Can the Pathophysiology of Autism be Explained by the Nature of the Discovered Urine Peptides?

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INTRODUCTION

Several laboratories have found increase in urinary peptides in autism (Fig. 1–3 and Table I), and that some of these are opioids and also exorphins (Israngkun et al., 1986; Reichelt et al., 1986; 1991; Shattock et al., 1990; Cade et al., 2000; Shanahan et al., 2000). The definite structure of these have been obtained by mass spectrometry and fragmentation mass spectrometry (Shanahan et al., 2000; Remme et al., 2001). The presence of the rare α-amino acid containing dermorphin has also been confirmed (Shanahan et al., 2000). Furthermore increase of opioids has been found in serum and CSF (Gillberg et al., 1985; LeBoyer et al., 1994), and some of these are bovine casomorphins (Reichelt et al., 1991; Reichelt and Reichelt, 1997; Cade et al., 2000; Shanahan et al., 2000). The time, therefore, seems ripe to see if we can explain the symptoms of the autistic syndromes as listed in Table II by referring to the properties of the isolated peptides. Below each symptom is probed for possible relationship to specific peptides found.

Social Indifference

The cardinal symptom of autistic syndromes is social indifference or aloofness. Panksepp demonstrated that opioids inhibit social bonding (Panksepp et al., 1978) and found that opioids also casomorphins, caused social indifference and abrogation of separation distress calls in new-born animals. A chronic effect of casomorphins found in urine from autistic patients, as well as gliadinomorphin (Shanahan et al., 2000) and glutemorphins, deltorphin and dermorphin could, therefore, explain this social indifference.

 Intracranio-ventricularly injected opioids isolated from urine (Hole et al., 1979) and casomorphine 1–7 injected IV in rats, induce acute, typical and similar effects (Sun and Cade, 1999) ranging from explosive motor behaviour, analgesia, wet dog shakes to later catatonia. Such acute changes are also seen when opioid drugs are used and could possibly explain periods of hyperactive agitation, aggressive and emotionally bizarre acting out behaviours as well as more catatonic phases. Furthermore, exorphins do
pass the blood–brain barrier (Ermisch et al., 1983; Nyberg et al., 1989) and are extremely psychosogenic as seen in postpartum psychosis (Lindstrøm et al., 1984). Exposing the blood–brain barrier to opioids during early growth in rats permanently alters the permeability to opioids in these membranes (Banks et al., 1996). The exorphins show a bell shaped dose response curve called hormesis (Reichelt and Reichelt, 1997). This may well explain the varied response to naloxone or naltrexone, ranging from good, to no effect and even worsening (Campbell et al., 1996) depending on the level of opioids in any given patient.

**Poor Habituation**

If palmar skin conductance is measured in autistic children, the conductance at rest fluctuates considerably more than in controls and most show exaggerated response to auditory stimulation with very poor habituation (Bernal and Miller, 1971). This indicates an increased sensory and autonomic
arousal of the CNS and, or insufficient reactive inhibition (lack of habituation) (Mednick et al., 1974). Lack of habituation would cause avoidance of new inputs and hence a strong preference for status quo and rituals. A chemical candidate for this reactive inhibition and habituation is serotonin. We found a peptide from autistic urines (pyroGlu-Trp-GlyNH₂) that increased the uptake of serotonin into platelets (Pedersen et al., 1999) and into synapses in the CNS (Persico et al., 1998). Increased platelet serotonin is a frequently reported finding in autism (Rogeness et al., 1992). PyroGlu-Trp-GlyNH₂ also increases the uptake into CHO cells transfected with the gene for the human serotonin transporter (Keller, 1997). Platelets are a much used pharmacological model for the serotonergic synapses. Increased uptake should decrease the level of serotonin in the synaptic cleft. It is well known that hypo-serotonergic states such as seen in carcinoid, causes excessive sensory responses and also poor habituation, sleep problems and impulse dominated behaviour. It is reasonable that lack of adaptation and stronger than usual reaction to sensory and emotional stimuli, will cause withdrawal from these and insistence on sameness (Mednick et al., 1974).

