psychopath initially behaves like a ‘difficult, hostile and selfish child’ who becomes increasingly self-centred with increasing age. Fagan and Lira (1980) characterize the primary psychopath as an emotionally indifferent individual who displays high sensation-seeking behaviour and is unresponsive to aversive stimuli. Newman et al. (1985) found both the primary and secondary psychopath exclusively responsive to reward conditions and totally unresponsive to punishment. Wells (1988) defines the ASPD as a narcissistic individual who derives pleasure in asserting his superiority by humiliating and embarrassing others, particularly when deception is involved. For Wells, the ASPD is characterized by (i) an incapacity for object love; (ii) an absolute need to dominate under all conditions; and (iii) a capacity to lie and deceive skilfully in the course of which the ASPD demonstrates his contempt for those he humiliates. Blackburn and Lee-Evans (1985) found the primary psychopath was free from anxiety and depression yet sensitive to perceived interpersonal provocation. Another characteristic of the ASPD that is seldom acknowledged, is their continuous fantasizing about criminal activity in that the crimes actually committed are infinitesimal compared with the number of crimes imagined (Yochelson and Samenow, 1976).

The above characteristics of the ASPD can be summarized as follows: (i) an absence of anxiety; (ii) enhanced cognitive ability; (iii) an absence of moral development; (iv) an inability to learn from negative experience; and (v) responsive only to reward socialization. In addition, ASPD is associated with the ‘low serotonin syndrome’ which includes: (i) low serotonin; (ii) low LDL cholesterol; and (iii) mild hypoglycaemia (Virkkunen et al., 1994). Virkkunen et al. (1994) have also found low blood glucose nadirs during oral glucose tolerance tests (OGTT) in violent offenders and fire setters.

In this study, Virkkunen et al. also established an association between violent offenders and (i) low cerebrospinal fluid (CSF) 5-HIAA; (ii) low CSF corticotropin; (iii) elevated CSF testosterone that correlated with (iv) unprovoked interpersonal violence; (v) an increased risk of suicide; (vi) early onset alcoholism in men; (vii) irregular sleeping patterns; and (viii) ‘desynchronized diurnal activity rhythm’ (1994). Fishbein et al. (1992) demonstrated a hypoglycaemic response to a 5-h OGTT in antisocial/aggressive subjects which was associated with elevated baseline prolactin (PRL) levels and downregulated cortisol compared to non-antisocial controls. Other research groups have also found an association between hypoglycaemia and aggressive antisocial personalities. Raine et al. (1994) studied the local cerebral uptake of glucose using positron emission tomography (PET) in a group of violent offenders during a continuous performance task. It was found that ‘murderers had significantly lower glucose metabolism in both the lateral and medial prefrontal cortex relative to controls’ (Raine et al., 1994, p. 365). This result concurs with that of Goyer et al. (1994) who found a negative correlation between high scores on an aggression scale and low glucose metabolism in the anterior frontal brain regions using PET.

O’Keane et al. (1992), in a study on violent male offenders convicted of murder found subsensitive serotonergic responses to a d-fenfluramine challenge, while Coccaro (1992) have reviewed numerous studies in which reduced central 5-HT function in the limbic—hypothalamic system was found to be associated with suicidal and/or impulsive/aggressive behaviours. That low serotonin and hypoglycaemia coincide in the ASPD is physiologically significant since some studies have shown that central nervous system (CNS) 5-HT concentrations are influenced by insulin (Azam et al., 1990; Bhattacharya and Saraswati, 1991; Atienza et al., 1992; Vahabzadeh et al., 1995). Vahabzadeh et al. (1995) found that a systemic injection of insulin induced hypoglycaemia in the brain with a concomitant increase in 5-HT and NE in the serotonergic and noradrenergic projections to the hippocampus. Bhattacharya and Saraswati (1991) found that intracerebroventricular (icv) administration of insulin induced hypoglycaemia coupled with a marked increase in 5-HT and ACh concentrations and a decrease in DA and NE concentrations in the midbrain-diencephalon and pons medulla. Thus, a systemic injection of insulin induced brain
hypoglycaemia and increased 5-HT, while icv administration of insulin induced brain hyperglycaemia and increased 5-HT. What is important to recognize in these apparently contradictory results, is that brain insulin appears to increase the levels of brain 5-HT, while the influence of insulin on glucose is a secondary effect. Thus, as insulin rises 5-HT rises and, conversely, as insulin decreases 5-HT decreases. This conjecture has been confirmed by Atienza et al. (1992) who found that fluctuating levels of insulin produce a parallel fluctuation in brain tryptophan (TRP), the precursor of 5-HT. Although energy metabolism in the brain has been considered insulin-independent (Baskin et al., 1983), Clarke et al. (1984) found that insulin increases glucose uptake in the brain. This means that elevated insulin and 5-HT will enhance glucose regulation and transport in the CNS. Conversely, reduced concentrations of insulin and 5-HT will inhibit glucose uptake in the brain and induce hypoglycaemia of the cells. This proposition has since been supported by Azam et al. (1990), who found that hypoglycaemia downregulated DA, NE and 5-HT, while availability of TRP depended on the level of circulating insulin. A relationship between insulin and brain monoamines is additionally supported by the finding that systemic administration of streptozotocin increases brain monoamines, an increase that is substantially accentuated when streptozotocin is administered via the icv route (Lackovic and Salkovic, 1990).

