Biochemical aspects in autism spectrum disorders: updating the opioid-excess theory and presenting new opportunities for biomedical intervention

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Autism is a lifelong condition usually described as affecting social, cognitive and imaginative abilities. For many years, parents and some professionals have observed that in concordance with the behavioural and psychological symptoms of the condition, there are a number of physiological and biochemical correlates which may also be of relevance to the syndrome. One area of interest that encompasses many of these observations is the opioid-excess theory of autism. The main premise of this theory is that autism is the result of a metabolic disorder. Peptides with opioid activity derived from dietary sources, in particular foods that contain gluten and casein, pass through an abnormally permeable intestinal membrane and enter the CNS to exert an effect on neurotransmission, as well as producing other physiologically-based symptoms. Numerous parents and professionals worldwide, have found that removal of these exogenously derived compounds through exclusion diets can produce some amelioration in autistic and related behaviours. There is a surprisingly long history of research accompanying these ideas. The aim of this paper is to review the accompanying evidence in support of this theory and present new directions of intervention as a result of it.

Keywords: autism, indolyl-3-acryloylglycine, inflammatory bowel disease, intervention, opioid-excess theory, peptides

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1. Introduction

Ben is three years old and until two weeks ago had never uttered a single word. Ben has autism. Following discussions with other parents, his mother decided to experiment by removing all gluten from Ben’s diet. Three days later, Ben started shouting; ‘I want bread. Give me bread.’ Was this pure coincidence? It could be, but similar coincidences have been reported tens of thousands of times worldwide.

Autism is classified as a pervasive developmental disorder. Typically apparent by 3 years, it is characterised by [1]:

- qualitative impairments in communication and reciprocal social interaction
- restricted and repetitive patterns of behaviour

Incidence rates of autism in the UK have varied due to the lack of a national registry. Estimates have been previously amended from an original calculation of 7 - 12 out of 10,000 to an approximate rate of 91 out of 10,000 people presenting the broader categorisation of an autistic spectrum disorder (ASD) [2], yet maintaining...
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the original ratio of 4:1 males/females [3]. Some of the most recent reports have suggested the incidence to be nearer to 62 per 10,000 fulfilling the criteria for ASD [6]. Co-morbidity of various epileptic conditions appears to be a feature in ~ one-third of case of autism [2], more commonly present if severe learning difficulties accompanies the diagnosis of autism. Rossi et al. [4] reported a rate of ~ 40% of young adults with autism presenting with various epileptic states. Most commonly cited was partial epilepsy, which was apparent in > 60% of cases of comorbidity in this study. Recent reports have suggested an increase in the number of cases of autism being diagnosed worldwide [5-8]. The reasons for this increase are not yet fully understood, although issues such as increased awareness of the condition, the application of wider diagnostic criteria and better screening and assessment for the condition are some explanations. Another explanation is that the increase is reflective of a true rise in the numbers of people presenting the condition. Recently it was reported that within the UK, 20% of local educational authorities (LEAs) questioned, thought that this increase may be due to a real increase in numbers [9]. A recent report published by the Medical Research Council (MRC) in the UK [101] commented that there was no way of ascertaining whether the increase in numbers of people with autism spectrum disorders is reflective of a real increase or purely down to factors of better awareness and diagnosis.

Studies examining the role of genetic influences on the aetiology of the syndrome have, for many years, dominated the research environment with regard to autism. Partly due to the lack of biochemical or physiological markers in the diagnosis of autism and an increasingly gene-directed philosophy to disease, significant resources have been allocated to establish a genetic cause in the aetiology of autism and related disorders. Certainly there is evidence of autism present in genetic disorders, such as Down's syndrome [10]. There is also evidence of higher concordance rates of autistic broader spectrum difficulties with siblings of people with autism [11] but as yet there is little agreement as to the exact location of possible genes involved. Among the many genetic candidates put forward in connection to autism and behaviours which characterise the syndrome, are findings of a shortened form of the serotonin transporter gene (HTT) [12] and longer triplet repeats in regions of the Reeler (RELN) gene. This gene is responsible for the production of reelin, a protein believed to be involved in neuronal migration through the CNS / peripheral (P)NS. [13]. Although of great interest, there has been no consolidation of these and other findings into a coherent theory and very little indication of any kind of derivative intervention that may be of use.