Stereotyped and Repetitive Behaviour

These are also dependent on lack of reactive inhibition (habituation), seen under point 2. However, increase in exorphins, which inhibit the uptake of dopamine into synaptosomes (Hole et al., 1979), would when dependent on meals, cause a fluctuating dopaminergic hyper-function in vivo. Dopaminergic hyper-function caused by amphetamine stimulation in animals, shows stereotypy as a typical feature. This dopaminergic hyperactivity would therefore be reinforced by simultaneous decrease in

TABLE I The total peptide levels eluting after hippuric acid in pre-puberty autistic children

<table>
<thead>
<tr>
<th></th>
<th>Autism</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age range</td>
<td>2–14</td>
<td>3–14</td>
</tr>
<tr>
<td>N</td>
<td>315</td>
<td>143</td>
</tr>
<tr>
<td>Peptide level (mean)</td>
<td>720</td>
<td>346</td>
</tr>
<tr>
<td>SD</td>
<td>471</td>
<td>108</td>
</tr>
<tr>
<td>95% CI Lower value</td>
<td>560</td>
<td>329</td>
</tr>
<tr>
<td>Higher</td>
<td>773</td>
<td>365</td>
</tr>
</tbody>
</table>

The units are Absorption in mm² under the UV 215 nm trace of the peaks eluting after hippuric acid and based on urine = 250 nmol creatinin. Only patients who have been diagnosed by certified psychiatrists are included. Ratio of UV 215/UV 280 was used to check of purity of individual peaks. Many drugs have high UV 280 nm peaks due to aromatic ring structures. The autistic children are different from controls with a p = 0.0001. Samples from 8 different countries and 16 MD’s did not differ statistically indicating that diagnosis has become quite standardized probably through the use of DSM III–IV.

<table>
<thead>
<tr>
<th></th>
<th>Autism</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Social indifference</td>
<td>10. Genetic basis</td>
<td></td>
</tr>
<tr>
<td>2. Poor habituation</td>
<td>11. Immune changes</td>
<td></td>
</tr>
<tr>
<td>3. Stereotypy and repetitive behaviour</td>
<td>12. Sleep disturbances</td>
<td></td>
</tr>
<tr>
<td>4. Insisting on sameness</td>
<td>13. Increased incidence in immigrants</td>
<td></td>
</tr>
<tr>
<td>5. Increase in epilepsy with age</td>
<td>14. Effect of diet</td>
<td></td>
</tr>
<tr>
<td>6. Varying trophic changes</td>
<td>7. Language problems</td>
<td></td>
</tr>
</tbody>
</table>

FIG. 3 Another boy with the same diagnosis and Childhood autism rating scale (CARS) score as the boy in Fig. 2. Notice the different but overlapping pattern in spite of having the same diagnosis, sex and age. This indicates that different enzyme defects are probably present in different families, but with overlaps.
serotonergic activity, because it is the ratio of functional dopamine to serotonin that seems important (Rogeness et al., 1992) in different brain areas. The decreased habituation is demonstrable by the changes in auditory brainstem evoked responses (Rosenblum et al., 1980) and decrease in post-rotational nystagmus in infantile autism (Ritvo et al., 1969). This may explain why many autistic children are endlessly fascinated by rotating movement and show great ability to rotate most objects and if possible also themselves.

**Increased Rate of Epilepsy with Age**

In ordinary children the frequency of fits and epileptic attacks decreases with age. In autistic children, an increase in epilepsy and EEG abnormalities is seen with increasing age, and at the age of 20 about 1/4–1/3 of the patients show EEG changes and/or epilepsy (Deykin and MacMahon, 1979). The frequency of epilepsy is increased celiac disease (Chapman et al., 1978; Gobbi et al., 1992), and increased urine peptide secretion including opioids has been found in celiac disease (Reichelt et al., 1998). In a group of children with autistic disorders and increased urinary peptide secretion, we unexpectedly saw a decrease in epileptic fits followed by a reduction of medication when the children were on diet (Reichelt et al., 1990), and a disastrous relapse (status epilepticus) when the diet was broken. This may be explained by the fact that exorphins and other opioids do have convulsant properties (Siggins et al., 1986) and also modify kindling.