This observed relationship between brain monoamines and insulin is of particular interest in relation to ASPD. Belfrage et al. (1992) studied platelet monoamine oxidase (MAO) activity in a group of mentally disordered violent offenders and found that MAO activity was significantly reduced among the nonpsychotic, violent offenders. Similarly, Alm et al. (1994) found reduced platelet MAO activity among a group of former juvenile delinquents who later progressed to adult criminal behaviour. Low platelet MAO activity has been correlated with personality characteristics such as: poor impulse control, an inability to anticipate negative future consequences, psychopathic behaviour, alcohol and substance abuse, violent suicide and hyperactivity (Alm et al., 1994). Alm et al. (1994) point out that low central serotonergic turnover is associated with low MAO activity which results in low levels of 5-HIAA in the CSF of violent offenders as indicated by Linnoila et al. (1983). This observed relationship between reduced platelet MAO activity and reduced CSF 5-HIAA levels is possibly due to a reduction in energy metabolism. Azam et al. (1990) found that hypoglycaemia caused a decrease of DA, NA and 5-HT, while insulin influenced TRP concentrations. Given that fluctuating levels of insulin produce a parallel fluctuation in brain TRP (Atienza et al., 1992), this reduces serotonergic turnover which may result in lowered MAO activity and low 5-HIAA in the CSF. But hypoinsulinaemia not only causes reduced serotonergic turnover, it also reduces LDL cholesterol.

A number of authors have advanced the proposition that reduced levels of LDL cholesterol leads to reductions of brain 5-HT which results in suicidal and/or impulsive aggressive behaviour (Engelberg, 1992; Hawton et al., 1993; Freedman et al., 1995). In fact monkeys, when fed a low cholesterol diet, exhibited a significant increase in aggressive behaviour (Kaplan et al., 1991). However, there are two interrelated physiological reasons for this cholesterol/serotonin association. Ballenger et al. (1979) point out that serotonin synthesis is controlled by the availability of plasma-free TRP relative to large neutral amino acids (LNAA; tyrosine, phenylalanine, valine, leucine, isoleucine) with which it competes for uptake into the brain. Consequently, when the LNAA:TRP ratio is biased in favour of LNAA, there is less TRP available for export to the brain for serotonin synthesis. The first factor that may disrupt the LNAA:TRP ratio was identified by Salter (1992) who points out that cholesterol-lowering diets reduce dietary fat intake which results in reduced availability of serum fatty acids. Serum fatty acids and TRP compete for binding sites on serum albumin with the result that reduced serum fatty acid concentrations increase the content of bound TRP which reduces the availability of free TRP for export to the CNS. The second factor is that hypoinsulinaemia reduces LNAA uptake in the skeletal muscle which alters the LNAA:TRP ratio in favour of LNAA and reduces the amount of free TRP available for serotonin synthesis (Pijl et al., 1993b). However, one of the most probable reasons for the conjoint symptoms of mild hypoglycaemia, low LDL cholesterol and low serotonin is, as previously mentioned, that elevated IFN-γ actually induces all of these effects.

ASPD patients appear not only to have a uniform pathophysiology, they also appear to have uniform structural abnormalities as well. Wong et al. (1994), in a retrospective study of 372 maximum-security mental hospital male patients,
found that those with the highest rating scores for violence also had temporal electrical abnormalities identified by an electroencephalograph (EEG); and structural temporal lobe abnormalities identified by computed tomography (CT) scan. In a longitudinal study of conduct-disordered patients, it was found that 20 years after the initial diagnosis 33 per cent had developed an ASPD (Storm-Mathisen and Vaglum, 1994), which means that either these temporal lobe abnormalities coincided with the original conduct disorder or they gradually developed over time. Neuropeptide abnormalities of the temporal lobe also occur in epilepsy, abnormalities that are not dissimilar to those found in ASPD. For example, Devinsky et al. (1993) reports that increased levels of NPY have been found in surgically-removed temporal lobe epileptogenic tissue, while Calabrese et al. (1993) found that endorphins, cortisol and corticotropin increase in the CSF during status epilepticus and remain elevated for sometime post seizure. In fact, it appears that several neuropeptides are epileptogenic. Intracerebroventricular injections of adrenocorticotropic hormone (ACTH), corticotropin-releasing hormone (CRH) and thyrotropin-releasing hormone (TRH) in animals have all induced epileptic seizures (Devinsky et al., 1993) as can elevated levels of endorphin (Calabrese et al., 1993). Both endorphin and ACTH are produced in the anterior pituitary, the release of which is stimulated by CRH (Träskman-Bendz et al., 1992) and interleukin-2 (IL-2) (Spangelo and Gorospe, 1995). Meyers et al. (1992) report that surgical resection of a tumour from the anterior pituitary induced acquired antisocial personality and behavioural changes that coincided with an ASPD. This suggests that dysregulation of the preopiomelanocortin (POMC) peptides (endorphin, lipotropin, ACTH, and melanocyte-stimulating hormone (MSH)) (Moore and Black, 1991) released from the anterior pituitary may play some role in the pathophysiology of ASPD.

