ENDOGENOUS OPIOIDS AND OPIATE ANTAGONISTS IN AUTISM: BRIEF REVIEW OF EMPIRICAL FINDINGS AND IMPLICATIONS FOR CLINICIANS

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Over the last 15 years, many theories have been proposed to account for the symptoms associated with autistic disorder (American Psychiatric Association 1987)/childhood autism (World Health Organization 1993). One of these is related to dysfunction of the endogenous opioid system (Panksepp 1979, Sahley and Panksepp 1987). The discovery that bio-active peptides such as beta-endorphin and ACTH were co-located in a single precursor, pro-opiomelanocortin (POMC), gave rise to many new theories about the interaction of peptides in behaviour and brain functions. According to the opioid hypothesis for autism, hyperfunction of the endogenous opioid system could explain some—even most—of the symptoms associated with autistic disorder. Such hyperfunction has been implicated because of the range of autistic-like behaviours elicited by opiate administration in man (most typically seen in addiction to opiates) and in opiate-treated animals (Panksepp 1979, A. Weizman *et al.* 1984, Deutsch 1986). These behaviours and symptoms include: (1) reduced socialization (and aloofness), (2) reduced clinging in animals, (3) diminished crying, (4) repetitive stereotyped behaviours, (5) promotion of convulsive activity, (6) insensitivity to pain, (7) episodes of motor hyperactivity alternating with hypo-activity, and (8) affective lability. Theoretically, the first four could be seen to represent constituents of the core syndrome of autism, promotion of convulsive activity could be linked to the raised incidence of seizures in autism, while the last three symptoms are common (but not invariable) co-morbid problems in autism.

Current hypotheses

In their original hypothesis, Herman and Panksepp proposed that heightened activity in some brain opioid systems may underlie autism. This hypothesis was derived from animal research demonstrating a relationship between brain opioid systems and social attachment in infant animals. Brain opioids inhibit separation distress, and opioid antagonists (such as naloxone) exacerbate distress, by blocking endogenous opioids. Furthermore, morphine decreases infant–maternal proximity maintenance time in animals (Herman and Panksepp 1978), and this has been taken as indirect support for the type of social dysfunction encountered in autism. However, infant–maternal proximity would probably best be conceptualized as a measure of social attachment, an area in which children with autism are not necessarily dysfunctional (Sigman and Ungerer 1984).

Most of the opioid hypotheses for

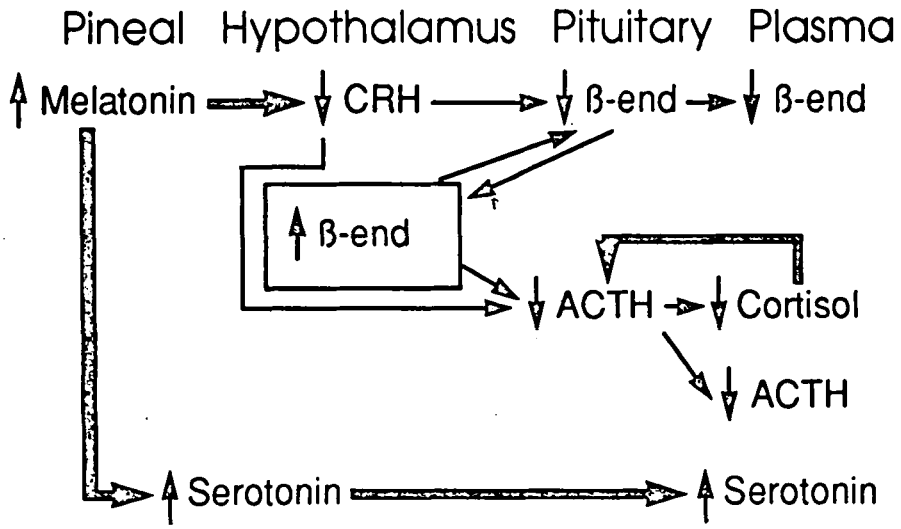

Fig. 1. A transactional model for opioid dysfunction in autism. Hypersecretion of melatonin induces serotonin increase in brain and blood. Pineal melatonin hypersecretion inhibits release of corticotrophin-releasing hormone (CRH). Decreased CRH causes decreased pituitary beta-endorphin (ß-end) and adreno-corticotrophin hormone (ACTH). This leads to decreased plasma beta-endorphin, ACTH and cortisol. Individuals with autism are further believed to have genetically determined hypersecretion of hypothalamic beta-endorphin, which in turn may contribute to inhibition of pituitary and plasma beta-endorphin (adapted from Chamberlain and Herman 1990).

autism have included some reference to self-injurious behaviour (SIB) and seemingly low pain sensitivity often observed in the syndrome.