It is furthermore, reported that acute exposure of celiac children below 7 years of age to gluten after a gluten free diet for 1 year, induced long standing EEG abnormalities in 72% of the children (Paul et al., 1985). Given the demonstrated effects of exorphins on the CNS outlined earlier, it is reasonable that such opioids may explain both the epileptic tendencies and the EEG abnormalities found. Unpublished data indicate that casomorphine 1–4 amide is of special importance to epilepsy in autism (under study).

**Trophic Changes**

These changes are not dramatic, but with MR-imaging techniques reduced brain stem size and especially decreased cerebellar volume can be measured (Hashimoto et al., 1992; Courchesne et al., 1994). Volume reduction was also reported for corpus callosum (Egaas and Courchesne, 1995). However, some 6–12% show hypertrophy (Piven et al., 1996). Furthermore, parietal volume reductions in 70–80%, as well as increases in the parietal cortex were found in about 10%.

Opioids inhibit brain maturation (Zagon and McLaughlin, 1987), and this involves the maturation of the dendrites and spines (Hauser et al., 1989). Although pruning by apoptosis takes place continuously, it is to be expected that during the brains most proliferative phase (proliferation dominating apoptosis usually during the first 5 years of life), the effects of opioids would be mainly inhibitory. However, during the extensive pruning (a phase where apoptotic removal of synapses and cells dominates) which takes place at puberty, and as much as 30% of the neuropil is removed (Feinberg, 1982/83), hypertrophy would be expected. Opioids do inhibit pruning (Tenconi et al., 1991), and inhibition of pruning will be seen as increased volume.

It is relevant to the dominant cerebellar changes in autism that gluten related ataxia mainly shows cerebellar changes (Hadjivassiliou et al., 1998), and antibodies to gliadin seem especially to react with the Purkinje cells of the cerebellum (Hadjivassiliou et al., 2002). In progressive myoclonic ataxia in celiac disease cerebellar damage is found (Bhatia et al., 1995). Furthermore, cerebellar damage in celiac disease is well established (Kinney et al., 1982). Relevant to these data are the found increase in antibodies to precisely gliadin and gluten of both IgG and IgA type in autism usually without transglutaminase increase indicating increased protein uptake from the gut (Reichelt et al., 1991; Lucarelli et al., 1995; Cade et al., 2000).

IV injection of casomorphin 1–7 induces the immediate early gene Fos antigen immuno-reactivity in rat brain (Sun et al., 1999), thus linking this opioid to the trophic effects. Post mortem morphological changes similarly point to disturbed cell numbers and relationships in the neuropil (Ritvo et al., 1986; Bauman, 1991), and that is what would be expected if brains are exposed to opioids. Damage to most cells is critically dependent on growth phase and state.

Decreased functional serotonin in the synaptic cleft because of increased uptake would likewise interfere with synapse maintenance and formation (Chen et al., 1980). Blocking the cortical serotonin availability may thus reduce the synaptic density by almost 30%.

**Varying Analgesia**

Autistic children may hurt themselves deliberately or in accidents apparently without much pain (Frith, 1988). This analgesia seems to vary from day to day and different times of the day. Exorphins would depend on the dietary input and consequently vary in level over a 24-h period and from one day to the next. Self-destructive behaviour is one of the most frequent signs ameliorated by opioid antagonists (LeBoyer et al., 1990), reinforcing a reasonable role for exorphins. The continuous fluctuation of opioid levels because exorphins must depend on feeding, would probably prevent permanent changes in receptor numbers and or sensitivity also in
the dopaminergic system, in spite of dopaminergic hyperactivity at times.