THE BORDERLINE PERSONALITY DISORDER

The prevalence of borderline personality disorder has been estimated at around 1.7 per cent of the general population and 26.7 per cent of the personality-disordered population (Widiger and Weissman, 1991). This means that a large proportion of personality-disordered patients are not receiving adequate care, in part due to an impoverished understanding of the neurochemistry that underlies this condition. As a consequence of this impoverished understanding, there is a paucity of appropriate pharmacological interventions available to medical practitioners. The aetiology of BPD has been appraised from a number of perspectives: biological, sociological and psychological. Psychological trauma, particularly childhood sexual abuse, has been proposed as a key aetiological factor that gives rise to the symptoms of dissociation and/or self mutilation (Paris, 1994). Sociological studies have estimated that one-third of all youth suicide cases have BPD, while the parasuicide rate for females with drug overdoses is steadily increasing (Paris, 1994). Biological models of BPD argue that this condition is fundamentally a mood disorder due to the fact that affective instability is a leading symptom of this condition (Paris, 1994). Coccaro and Kavoussi (1991) view the BPD as manifesting a triad of principal symptoms: (i) affective instability; (ii) transient psychotic phenomena; and (iii) impulsive aggressive behaviour. They advance the view that affective instability may be associated with abnormalities in the brain’s adrenergic and cholinergic systems; that transient psychotic phenomena may involve the dopaminergic system; while impulsive aggressive symptoms may involve the serotonergic system. It has been hypothesized that the affective component of BPD predisposes more females to develop this condition than males, whereas males are significantly more likely than females to meet the criteria of antisocial, narcissistic or obsessive-compulsive personality disorder (Widiger and Weissman, 1991; Golomb et al., 1995). However, not all studies have supported the existence of a gender bias, in favour of females, in relation to BPD (Golomb et al., 1995). A recent study examining the personality traits of men who are habitually involved in domestic violence, found that batterers had high borderline-antisocial personality traits which were associated with a childhood history of abuse (Else et al., 1993). These findings are interesting in the light of PET scan data on antisocial violent offenders in which there is reduced glucose uptake in the prefrontal cortex (Raine et al., 1994). In BPD patients there is also a significant decrease in the regional cerebral metabolic rate of glucose (rCMRG) in the frontal cortex (Goyer et al., 1994) together with a trend towards higher right than left glucose uptake in the posterior part of the temporal lobe (de la Fuente et al., 1994).
Soloff et al. (1991) report on a number of studies in which it was found that (i) a high incidence of affective disorder occurs among BPD patients; (ii) nondepressed BPD patients often develop an affective disorder at some stage during a 6–36-month follow-up; and (iii) BPD patients have a high prevalence of affectively ill relatives. Hollander et al. (1994) subjected 12 BPD patients to an oral m-chlorophenylpiperazine (m-CPP) challenge following which male and female patients experienced a remediation of symptoms — a reduction of anger and fear. In this study it was also found that male BPD patients exhibited higher cortisol and blunted PRL responses following an m-CPP challenge compared to female BPD patients and normal controls. Given that m-CPP is a partial 5-HT agonist, these authors inferred that marked serotonergic abnormalities coincide with BPD. Coccaro et al. (1994) reported blunted PRL responses to fenfluramine challenge in BPD patients which they also believe implies serotonergic dysfunction. Coid (1993) studied the pattern of affective instability in 72 female BPD patients detained in maximum-security hospitals. Coid found that 92 per cent of the subjects complained of racing thoughts; 68 per cent complained of rapid mood swings; and 58 per cent complained of depersonalization. In addition these patients' symptoms congregated into four factors of (i) anxiety — emptiness and fearfulness; (ii) anger — hatred, loss of appetite, irritability; (iii) depression — early morning waking, restlessness, poor concentration; (iv) tension — trembling, sleep disturbance. Coid reports that for most patients, self-mutilation was not associated with any appreciable pain but did induce a significant relief of their mood-related symptoms. Coid detected a cyclical quality to the expression of symptoms. Following mutilation of either themselves or others, they experienced an ecstatic feeling together with an amelioration of their affective symptoms, this was followed by a diminution of depersonalization and the gradual return of pain sensation whereupon the affective symptoms would re-emerge. These symptoms would typically commence around menarche and become progressively worse until their mid-twenties, finally subsiding from mid-thirties onwards. This pattern of illness progression suggests some steroid hormonal involvement, and many women believed their affective symptoms exacerbated during the premenstrual week.