In the original model, no assumption was made regarding the basic cause of the hypothetically heightened opioid activity in autism. However, theoretically a number of different possibilities present themselves, none of which are necessarily mutually exclusive. First of all, endogenous opioids may be increased for genetic reasons, whether because of primary overproduction, deficient degradation, abnormal messenger mechanisms within the nerve cells, or feedback dysregulation mechanisms. Such primary hyperfunction of the opioid system could produce the symptoms associated with autistic disorder as well as decreased sensitivity to pain. This latter problem, in turn, could lead to deficient self-regulation of stereotypic behaviours normally producing pain (such as SIB). Second, endogenous opioids may be hyperfunctioning as a result of developmental delay (not necessarily equivalent to over-production) in the maturational process leading to decline in opioid levels in the brain. Third, opioids may be pushed up by repetitive activities, including SIB. Such a mechanism would account for a feedback process in which stereotypical motor behaviours increased brain opioid levels, indirectly producing euphoria, autistic symptoms and relative pain insensitivity. In order to maintain the hyperfunctioning state, further excess repetitive activities would be required. In theory, increased brain opioid levels could also be achieved through physical exercise.

In a refined model, Panksepp (1979) suggested that autism may be due to a specific failure of striatal beta-endorphin to diminish with maturation. In accordance with this model, children with autism may not need social attachments because they may receive enough stimulation from their own developmentally relatively hyperfunctional opioid system. This is in line with the second causation model referred to above.

Recently, Chamberlain and Herman (1990) presented a more complex model, linking dysfunction in brain melatonin, POMC peptides and mono-amines (specifically serotonin) in autism (Fig. 1).

This model predicts POMC and serotonin dysfunction in autism. Pineal melatonin has an orchestrating role as the co-ordinator for the sequence of these dysfunctions. However, although the model is well-elaborated and interesting, it rests on the unproven assumption that both melatonin and serotonin are assumed to be elevated in the brains of individuals with autism. The empirical evidence for raised melatonin is lacking, and the evidence for raised serotonin is circumstantial.

Empirical findings

Table I summarizes the findings regarding opioid peptide dysfunction in autism.

There appears to be support for a decrease in beta-endorphin, both in the plasma and the CSF of children with autism. However, conclusions can only be preliminary since numbers have been small and the control subjects may not always have been truly representative, particularly in the CSF studies. Furthermore, discrepancies across studies could be accounted for by confounding factors that have not been adequately controlled for, including age, gender and associated problems such as mental retardation, epilepsy, motor control problems and known medical disorders. In general, there is limited support for some kind of endorphin dysfunction in autism. Further study is needed to provide a more definite framework for theory development in the field.

Most of the data further suggest that SIB, whether associated with autism or not, may be correlated with opioid dysfunction. Thus Herman (1990), for instance, found that plasma beta-endorphin levels in male children with SIB were about half those found in age-matched male controls. By contrast, Sandman (1988) found plasma beta-endorphin levels to be significantly raised in adults living in institutions because of mental retardation and SIB. Our own study of young people with autism (Gillberg *et al.* 1985) found a relationship between the presence and degree of SIB on the one hand and the level of endorphin fraction II on the other. It needs to be emphasized that the opioid fraction measured in the Swedish study comprised little, if any, beta-endorphin.

The metabolisms of the mono-amines and melatonin are relevant to the model for autism developed by Chamberlain and Herman (1990). Several groups of researchers have reported that children with autism have higher blood and platelet serotonin than controls (see Gillberg and Coleman 1992 for a recent review). The finding is not specific to autism, however, as children with mental retardation generally comprise a large subgroup with hyperserotoninaemia. Todd and Ciaranello (1985) reported preliminary evidence that hyperserotoninaemia in autism may be caused by circulating blood and CSF antibodies directed against human brain serotonin receptors. Perhaps autism involves an autoimmune abnormality in which antibodies to serotonin are produced in response to excess concentrations of serotonin or excess serotonin receptor density. In spite of extensive studies of platelet serotonin in children with autism, there is no evidence that high blood serotonin reflects high brain serotonin. The only study to date which has examined the relationship of blood/brain serotonin in a human child found a high blood serotonin level in conjunction with a low brain serotonin level (Coleman *et al.* 1977).