Several researchers have begun to view the role of genetics as being part of a wider scheme with more emphasis placed on the notion of susceptibility in at least some cases of the condition [14]. In view of the incompatibility of increasing rates in the incidence of autism spectrum disorders and the genetic model (a relatively static gene pool), the issue of susceptibility is becoming more widely accepted as a possible explanation.

Traditionally, interventions in autism have been based on the use of behavioural and educational strategies in an attempt to ameliorate the symptoms of the syndrome. In recent years research has pointed towards various organic elements to the syndrome possibly related to the onset and prolongation of the symptoms, suggesting that other avenues of intervention may also be beneficial.

One such area of inquiry into a possible organic basis to the syndrome is the opioid-excess hypothesis. The theory suggests that autism (or a substantial subgroup of cases of autism) may be the result of excessive absorption of incompletely broken down compounds with opioid activity, causing disruption to a variety of biochemical and neuroregulatory processes. The research relating to this hypothesis has a surprisingly long history. Initially two strands of research, which are considered supportive to the opioid-excess theory, will be discussed:

- Firstly, research relating to the biochemistry of autism
- Secondly, research examining the effectiveness of exclusion diets (withdrawal of the foods considered to be the exogenous source of these compounds)

along with other biomedical interventions related to the theory.

2. Opioid-excess theory of autism

The main premise of the opioid-excess theory suggests that excessive levels of incompletely metabolised peptides from foods that contain proteins, gluten and casein, pass through the intestinal and blood–brain barriers (BBBs) into the brain. There they either directly regulate transmission in all the main neurotransmission systems or alternatively form ligands for peptidase enzymes that would normally hydrolyse naturally occurring opioid peptides.

Panskepp [15] first reported similarities between autism symptoms and long-term effects of morphine, for example:

- reduced desire for social contact,
- insistence on sameness,
- decreased pain sensitivity
- delay in developmental milestones

It was hypothesised that children with autism may have elevated levels of the endogenous opioid ‘β-endorphin’. This hypothesis has been corroborated by several findings including elevated levels of endorphin fractions in the cerebral spine fluid (CSF) of a group of children with autism [16] and elevated beta-endorphin levels in peripheral blood mononuclear cells (PBMCs) [17]. Nelson et al. [18] reported elevated levels of endogenous peptides, such as vasoactive intestinal peptide (VIP), calcitonin gene-related peptide (CGRP) and brain derived neurotrophic factor (BDNF) in new-borns who later went on to develop autism (elevated immunoactivity levels of BDNF in the basal forebrain of a group of people with
autism has also been reported [19]). Evidence has also emerged for a possible familial connection. Leboyer et al. [20] reported elevated levels of $\beta$-endorphin protein immunoreactivity in over half of mothers of people with autism. Pharmacological studies examining the use of opioid antagonist drugs, such as Naltrexone™ (Revia), in an attempt to alleviate the symptoms of autism have reported success in a subgroup of patients [21-23]. The main types of improvements were reported in social withdrawal and self-injurious behaviour.

Since the original descriptions of the opioid-excess hypothesis, there have been several adaptations made to the theory see Figures 1A to 1D [24-28]. Reports have suggested that there may be a genetically determined reduction in levels of key peptidase enzymes in autism [31]. Persico et al. [32] reported initial evidence of an association between the genetic involvement of adenosine deaminase alleles and autism and in particular, the relation to the functioning of peptidase enzymes. The use of the gastrointestinal hormone secretin in autism may also be of particular relevance here. Initial results reporting an amelioration of autistic and concurrent gastrointestinal symptoms in a small number of children have been reported [33]. Subsequent double-blind crossover trials have not found significant sustained positive effects following the administration of secretin [34], there have been some indications of short-term benefits [35]. The main gastrointestinal effects of secretin are:

- an alteration of acidity in regions of the gut (through stimulation of the pancreas to release bicarbonate and water)
- a corresponding increase in the production of peptidase enzymes [36]

It has also been reported in unpublished data that a subgroup of children with autism present reduced activity of a specific peptidase enzyme (dipeptidylpeptidase-IV) (A Friedman, pers. commun.) This work has not, as yet, been formally rep-

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**Figure 1A. Normal passage of peptides into the CNS.** A mechanism for the process that would occur in a clinically normal subject is shown. Each star represents a single peptide molecule with opioid activity. A proportion of these peptides will normally cross from the intestine into the bloodstream, even in a healthy subject with no major problems with intestinal wall permeability [29]. Furthermore, a proportion of these peptides in the bloodstream will cross through the BBB [30] and have neuroregulatory functions (either peripherally or directly).

**Figure 1B. Excessive peptide production in the gut.** Increased levels of peptides in the intestine is illustrated, possibly due to problems with peptidase enzymes (due to abnormal intestinal conditions, such as gut pH or deficiencies within enzyme systems).

**Figure 1C. Excessive permeability of the intestinal membrane.** A situation whereby levels of peptides in the gut are normal is shown but there is a problem with intestinal membrane permeability.

**Figure 1D. Excessive permeability of the intestinal membrane and BBB.** A situation where combined with an increase in intestinal permeability, the BBB is excessively permeable is illustrated. This allows greater levels of biologically active peptides to enter the brain.

BBB: Blood–brain barrier; CNS: Central nervous system.
licated and published. Certainly in an environment with low levels of endogenous secretin, one would expect deficiencies in peptidase enzymes.

Therefore, increased levels of peptides are circulating in the bloodstream and by mass action there will be elevated levels crossing the BBB to reach the CNS.

Increased intestinal permeability has been found in a proportion of people with autism [37]. The related findings of impaired sulfur metabolism of people with autism [27,38,39] may also be of relevance to the gastrointestinal mucosa. Low levels of available sulfate would cause abnormal sulphation of mucoproteins contributing to abnormal porosity of the intestinal membrane. The significance of gastrointestinal disturbances associated with autism has also begun to receive attention in research literature [40]. The findings of lymphoid nodular hyperplasia, following colonoscopic investigation [41,42] and accompanying epithelial damage [44] suggests direct physical damage, through infection to areas of the intestinal membrane (illeal lymphoid nodular hyperplasia has also been detected in a small group of people diagnosed with attention-deficit hyperactivity disorder (ADHD)) [43]). More controversially, it is suggested that persistent measles infections that result from the combined measles-mumps-rubella (MMR) vaccine may trigger autism by causing intestinal permeability in a subgroup of children who develop symptoms of autism within a short period of receiving the vaccine. The identification of nodular hyperplasia containing antibodies to measles in this subgroup of children [42] would appear to support the parental allegations. The detection of measles virus in PBMCs [45] and elevated measles titre levels in serum of a sub-group of people with autism [46] has also been reported. In a blind study [47] the presence of measles RNA in the intestines of a subgroup of children with autism has been reported. All of these findings illustrate a greater transport of compounds through the intestine, although further studies are needed to investigate the mechanism between autistic symptoms and gastrointestinal inflammation, and indeed the immune system of people with autism in general.

Whitcomb et al. [48] concluded that peptides could traverse permeable regions in the barrier and bind to specific receptors in the brain. The ability to increase permeability across the BBB has been examined from many different perspectives (e.g., bacterial meningitis [49]; glycosylation enhancing peptide transport [50]).

With regard to autism, complications arising from acquired viral infections, such as encephalitis or meningitis have been documented. Gillberg [51] presented the account of a previously healthy man who contracted herpes encephalitis and developed symptoms similar to those displayed in autism as a result. Barak et al. [52] postulated a connection between co-morbid autism, epilepsy and seasonal viral meningitis. The role of virus-induced inflammation on biological processes, such as the BBB needs further study with regard to autism, given that one expects such viral episodes to affect other areas of the CNS as well.