There is now a growing body of literature that suggests the affective instability and SIB in relation to BPD, may be due to a dysregulation of the opioid system, particularly that of β-endorphin. Favazza and Rosenthal (1993) have identified three types of SIB: (i) infrequent acts of severe mutilation associated with psychoses and acute intoxications; (ii) rhythmical SIB with stereotypy associated with mental retardation; and (iii) moderate SIB such as skin cutting, burning and scratching usually associated with BPD. BPD patients report rapid relief from their symptoms of anxiety, anger and racing thoughts following acts of SIB. It is estimated that around 50 per cent of repetitive self-mutilators have a comorbid diagnosis of anorexia or bulimia nervosa (Favazza and Rosenthal, 1993), the latter of which is known to be associated with the downregulation of 5-HT, dysregulation of β-endorphin, and elevation of NE, cholecystokinin (CCK) and peptide YY (PYY) (Kaye and Weltzin, 1991). Ghaziuddin et al. (1992) found a high prevalence of SIB among a group of adolescent inpatients who were clinically depressed and who tended to self-mutilate in the afternoon. This is an interesting observation in the light of the circadian rhythm of β-endorphin which is elevated in the morning and decreases in the afternoon (Sandman et al., 1990). It has also been demonstrated that levels of β-endorphin fluctuate throughout the menstrual cycle, being elevated during the menstrual and follicular phases and downregulated during the luteal and premenstrual phases (Taylor et al., 1993). Among mentally retarded patients, the incidence of SIB increases during the phases of increased β-endorphin and declines during the phases of decreased β-endorphin. It was hypothesized by Taylor et al. (1993), that the pain experience was more acute during periods of β-endorphin decline, a factor which induced a concomitant decrease in the incidence of SIB. Whether a similar pattern of SIB occurs in BPD remains to be investigated, but there are some indications that there may be some correspondence. First, BPD patients repeatedly report the absence of pain when they self-mutilate (Coid, 1993; Russ et al., 1994) which implies that β-endorphin may well be elevated, particularly in view of the fact that naloxone induces a trend towards increased pain perception, following a cold pressor test, in BPD patients who report no pain when they self-mutilate (Russ et al., 1992). Second, anxiety and depression are associated with elevated levels of β-endorphin (Darko et al., 1992; Goodwin et al., 1993), and BPD patients report relief from symptoms of anxiety following acts of
self-mutilation (Favazza and Rosenthal, 1993; Russ et al., 1994). Thus, there are several reasons to support the assumption that SIB in BPD is associated with elevated b-enkephalins, a factor which also coincides with symptoms of anxiety and depression. However, it is hypothesized here that the natural circadian rhythm of b-enkephalin may also be dysregulated in BPD — a dysregulation that gives rise to rapid cycling of moods and racing thoughts on the one hand, and the symptoms of anger, hatred, irritability and loss of appetite on the other.

THE NEUROPEPTIDES AND ANTISOCIAL AND BORDERLINE PERSONALITY DISORDER

It is hypothesized here that the two neuropeptides most seriously dysregulated in BPD and ASPD are b-enkephalin and NPY. Cintra et al. (1991) point out that b-enkephalin plays a central role in pain and mood control, as well as the regulation of the neuroendocrine and cardiovascular systems, and temperature control (Spanagel et al., 1991). Spanagel et al. (1991) found elevated b-enkephalin concentrations in areas of the limbic system that modulate motivation and mood. b-Enkephalin increases DA release in the nucleus acumbens (Spanagel et al., 1991), but inhibits DA synthesis, turnover and release in the hypothalamus (Desjardins et al., 1993). b-Enkephalin also modulates (i) lymphocyte proliferation; (ii) natural killer (NK) cell activity; (iii) IFN-g production; and (iv) antibody synthesis (Heijnen et al., 1991). Carr (1991) reports that b-enkephalin augments IFN-g production — an important insight given that IFN-g is elevated in BPD (Naidenova et al., 1994). As previously mentioned, elevated IFN-g dysregulates brain insulin due to the excitatory and/or inhibitory influence of IFN-g on insulin secretion. The influence of b-enkephalin on mood is also found in certain nonpsychiatric conditions such as diabetes mellitus (Goodnick et al., 1995), low-back pain (Polatin et al., 1993), and spinal cord-injured (SCI) patients (Twist et al., 1992). Goodnick et al. (1995) report an 8–27 per cent incidence of depression in diabetic patients which is not surprising given that b-enkephalin and IFN-g are elevated in both depression (Goodwin et al., 1993; Maes et al., 1994) and diabetes (Dalayeur et al., 1993; Terzic et al., 1994; Pennline et al., 1994). Similarly, Polatin et al. (1993) report a 77 per cent incidence of psychotic disorder in patients suffering from chronic low-back pain which, in the majority of cases, preceded the onset of low-back pain. The psychiatric disorders most frequently exhibited in this study were: major depression, anxiety disorder, personality disorder and substance abuse. Once again, there is a common pattern of b-enkephalin dysregulation in each of these disorders. For example, chronic pain downregulates CSF b-enkephalin in diabetic polyneuropathy (Tsigos et al., 1995), while chronic stress elevates b-enkephalins (Young et al., 1993).

The influence of stress on b-enkephalin has particular relevance to BPD since early and sustained childhood sexual abuse is frequently present in the childhood histories of these patients (Paris, 1994). Farabollini et al. (1993) has found that acute (restraint) stress reduced b-enkephalin levels in the periaqueductal gray matter, and IFN-g production in rats. They also found that reduced IFN-g production was more marked in female rats than male rats. This finding may be relevant to BPD since chronic stress elevates b-enkephalin/b-lipotropin ratio which may well elevate IFN-g as well. Twist et al. (1992) report that patients with recent SCI had higher baseline levels of circulating b-enkephalins, while patients with chronic SCI had lower levels of circulating b-enkephalins accompanied by depressed circadian rhythm and dysregulated cortisol. This finding corresponds with the that of Tsigos et al. (1995) who found downregulated b-enkephalin was associated with chronic pain. Twist et al. (1992) also report that during the acute phase of SCI approximately 50 per cent of patients suffer from major depression, both of which conditions are associated with elevated b-enkephalins (Polatin et al., 1993).