Language Problems

Children with autistic disorders show language deficits ranging from mutism to fluent speech, but often lacking in prosody. Grammatical abnormalities like pronoun reversal are known, and many show a tendency to use repetitive language.

To comprehend a series of words, it is necessary to keep these in the working memory, and the apparatus responsible for processing a single word must be sufficiently inhibited to make place for the next word. With lack of habituation it follows that words will tend to overlap, and be conceived as absurd clusters of sounds or words. Patients we have treated with diet, tell us that this was exactly the problems with sentences. They were conceived as overlapping series of sounds, and consequently quite meaningless.

Early and Late Onset Subtypes

We all take up peptides (Gardner, 1994) and proteins (Husby et al., 1984; Gardner, 1994) from the gut and inhibition of peptidases increases the uptake (Mahe et al., 1989). These dietary proteins can be demonstrated in mothers’ milk (Kilshaw and Cant, 1984; Troncone et al., 1987). Feeding babies also ingest human casomorphins in the mothers’ normal milk. It is, therefore, conceivable that lack of peptidases or inhibited peptidases may cause problems pre-natally and definitely post-natally in early onset autism.

If the gut is made leaky at some later point in late onset autism or CPDD, this would easily induce such problems by increasing the post prandial overload of peptides. Recent work on Ileal-lymphoid-nodular hyperplasia in CPDD (Childhood onset pervasive developmental disorder) (Wakefield et al., 2000; Furlano et al., 2001) may indicate such a mechanism. The initially published data has been vastly expanded with essentially the same results. Upper intestinal lesions related to autism have also been reported (Horvath et al., 1999; Torrente et al., 2002), and increased low molecular gut permeability in autism is known (D’Eufemia et al., 1996). It has been suggested that the latter could be due to decreased sulphation of aminoglycans in the gut (Waring and Ngong, 1993), but peptidase defects or inhibition also increases gut uptake of peptides (Mahe et al., 1989).

Late onset autism could also be caused by introduction of gluten containing foods from about 6 months onwards. As we and others find that different autistic children have different chain lengths of their exorphins in their urine (Reichelt et al., 1997), this may indicate that different sets of peptidases are malfunctioning in different families. Thus using mass spectrometry, we find the following distribution of a random subset of 34 autistic children. Bovine beta casomorphin 1–8 or Cm 1–8 in 38.2%; Cm 1–7 in 29.4%; Cm 1–5 in 41.2%; Cm 1–4 NH2 in 94.1%; Glutemorphin A5 (G-Y-Y-P-T) in 32.4% and Glutemorphin B 5 (Y-G-G-W-L) in 64.7%. None of these 34 were without increase over controls in one or more opioids, but could be completely without some of the remaining opioids. Most peptides are found in “families” of different chain lengths. Opioids with different chain lengths would have very similar biological effects.

Thus diamino peptidase IV could be one of these enzymes involved (Shaw W personal communication), because the casomorphins start with Tyr-Pro (Y-P), and diaminopeptidase IV is also known to be an Adenosine deaminase binding protein. The deaminase may be involved in some cases of infantile autism (Persico et al., 2000). Furthermore, glycosylation defects would also affect this enzyme as well as other peptidases and could also thus be one of the genetic causes. Another enzyme may be Tyr and Pro-aminopeptidase. For isolated peptides see Table III. Their isolation has been extensively described (1,5).

A parallel to our model is Fellings disorder. Even though phenyl-ketonuria is a genetic disease, it would never have become manifest in a protein environment containing very little phenyl-alanine. We think that a limited break down capacity (peptidases) would only become manifest if subjected to a dietary overload of peptides and, or proteins caused by increased uptake. A limited peptide break down ability could likewise explain recently published data on neuropeptide and neurotrophin increases in the blood of neonatal autistic children (Nelson et al., 2001) as well as increase in oxytocin precursor peptides (Green et al., 2001). Because peptides in general are good peptidase inhibitors (LaBella et al., 1985) this makes sense.