Other mono-amine abnormalities have also been found in autism, including hyperfunction of the dopamine system (as reflected in CSF homovanillic acid concentration; Gillberg *et al.* 1983), and relative norepinephrine hypofunction (as evidenced by high homovanillic acid:hydroxymethoxyphenylglycol ratios; Gillberg and Svennerholm 1987). The evidence here is weaker than in the field of serotonin dysfunction; nevertheless, the findings suggest that if dopamine:norepinephrine dysfunctions exist, they may be less dependent on concomitant mental retardation than is serotonin abnormality (Gillberg and Coleman 1992).

Melatonin dysfunction has not been studied systematically in autism. The recent report of a possible association between hypomelanosis of Ito and autism (Åkefeldt and Gillberg 1991, Zappella 1992) and, in particular, the concurrence

TABLE I
Studies of endogeneous opioids in autism and of opiate antagonists in autism and SIB

Study	*Finding*	*Reference*
Endogenous opioids in autism		
Plasma endorphin	Plasma humoral endorphin reduced in 10 patients with autism compared with 12 chronic patients with schizophrenia and 11 normal controls; age- and sex-match included	R. Weizman *et al.* (1984)
Plasma endorphin	No significant finding, but trend towards lower beta-endorphins in autism	Herman *et al.* (1986)
Plasma endorphin	Beta-endorphin reduced in eight unmedicated patients with autism compared with age- and sex-matched individuals with unmedicated schizophrenia and normal controls	R. Weizman *et al.* (1988)
Plasma endorphin	Beta-endorphin reduced; trend towards even lower values in institutionalized adults with mental retardation	Sandman *et al.* (1991)
CSF endogenous opioids	High fraction II (small contribution from POMC) compared with unaffected children who were somewhat younger; suggestions of link between high fraction II levels and SIB and insensitivity to pain	Gillberg *et al.* (1985)
CSF endorphins	High beta-endorphin in nine individuals with autism compared with age- and sex-matched normal controls; trend towards lowering of high levels with fenfluramine	Ross *et al.* (1987)
CSF endorphins	Low beta-endorphin in 31 young children with autism and eight girls with Rett syndrome compared with five infants with infantile spasms and healthy young adult men (N = 6) and women (N = 45); no age trend of beta-endorphin in affected groups	Gillberg *et al.* (1990)
Opiate antagonists in autism and SIB		
Naloxone in SIB	Reduction of SIB: case study	Davidson *et al.* (1983)
Naloxone in SIB	Reduction of SIB: case studies	Sandman *et al.* (1983)
Naloxone in SIB	Initial increase of SIB during infusion; reduction for several days thereafter: case study	Richardson and Zaleski (1983)
Naltrexone in SIB	Reduction of SIB: four cases, double-blind placebo-controlled trial	Sandman (1988)
Naloxone and naltrexone in SIB	Increase of SIB on subcutaneous naloxone, decrease on oral naltrexone: one girl with SIB and autism; double-blind placebo-controlled trial	Barrett *et al.* (1989)
Naltrexone in autism	Reduction of abnormal motor behaviours, no social effects: five cases, open trial	Herman *et al.* (1986)
Naltrexone in autism	Reduction of 'autism factor', increased verbal production and reduction of general behaviour problems: 10 children, open trial	Campbell *et al.* (1989)
Naltrexone in autism	Reduction of withdrawal and (most pronounced) hyperactivity, best result with low (0·5mg/kg/dose) and high (2·0mg/kg/dose) dosages: four children, double-blind placebo-controlled trial	Leboyer *et al.* (1992)
Naltrexone in autism	Best study to date: decreased hyperactivity and tendency towards reduced SIB: 41 children aged three to eight years, double-blind placebo-controlled trial	Campbell *et al.* (1994)

SIB = self-injurious behaviour.

of these disorders in identical twins (Zappella 1993), indicate that this may prove to be a fruitful area of research. Zappella (1993) found extinction of the normal diurnal blood melatonin rhythm in one of a pair of male monozygotic twins with 'autism' and hypomelanosis of Ito. The twin with melatonin dysfunction had more severe autism, more pronounced mental disability, more sleep problems and SIB, and was of considerably shorter stature than the co-twin with normal circadian melatonin cycling. Zapella's observation raises the question of whether melatonin may actually be depressed in autism, rather than elevated as predicted by the Chamberlain and Herman model.