Persistent substance abuse may also indirectly be related to b-enkephalin. For example, marijuana elevates IFN-g (Watzl et al., 1991) which is associated with elevated b-enkephalin (Heijnen et al., 1991). Acute ethanol intake initially decreases pituitary b-enkephalin but increases serum b-enkephalin, while chronic ethanol intake decreases hypothalamic b-enkephalin content (Adams and Cicero, 1991). Reddy et al. (1995) found that low doses of ethanol enhanced b-enkephalin secretion from culture hypothalamic neurons, while Vescovi et al. (1992) found chronic ethanol intake downregulates b-enkephalin. It is also noteworthy that naltrexone, a b-enkephalin antagonist, reduces ethanol craving in human patients (Reddy et al., 1995). It is possible, therefore, that chronic ethanol abuse may represent an
effort to self-medicate against the anxiety-inducing and/or depressive-inducing effects of elevated β-endorphin. Given that β-endorphin inhibits DA synthesis, turnover and release in the hypothalamus (Desjardins et al., 1993) it is not without interest that cocaine stimulates DA release by increasing DA availability at dopaminergic synapses in the brain (Extein and Gold, 1993). Given that cocaine stimulates DA release which is inhibited by β-endorphin, cocaine abusers may well be self-medicating against elevated β-endorphin. In support of this contention, Extein and Gold (1993) report that approximately one-third of cocaine abusers meet the criteria for major depressive disorder following detoxification — a condition characterized by elevated β-endorphin (Darko et al., 1992; Goodwin et al., 1993), IFN-γ (Maes et al., 1994) and reduced availability of DA (Extein and Gold, 1993). On the other hand, heroin and morphine are known to downregulate β-endorphin (Kosten et al., 1992). This may be why over 62 per cent of heroin addicts also meet the above criteria for major depression following detoxification. This could be due to the fact that heroin and morphine abusers are also self-medicating against elevated β-endorphin levels and, consequently, withdrawal from heroin or morphine increases β-endorphin to the original baseline levels which reduces DA availability (Extein and Gold, 1993) and re-establishes the symptoms of anxiety and depression (Darko et al., 1992; Goodwin et al., 1993). It would appear therefore, that following detoxification from either cocaine, heroin or morphine, β-endorphin levels increase, DA availability decreases and the patient experiences symptoms of major depression.

But while β-endorphin downregulates NE and DA, inhibits cognitive performance, and induces amnesia (Flood et al., 1992), nicotine has the opposite effect in that it elevates β-endorphin, and circulating plasma levels of epinephrine, NE and DA (Pomerleau, 1992). But since nicotine elevates β-endorphin, for patients whose β-endorphin levels are already elevated, smoking would rapidly become self-perpetuating. This is because increasing levels of nicotine would be required to elevate epinephrine, NE and DA in order to counteract the downregulating influence of β-endorphin on the catecholamines. This correspondence between elevated β-endorphins in both major depression and the Cluster B personality disorders possibly accounts for the findings of Zimmerman et al. (1988). These authors studied a group of patients with major depression, including bipolar affective disorders, and found that the depressed sample included 25 per cent of histrionic patients, 24 per cent of BPD patients, and 15.5 per cent of antisocial and dependent patients (Zimmerman et al., 1988). Consequently, from a neurophysiological perspective, all these conditions are interrelated since all have elevated levels of IFN-γ and elevated β-endorphin. What may mark the difference between each of these disorders is the relative expression of other neuropeptides such as NPY.

Finally, β-endorphin also influences the steroid hormones in both ASPD and BPD. β-Endorphin has been found to inhibit gonadotropin secretion in the monkey in that (i) β-endorphin administration inhibits gonadotropin release; and (ii) β-endorphin neuronal cell bodies are highly concentrated in brain areas involved in the regulation of gonadotropin secretion (Ferin et al., 1984a). Consequently, β-endorphin can inhibit the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH) resulting in amenorrhoea (Ferin et al., 1984a) — a symptom not uncommon to eating disorders (Ferin et al., 1984b; Golden and Shenker, 1994) and which are frequently comorbid with BPD (Favazza and Rosenthal, 1993). Bonavera et al. (1994) have found that icv administration of β-endorphin, followed by two consecutive intravenous injections of N-methyl-D-aspartate (NMDA), an excitatory amino acid (EAA) agonist, significantly enhanced LH release in castrated rats. This capacity of the opioid peptides to potentiate the NMDA-induced LH release was further confirmed in ovariectomized female rats. This means that if ASPD coincided with elevated NMDA concentrations, then the normal negative feedback interaction between testosterone and LH in the pituitary may be overcome. If this negative feedback interaction between testosterone and LH is overcome, it could explain the presence of elevated CSF testosterone levels found in ASPD patients (Virkkunen et al., 1994).