3. Identification and characterisation of compounds in biological fluids

Several research teams have published data on the presence and identification of elevated levels of certain compounds found in various biological fluids of people with autism when compared to controls [24,53,54]. Page et al. [55] reported increased de novo purine synthesis as a function of elevated uric acid excretion in urine. Initial results using high-performance liquid chromatography (HPLC) have identified elevated levels of certain excitatory amino acids (glutamic and aspartic acid) in the plasma of children with autism [56]. Increased peptide excretion in urine samples analysed from people with autism has also been reported [53,57,58].

Reichelt et al. [59] produced preliminary data on the identification of specific peptides in the urine of people with autism. Using radio-immunoassay techniques with antibodies against bovine casomorphin fragments combined with chromatography against standards, they reported an initial correspondence to bovine casomorphin 1 - 8 following fraction collection of urine from people with autism. Unpublished data has reported the presence of casomorphin and other peptides found in the urine of people with autism using mass spectrometry (MS) (A Friedman, pers. commun.). This work has not, as yet, been formally replicated and published. Pederson et al. [58] using MS, isolated and reported elevated levels of a tri-peptide that stimulates the uptake of serotonin into platelets, in the urine of people with autism. Unpublished data has reported the presence of new opioid peptides, such as dermorphin (Tyr-d-Ala-Phe-Gly-Tyr-Pro-Ser-NH2) in the urine of people with autism (A Friedman, pers. commun.). This work has not, as yet, been formally replicated.

Several teams have reported the presence of indolyl-3-acryloylglycine (IAG) in the urine of people with autism [60,61]. Although still under investigation, IAG is thought to be an abnormal metabolite of the amino acid tryptophan [62], where the acid precursor, indolyl-3-acrylic acid (IAA) is conjugated with the amino acid glycine. Castejon et al. [63] reported elevated levels of the amino acid glycine in the plasma of people with autism and ADHD. The significance of IAG and precursors to autism has not been fully elucidated, although preliminary research suggests that because of its planar geometry, the acid precursor, IAA, may disrupt membrane structures [64]. This would have implications for the permeability of membranes.

The exact route of formation for the acid precursor is yet to be elucidated, although the role of anaerobic catabolism in the gut has been suggested [65]. Disruption of the gut flora in autism has also been discussed in the literature. Lis et al. [66] reported elevated levels of 4-hydroxyhippuric acid in the urine of people with autism, suggesting the involvement of intestinal bacteria as being related to the finding. Sandler et al. [67] reported small scale success following the administration of oral vancomycin, suggesting the role of overcolonisation of neurotoxin producing species in relation to symptomatology.
More recently Anderson et al. [68] have described the inhibitory role of organo-phosphate compounds on key enzymes (kynureninase and tryptophan hydroxylase) as being a possible route to the formation of IAG. The role of environmental factors, such as organophosphate compounds in psychiatric syndromes has been previously discussed in the literature [69]. Of particular interest is the inhibition of the kynurenine pathway in order to block the formation of the neuroconvulsant, quinolinate and promote the formation of the neuroprotective agent, kynurenate. This may be relevant, when considering the connection between autism and epilepsy.

4. Biomedical interventions in autism - ‘the Sunderland protocol’

A preliminary description of the use of certain unorthodox biomedical interventions in ASDs in a logical sequence has been previously reported [28]. The objective of these interventions is two-fold:

- First, to remove the source of the biologically active compounds (peptides).
- Second, to increase the integrity of the membranes of the intestinal and BBB.

If complete membrane integrity is achieved, it should be theoretically possible to resume a normal diet. Other interventions (enzyme supplementation, betaine hydrochloride etc.) are designed to encourage a more complete digestion of peptide materials.