Genetics

Solid evidence for a genetic disposition for autism has been presented (Bailey et al., 1995), but the genes for this disorder have been difficult to pin down. As we and others find that different autistic children have different chain lengths of their exorphins in their urine (Reichelt et al., 1997), this may indicate that different sets of peptidases are malfunctioning in different families. Thus using mass spectrometry, we find the following distribution of a random subset of 34 autistic children. Bovine beta casomorphin 1–8 or Cm 1–8 in 38.2%; Cm 1–7 in 29.4%; Cm 1–5 in 41.2%; Cm 1–4 NH2 in 94.1%; Glutemorphin A5 (G-Y-Y-P-T) in 32.4% and Glutemorphin B 5 (Y-G-G-W-L) in 64.7%. None of these 34 were without increase over controls in one or more opioids, but could be completely without some of the remaining opioids. Most peptides are found in “families” of different chain lengths. Opioids with different chain lengths would have very similar biological effects.

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Immunological Changes

The extensive regulation of the immune system, by neuropeptides, has been reviewed by Singh (1995). Exorphins would easily react with opioid receptors on immuno-competent cells, and an effect of the antagonist naltraxone on the CD4/CD8 lymphocytes in autism has been found (Scifo et al., 1996). A series of immunomodulating peptides are formed from casein (Migliore-Samour and Jollet, 1988). Thus depressed lymphocyte responsiveness in autistic children (Stubbs et al., 1977) could easily be explained by a dietary aetiology and exorphins in particular.

An increased frequency of the mucosal IgA antibodies in serum against gliadin, gluten and casein has been found (Reichelt et al., 1990; Lucarelli et al., 1995; Cade et al., 2000), usually without endomycium antibody increase. These immunological changes reflect an increased protein uptake in about 1/3 of the autistic children and again points to a dietary aetiology. It is also interesting that IgA antibodies against gliadin and gluten have a very strong affinity for cerebral blood vessel structures (Pratesi et al., 1998) and may alter the permeability of these vessels. The recent data on antibodies against a protein in MMR vaccines (Singh et al., 2002) dovetails nicely with Wakefields data and would of course through inflammatory mucosal changes cause increased uptake, and possibly explain the Th1 to Th 2 shift and cytokines increases such as interleukin 2, 12 and interferon-γ (Singh et al., 2002).

Sleep Problems

These are common in early childhood in children with autism. Colic and screaming and apparent lack of tiredness after the briefest of naps are commonly reported. Non-autistic children showing similar behaviour are often helped by removal of cow’s milk from the mother if nursing and from the diet, if the child if getting diluted cow’s milk directly (Lucassen et al., 1998). In normal children with these problems antibodies to beta-lactoglobulin have been demonstrated (Kahn et al., 1987). If opioids are involved and with bell shaped dose response curves, all manner of gut and sleep problems are to be expected, especially since enkephalin is a transmitter for mucosal ganglion cells. Therefore, our hypothesis that exorphins are key elements in development of autism, is strengthened also by the data from normal sleepless infants. Low synaptic cleft serotonin should reinforce this state of affairs, because functional serotonin decrease causes insomnia in carcinoid disease.

Increased Incidence in Immigrants from Certain Countries

Immigrants from the Developing World to Western Europe have an increased rate of autistic syndromes (Gillberg and Gillberg, 1996). Generally these families move from a low grain, low milk area to an extremely high milk and grain consuming area, not the least because this is the cheapest food in Western Europe/USA. Therefore, such data are to be expected, if our model is correct.