As previously mentioned, the hallmark of the ASPD is the ‘low serotonin syndrome’ that coincides with low 5-HT, low LDL cholesterol and mild hypoglycaemia. It has also been mentioned that each of these symptoms directly results from elevated levels of IFN-γ. IFN-γ also downregulates insulin-like growth factor-II (IGF-II) (Martin et al., 1993; Garmey et al., 1993) which downregulates NPY (Sahu et al., 1995). IFN-γ induced hypoglycaemia causes an increase in TRP and the TRP metabolite, quinolinic acid (QUIN),

in serum, brain and CSF (Heyes et al., 1990). QUIN is an NMDA receptor agonist that activates intracellular free calcium and causes cellular damage in the absence of IGF-II protection (Mattson and Cheng, 1993). In the case of ASPD and BPD, it is postulated that IGF-II is down-regulated by IFN-γ (Martin et al., 1993; Garmey et al., 1993). Calcium influx causes neurotoxicity which further elevates IFN-γ (Holliday and Gruol, 1993), and thus hypoglycaemia, which increases QUIN and causes an NMDA-induced release of glutamate (Milusheva et al., 1992). Overexpression of glutamate also causes NMDA receptor-mediated damage via calcium influx, through which glutamate is transformed from a ‘neurotransmitter to a neurotoxin’ (Virgin et al., 1991; Sapolsky, 1993). QUIN then activates indoleamine-2,3-dioxygenase (IDO) which is the first enzyme in the kynurenine pathway (Taylor and Feng, 1991; Heyes et al., 1992). But IDO is also activated by IFN-γ (Heyes et al., 1992) which leads to a circularity of biochemical events since hypoglycaemia increases TRP which induces an elevation of QUIN. QUIN then stimulates IFN-γ release via calcium-induced neurotoxicity, while IFN-γ enhances QUIN synthesis via activation of IDO in the kynurenine pathway — a process which is represented diagramatically in Figure 1.

As can be seen from Figure 1, the biochemistry of ASPD and BPD will rapidly become self-reinforcing and self-perpetuating. In addition, IFN-γ-induced hypoglycaemia will negatively influence serotonin synthesis in that any free TRP will be diverted down the kynurenine pathway to produce QUIN, thereby compounding the down-regulatory influence of IFN-γ on serotonin synthesis. This conjecture is supported by Saito et al. (1991) who found that repeated injections of IFN-γ stimulated IDO activity in lung and brain causing a concomitant increase in QUIN brain and plasma levels. This means that IFN-γ levels will continuously increase in ASPD and BPD due to the persistent activation of IDO by IFN-γ which increases QUIN levels even further (Saito et al., 1991). Given the foregoing, it is postulated that elevated NMDA concentrations are present in ASPD which can account for the combined effect of β-endorphin and NMDA-receptor elevation of LH, leading to an elevation of CSF testosterone in ASPD (Virkkunen et al., 1994).

Figure 1. A self-perpetuating model of the kynurenine pathway that causes reduced serotonin synthesis in ASPD and BPD.
In summary, it is hypothesized here that in BPD, circulating levels of β-endorphin are subject to rapid fluctuations, which may imply that the circadian rhythm of β-endorphin is concomitantly dysregulated. It is further hypothesized, with respect to BPD that circadian dysregulation of β-endorphin gives rise to a rapid cycling mood disorder that frequently accommodates this condition. In addition, elevation of IFN-γ gives rise to NMDA receptor activation which, when occurring in conjunction with elevated β-endorphin, causes an increase in testosterone associated with ASPD and estrogen associated with BPD. This process also compounds the downregulation of 5-HT due to the IFN-induced diversion of TRP down the kynurenine pathway, resulting in elevated levels of QUIN and increased neurotoxicity due to calcium mobilization from the overexpression of both QUIN and glutamate.

Earlier, it was mentioned that IFN-γ downregulates IGF-II (Martin et al., 1993; Garmey et al., 1993) which inhibits NPY (Sahu et al., 1995). NPY is a cerebral vasoconstrictor associated with ASPD and is both negatively regulated by insulin (Marks et al., 1993) and can itself regulate insulin (Akabayashi et al., 1994). Elevation of NPY is known to be responsible for hyperphagia and polydipsia (McKibbin et al., 1992), in addition to which NPY also has powerful analgesic properties (Wettstein et al., 1995) that parallel those of β-endorphin. In fact, Kalra et al. (1993) have recently identified the lines of communication between β-endorphin and NPY. They have found that the ‘NPY axon terminals synapse with β-endorphin-immunopositive dendrites and soma in the arcuate nucleus of the hypothalamus’ (Kalra et al., 1993, p. 13) which they believe implies a ‘regulatory role of NPY in governing the discharge of β-endorphin’ (Kalra et al., 1993, p. 13). Pau et al. (1991) report that: (i) NPY enhances LH response to gonadotropin-releasing hormone; (ii) that this stimulatory effect is steroid dependent; and (iii) NPY exercises a direct action on the primate anterior pituitary. This means that since NPY also increases LH, this will further enhance the release of testosterone induced by the synergistic effect of β-endorphin and NMDA. But increased levels of testosterone will further increase the availability of NPY, since testosterone increases NPY selectively in the median eminence (Kalra et al., 1993).