5. Gluten- and casein-free dietary intervention

Dietary intervention used in the amelioration of disease is well documented. Restrictions, such as a low phenylalanine diet together with tyrosine supplements are shown to eliminate the condition phenylketonuria (PKU) [70,71]. Similarly, treatment of coeliac disease using a gluten-free diet has been shown to provide general health improvements [72] as well as cognitive functioning improvements [73]. Previous research has shown that a proportion of people with psychotic disorders improved on ratings of a psychotic profile during a gluten-free diet period and later relapsed at the re-introduction of gluten back into the diet [74]. Dohan et al. [75] demonstrated a connection between the use of cereal- and milk-free diets and improvements in behaviours connected to schizophrenia. It is important to realise that within the opioid-excess theory, the focus regarding the action of the gluten-free diet is not the same as that of in coeliac disease. Coeliac disease is a life-long gluten-sensitive disorder, characterised by malabsorption and typical small bowel mucosal atrophy. Classic signs of the disease include:

- diarrhoea
- weight loss and weakness
- milder symptoms include indigestion in adults and recurrent abdominal pain in children

Other neurological symptoms include: intellectual deterioration and brain atrophy, ataxia and epilepsy. Diagnosis of coeliac disease is made through serum gliadin antibody tests (IgG and IgA antigliadin antibodies), IgA anti-endomysium antibody test, and intestinal biopsy. Treatment is the implementation of a gluten-free diet.

ASDs are frequently characterised by abnormal behaviour towards food [76,77]. Specific food cravings have been reported with children with autism, linked to non-specific modulations in behaviour [78]. Mercer et al. [79] described the connection between altered endogenous opioid peptides and food intake changes (for example, intensified food cravings and increased food intake). In view of the principles of the opioid-excess theory, it could be assumed that peptides derived from the exogenous source of gluten and casein in the diet, might also have similar effects.

Knivsberg [80] has published a review of the history of research examining the effectiveness of gluten- and casein-free diets to ameliorate the symptoms of autism. Although to date there have been no double-blind crossover trials of the use of this type of intervention in autism, there have been several open trials of various combinations of the diets [26,81-83]. All studies that have excluded gluten and/or casein from the diet have demonstrated significant improvements in the behaviour of subgroups of people with autism and related spectrum disorders. The types of behavioural changes reported include improvements in language, emotional responses and cognitive functioning (with subsequent regression in skills when the diet/s are challenged). Knivsberg et al. [81,82] also reported a decrease in epileptic seizures following gluten and casein removal. Although no formal explanation has been provided for these phenomena, previous studies have found an association between gluten withdrawal and reduced epileptic seizures in coeliac disease [84].

The opioid-excess theory implies that the positive effect of gluten and casein removal from the diet on behaviour is due to the absence of exogenously derived peptides from these foods in the body. Reichelt et al. [59] reported a decrease in peptiduria in samples from people with autism after 2 years on gluten- and casein-free dietary intervention. Whiteley et al. [26] also reported a decrease in peptide-like material and levels of IAG (as a ratio of creatinine) after 5 months on a gluten-free diet. The exact relevance of the latter finding is yet to be fully elucidated.

6. Other offending foods

Other foods have also been suggested to exacerbate the behavioural problems in autism. O’Banion et al. [85] reported a case study of an 8-year-old boy with autism whose behavioural problems were diet related (problem foods included corn, tomatoes, sugar and mushrooms, as well as wheat and dairy produce). Waring et al. [27] commented on the connection...
between inhibition of the phenol-sulphotransferase (P-ST) enzyme by dietary factors, as a reason for low sulphotransferase levels previously found in subgroups of people with autism. Subsequent removal of offending foods connected to P-ST inhibition, which included chocolate, bananas, orange juice and food colourings, were reported to be associated with a reduction in hyperactive behaviour [86].