Relevant studies

A number of studies have examined the effects of opiate antagonists in autism, on the assumption that opioid hyperfunction may be an important mediator of autistic symptomatology and that blocking the effect of endogenous opioids would therefore have positive effects on autism symptoms. The results of these studies are reviewed in Table I. Most of the studies have reported on the effects of naltrexone in autism, which have been modest at best, and have pertained mainly to hyperactivity (which has been reduced). No untoward effects have been observed, apart from drowsiness and decreased appetite in a few cases. The combined results of several studies suggest that moderate and severe SIB might be reliably reduced by naltrexone, but the evidence is too patchy to enable us to make conclusive clinical recommendations.

A double-blind placebo-controlled study of the neuropeptide ORG 2766 (a synthetic analogue of ACTH) was performed by Buitelaar *et al.* (1992). ORG 2766 treatment (20mg per day for four weeks) of 14 children with autism was associated with increased and improved social interaction, and motor stereotypies were temporally disconnected from verbal initiatives.

Increased physical exercise has been shown to be effective in reducing disruptive behaviours in individuals with autism and mental retardation (McGimsey and Favell 1988, Elliott *et al.* 1994). Although it has not been empirically demonstrated, it is possible that this reduction could be associated with raised endogenous brain opioid levels following physical exercise.

Conclusion

As yet, empirical study of the opioid hypothesis for autism has produced little of clinical relevance. Some of the most promising works relate to physical exercise as a means of reducing the symptoms associated with autism, and perhaps altering/raising endogenous opioid levels. Naltrexone, although probably relatively free of serious negative side-effects, has not yet been shown to have a positive influence on symptoms. However, SIB has been reduced in several studies, although not always in a statistically significant way. At present, naltrexone should not be a first-line treatment either for individuals with autism generally or for those with SIB with or without autism. Further research appears to be warranted, particularly with regard to the effects of naltrexone on patients with moderate or severe SIB.

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SUMMARY
Endogenous opioid dysfunction hypotheses for the development of autism are reviewed, along with clinical empirical studies of opiate antagonists in autism and self-injurious behaviour. There is not yet sufficient evidence to suggest the use of opiate antagonists in the treatment of autism. Further research, particularly of natrexone in severe self-injury, is warranted.

RÉSUMÉ
Endorphines et antagonistes des opiacés dans l'autisme: une brève revue des données empiriques et des implications pour les enfants
Une brève revue est faite, des hypothèses sur un dysfonctionnement des endorphines dans le développement de l'autisme, ainsi que des études cliniques sur l'action des antagonistes d'opiacés dans l'autisme et les comportement d'auto-agression. Il n'y a pas encore d'évidences suffisantes pour

conseiller l'utilisation des antagonistes d'opiacés dans le traitement de l'autisme. Des recherches ultérieures, notamment sur l'action de la naltrexone dans l'auto-agression grave, sont indispensables.

ZUSAMMENFASSUNG

Endogene Opioide und Opiat-Antagonisten bei Autismus: ein kurzer Überblick über die empirischen Befunde und die Schlußfolgerungen für Kinder

Es werden die Hypothesen einer endogenen Opioiddysfunktion als Ursache für die Entwicklung eines Autismus im Zusammenhang mit klinisch-empirischen Studien über die Wirkung von Opiat-Antagonisten bei Autismus und selbstverstümmelndem Verhalten überprüft. Es gibt noch keine ausreichenden Befunde, um Opiat-Antagonisten für die Therapie des Autismus empfehlen zu können. Weitere Untersuchungen sind erforderlich, insbesondere mit Naltrexon bei schwerem selbstverstümmelndem Verhalten.

RESUMEN

Opioides endógenos y antagonistas del opio en el autismo: breve revisión de los hallazgos empíricos y sus implicaciones en niños

Se revisa la hipótesis de la disfunción en los opioides endógenos en el desarrollo de autismo, así como los estudios clínicos empíricos sobre antagonistas del opio en el autismo y en el comportamiento autoagresivo. Todavia no hay suficiente evidencia para sugerir el uso de los antagonistas del opio en el tratamiento del autismo. Está justificado el proseguir con los estudios, especialmente de la naltrexona en los casos de grave autoagresión.

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