However, the most interesting and important effect of NPY in relation to ASPD, is its influence on cognition and learning. Apart from being a powerful analgesic, NPY is also a powerful anxiolytic that has a selective influence on memory and learning (Heilig et al., 1992; Wettstein et al., 1995). Heilig et al. (1992) studied the behaviour of rats under three conditions: (i) lever-pressing for food reward (unpunished responding); (ii) lever-pressing with no consequences; (iii) lever-pressing that produced food-reward combined with an incremental foot-shock (punished responding). Rats were then given various doses of NPY and β-endorphin into the lateral cerebral ventricle. It was found that ‘NPY markedly and dose-dependently increased punished responding’ (Heilig et al., 1992, p. 61), whereas β-endorphin had no effect on this condition. This means that elevated NPY can possibly explain three predominant symptoms of ASPD. First, since NPY is a powerful anxiolytic, elevated NPY can explain the marked absence of anxiety in ASPD; second, NPY enhances cognitive performance and improves memory retention (Wettstein et al., 1995); third, NPY increases punished responding which can account for the peculiar inability of ASPD patients to learn from negative experience. In fact, many studies have observed that both ASPD and conduct disorder patients are only responsive to reward socialization — (unpunished responding) (Newman et al., 1985; Marlowe, 1993). These combined factors may serve to explain the heretofore inexplicable absence of moral development in ASPD individuals. If the absence of anxiety following commission of prohibited acts, co-occurs with imperviousness to punishment, the fundamental basis of moral development is completely absent. And, since NPY also enhances cognitive performance and memory retention, this provides for the paradoxical observation of ASPD individuals appearing to be simultaneously intellectually able and yet morally degenerate.

In summary, the neurochemistry of ASPD and BPD can be described as follows: elevated IFN-γ downregulates IGF-II and insulin, the latter of which upregulates NPY. IFN-γ also causes the downregulation of 5-HT both directly and indirectly: First, via the kynurenine pathway resulting in elevated QUIN, causing calcium-induced neurotoxicity which elevates IFN-γ even further. Second, elevated IFN-γ causes hyperglycaemia which increases concentrations of TRP and QUIN in serum, brain and CSF (Heyes et al., 1990), but which reduces 5-HT concentration in the brain. Increased presence of brain QUIN, activates
the NMDA receptors which, in conjunction with 
β-endorphin, increase LH and circulating levels of testosterone in males and estrogen in females 
(Bonavera et al., 1994) — a factor which may also contribute to the perceived gender bias of these 
disorders. Finally, elevated β-endorphin is also 
associated with SIB in both BPD and aggressive/ 
antisocial hospitalized forensic patients (Hillbrand 
et al., 1994). This pattern of dysregulation is repre-
sented diagramatically in Figure 2.

As can be seen from Figure 2, the basic neuro-
chemistry of BPD and ASPD is self-perpetuating. 
The key factors are the nexus of neuropathology 
that obtains in the interaction between IFN-γ, 
NPY, β-endorphin and insulin. From the figure it 
can be seen that the downregulatory influence on 
insulin comes from three sources: IFN-γ, NPY and 
β-endorphin; the upregulatory pressure on IFN-γ 
derives from three sources: QUIN, NMDA-
induced neurotoxicity and β-endorphin; the up-
regulatory pressure on NPY derives from three 
sources: insulin, β-endorphin and testosterone; 
while the upregulatory pressure on β-endorphin 
also derives from three sources: IFN-γ, NPY and 
insulin. It has frequently been observed in the 
clinical arena that the intensity of symptoms 
relating to BPD and ASPD seems to abate with 
age (Coid, 1993; Gunderson, 1988). This observa-
tion may be explained by the fact that both 
β-endorphin (Kowalski et al., 1992; Wang et al., 
1993) and NPY (Beal et al., 1991; Kowalski et al., 
1992) concentrations decrease with age — a factor 
that lends further credence to the above proposed 
neurochemical model of these disorders. However, 
it should be emphasized that this model is 
necessarily incomplete since information in relation 
to the expression of many other neuropeptides is 
not yet available. The same argument also applies 
to the cytokines. All that is known to date is that 
IFN-γ is elevated, and studies have yet to be 
undertaken in relation to the relative expression of 
IL-1, IL-2, IL-6 and TNF-α the results of which 
would also shed some light on the relative expres-
sion of the neuropeptides since the cytokines and 
neuropeptides are causally interactive.