7. Yeast infection

Studies have reported the presence of metabolites of fungal origin in the urine of people with autism [87]. However, whether the existence of such organisms implies direct involvement in the causation of autistic symptoms or merely reflects opportunistic fungal overgrowth as a result of impaired immune functioning for example, remains to be seen. There have been anecdotal reports of success following the use of antifungal preparations, such as Nystatin™ (Paddock Laboratories, Inc.) to ameliorate some of the physiological and behavioural symptoms of autism, although there is a lack of experimental data to validate these observations.

8. Parasitic infection

The problem of pica (mouthing, eating and chewing of inedible substances) is a feature of several psychiatric conditions, including autism. Ruling out iron or zinc deficiency as a cause of pica in autism has been suggested [88], although the exact underlying reason for the behaviour has yet to be fully elucidated. The presence of higher than average intestinal parasitic infection, partly as a result of pica, in residents of psychiatric institutions has been recorded [89]. Duvaux-Miret et al. [90,91] reported the presence of β-endorphin in a specific species of parasite and discussed the role of this endogenous opioid peptide in the modulation of the host immune system for parasite survival. In view of the suggestion of increased levels of opioid peptides derived from diet in autism and the immunoregulatory role of these compounds on the person, the additional stress of parasitic organisms also producing opioid peptides seems to complicate the situation further.

9. Sulphation

Problems relating to sulphation ability in autism have been previously mentioned [27]. There are many significant consequences of this primary deficit. These include a reduction in the ability to de-activate classical neurotransmitters as well as environmental toxins and a reduction in the activity of certain hormones (cholecystokinin and gastrin for example). Most significantly, perhaps, there will be abnormalities in the structure of the intestinal wall and the protective mucus coat. There will be a consequent reduction in intestinal integrity and enhanced passage of peptides. Anecdotal evidence reports that attempting to replace sulfate by taking precursor amino acids (such as cysteine) has not been effective possibly due to the inefficiency of sulfate ions when absorbed from the intestine. Transdermal absorption of magnesium sulfate (epsom salts) in bath water may be an alternative way of increasing sulfate in the body. Although no formal trials into the efficacy of epsom salts with people with autism have been performed, anecdotal reports suggest improvements in behaviour and physiology, in a subgroup of people.

10. Stimulation and/or supplementation of enzymes

Gastrointestinal conditions, in particular the acidity of certain vessels of the gut and the subsequent connection to activation of certain enzymes has received preliminary examination in autism (e.g., low intestinal carbohydrate-digesting brush-border enzymes [40]). Although support for secretin in the treatment of all cases of autism has diminished, the mode of action involved with the natural release of the hormone is possibly relevant to autism. The release of secretin, primarily because of acid wash in the duodenum (as well as bile and other nutrients entering the duodenum), is well documented [92]. Although there has been no specific explanation as to why secretin is effective in some cases of autism, one possibility is that a lack of intrinsic secretin could be due to insufficient acid production (achlorhydria) in the gut. Following on from the opioid-excess theory, it has been found that opioid substances can inhibit gastric secretions [93] in particular compounds, such as β-endorphin [94] and the mu agonist dermorphin [95]. Furthermore, increased gastric acidity has been found to be bactericidal [96], hence low gastric acidity would be better conditions for the colonisation of certain bacteria.

Anecdotal evidence following the use of preparations, such as betaine hydrochloride (trimethylglycine) to increase gastric acidity has reported some benefits in behavioural aspects of autism in a small number of cases. This work has not been formally replicated.

The additional possibility that certain artificial enzymes (particularly peptidase enzymes) may be useful for people with autism is also under investigation, with a number of artificial enzymes already on the market.

11. Conclusion and expert opinion

The evidence for the plausibility of the opioid-excess theory of autism is growing. A range of interventions that are being used, exist without the endorsement of the medical establishment, for the treatment of autism. These interventions, although largely unproven in terms of efficacy, present a minimal risk of harm and are based upon scientific research and logic. Many of these interventions have been employed, discreetly, for many years. Given the numerous elements to this theory several areas exist which, given further research, could present further opportunities
to medicine for the amelioration of the symptoms of ASDs.

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**Website**


The Medical Research Council report on autism.

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