Hayashi (1992) identified a number of neurotic 
symptoms that frequently co-exist with BPD which 
included a range of high anxiety states such as

![Image](image.png)

Figure 2. A neuroimmunological model of antisocial and borderline personality disorder

depersonalization, dissociation (Demitrack et al., 1993), obsessive-compulsive symptoms (Marlowe, 1993) and various phobias and panic attacks all of which involve elevated \( \beta \)-endorphin and, with respect to panic attacks, elevated CCK as well (Raiteri et al., 1993; Lydiard, 1994). Coid (1993) pointed out that anxiety and depression form part of the clinical features of BPD. In major depression and BPD, \( \beta \)-endorphin is elevated (Darko et al., 1992; Goodwin et al., 1993; Maes et al., 1994), but in major depression NPY is downregulated (Heilig et al., 1992; Lieberman and Koreen, 1993), whereas in BPD, NPY is elevated, which may engender the clinical impression that BPD patients' stated feelings of depression is somewhat disingenuous. There also appears to be a gradation of biopathology in relation to \( \beta \)-endorphin and BPD: during the angry phase, which possibly coincides with the luteal and premenstrual phases of the menstrual cycle, \( \beta \)-endorphin is downregulated; during the anxious and depressive phase, possibly coinciding with increased SIB, substance abuse and the menstrual and follicular phases of the menstrual cycle, \( \beta \)-endorphin is elevated. Following episodes of SIB, \( \beta \)-endorphin is elevated even further leading to euphoria; while following substance abuse of either heroin, morphine or cocaine, \( \beta \)-endorphin is downregulated below the level associated with depressive-inducing symptoms. Given the difficulties these patients encounter in obtaining alleviation of symptoms from conventional sources, it is small wonder that many of these BPD patients gravitate to abuse of substances such as cocaine, heroin and/or morphine since all these influence \( \beta \)-endorphin (Kosten et al., 1992; Extein and Gold, 1993) and, thereby, provide considerable symptom relief.

**CONCLUSION**

The pharmacological armamentarium currently available to address the problem of BPD and ASPD is scant. Wettstein et al. (1995) point out that 'receptor-selective antagonists of NPY are not available'. Although Wettstein et al. indicate the availability of some partial antagonists to NPY such as benextramine, PYX-1 and PYX-2, \( \beta \)-myo-inositol-1,2,6-triphosphate and He 90481, these authors point out that none of these compounds are pharmacologically conventional. One possible exception to this lack of pharmacological convention is the compound \([\text{\textit{\textbeta}}\text{-Trp}^{\text{\textgamma}}]\text{NPY}\) which has shown some NPY antagonist properties.

In addition, there is also some suggestion that haloperidol may be an effective NPY antagonist (Wettstein et al., 1995). In a recent study conducted by McCarthy et al. (1995) into the effects of IL-1\( \beta \)-induced anorexia and pyrexia on hypothalamic NPY, it was found that indomethacin (0.25 mg/100 g i.p.) reduced IL-1\( \beta \) and normalized NPY concentrations in rats. While haloperidol may be an effective NPY antagonist, it may also be useful in downregulating \( \beta \)-endorphin. In a study conducted by Ernst et al. (1993), that assessed the \( \beta \)-endorphin levels of autistic children, it was found that \( \beta \)-endorphin levels were downregulated — a downregulation that directly correlated with the severity of stereotypes in all children. In this study it was found that short-term administration of haloperidol was of initial benefit since haloperidol increased plasma \( \beta \)-endorphin, however, long-term administration decreased plasma levels of this opioid peptide even further. Although both naltrexone and naloxone antagonize \( \beta \)-endorphin, naltrexone had no effect on plasma \( \beta \)-endorphin levels in this study with autistic children (Ernst et al., 1993). In addition, since these medications are restricted drugs they are of limited therapeutic usefulness in this context. One drug that does appear to inhibit \( \beta \)-endorphin, is the anti-anxiety triazolobenzodiazepine, adinazolam, by inhibiting CRH-induced \( \beta \)-endorphin release (Saland et al., 1992). It is important to identify a satisfactory antagonist for \( \beta \)-endorphin, since Van den Bergh et al. (1994) have found that 'two peptide fragments of beta-End, i.e. beta-End6-31 and beta-End18-31, that lack of N-terminal enkephalin part' increase IFN-\( \gamma \). This means, that prolonged elevation of \( \beta \)-endorphin may induce sustained elevation of IFN-\( \gamma \) and, consequently, perpetuate the biochemical reactions identified in Figure 1. However, given that \( \beta \)-endorphin and IFN-\( \gamma \) are causally interactive, an alternative approach to the re-regulation of \( \beta \)-endorphin and NPY may be through targeting IFN-\( \gamma \) directly. One drug currently available that downregulates IFN-\( \gamma \) is piroxicam — a nonsteroidal antiinflammatory drug — but it also downregulates IL-1, IL-6 and TNF-\( \alpha \) as well, and upregulates IL-2 in peripheral blood mononuclear cells (Rosenstein et al., 1994). Until the full cytokine profile of BPD and ASPD is known, employment of broad-based Pharmaceuticals may well be counterproductive.

In this paper we have attempted to produce a neuroimmunological model of BPD and ASPD, but it must be emphasized this model is necessarily
incomplete. The most salient feature of this model is the role of NPY in the development and maintenance of ASPD since long-term elevation of this peptide inhibits moral development and induces the antisocial symptoms associated with this disorder. Admittedly, in this proposed model we have inferred a probable association between ASPD and NPY on the basis of the demonstrated influence of NPY on learning in rat models. However, we believe that identifying the relative expression of NPY in ASPD and BPD may well prove a fruitful area for future research, and developing an antagonist to this peptide even more fruitful.

REFERENCES


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NEUROBIOLOGY OF PERSONALITY DISORDERS