Effect of Gluten and, or Casein Free Diet

It has been difficult to run double blind controlled dietary experiments, because the control group tends to quit after weeks without change. However, testing before and after intervention, and also testing without knowing who is on diet has been carried out (Reichelt et al., 1990; 1991; Knivsberg et al., 1995; Lucarelli et al., 1995; Whiteley et al., 1999; Cade et al., 2000; Knivsberg et al., 2002). It has been argued that placebo may account for some of the changes reported. It should be noted, though, that

<table>
<thead>
<tr>
<th>Compound</th>
<th>Cochrom. HPLC</th>
<th>Antibody binding</th>
<th>Receptor binding</th>
<th>Correct comp</th>
<th>Mass. Sp MW</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAG</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>CM 1–8</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>CM 1–7</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
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<td>CM 1–5</td>
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<td></td>
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<tr>
<td>CM 1–4</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CM 1–4NH2</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A4</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
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<tr>
<td>A5</td>
<td></td>
<td>+</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GM</td>
<td></td>
<td>+</td>
<td>+</td>
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</table>

The preliminary receptor assay was carried out by Dr L. Terenius, Stockholm. CM is Casomorphin (bovine), IAG = indolyl acryloyl glycine, A4 and A5 are glutemorphins and CM: gladinomorphin (Usually several peaks due to deamidation of glutamine: Shanahan et al., 2000). Composit.: Is amino acid composition after acid hydrolysis and amino acid analysis: 1. IAG yielded only glycine; CM 1–8 gave: Y (0.8), P (4), F (0.9), G (1.3); CM 1–7: Y (0.7), P (3), F (0.8), G (1.3) I (1); CM 1–5: Y (0.7), P (2.2), F (0.7), G (1.5), CM 1–4: Y (0.7), P (2), F (0.8). The two glutemorphins came out with: A4: Y (1.8), P (1), G (1.3) I (1); A5: Y (1.7), P (1), G (1.5), I (1). Found mass spectrometry weights and theoretical based on average istopic mass in parenthesis (Mono isotopic mass is usually lower). Mass spectrometry was run on the Pesciex AP 2000 MS/MS machine with samples dissolved in methanol/water (50% by volume) and 0.01 M formic acid and in the positive mode.
the intervention periods in some of these projects are one year or more and in one of trial four years (Knivsberg et al., 1995) (Table IV). Placebo has not been reported to last that long. Furthermore, an inquiry by family questionnaire (Rimland, 1988) and also a small sociological investigation (Shattock, 1995) as well as numerous identical anecdotal reports all point in the same direction; that diet ameliorates the disease process. As may be expected, dietary intervention works better the younger the child and the shorter the history. The spontaneous reports pointing out abstinence or withdrawal symptoms by many parents also reinforce a probable effect of diet. Rashes, itching, pupillary changes, diarrhoea and sleep problems that appear transiently are not easy to misjudge.

Gut–Brain Connection

It has been demonstrated that late onset and regressive autistic children often have regional nodular ileitis and colitis of the upper colon (Wakefield et al., 2000; Furlano et al., 2001). Further evidence has been found of mucosal damage found also in the upper gastrointestinal tract (Horvath et al., 1999; Torrente et al., 2002). Mucosal damage would clearly entail increased gut permeability especially since the enterocytes form close to a monolayer. This might explain the increased uptake of protein measured as specific IgA antibody increases in serum (Reichelt et al., 1991; Lucarelli et al., 1995; Cade et al., 2000) and increased low molecular weight permeability (D’Eufemia et al., 1996). Several papers have furthermore, established that inflammatory gut disease regularly causes white matter lesions in the brain (Geissler et al., 1995; Hart, 1998). Peptides may easily be seen to mediate such actions especially because of the opioid link also to epilepsy as outlined. Also in celiac disease increased peptide excretion is found (Reichelt et al., 1998).

Animal Models

Animal not usually eating gluten ought to demonstrate effects of excess feeding of gluten and psycho-physiological changes. Feeding gluten to cats causes profound changes in monoamines, the amino acids profile and dopamine beta-hydroxylase in the brain of these cats (Thibault et al., 1988). Thus gluten can clearly have effects on the CNS. Excessive gluten fed to rats causes these animals to learn to attend to redundant stimuli usually ignored in a conditioned reflex paradigm (Harper et al., 1997). This inability to differentiate essential and non-essential inputs is typical for the autistic state (Frith, 1988).

CONCLUSION

Based on the above data, we may present our simple model. The genetic fault is believed to be primarily found in at least two or more peptidases or peptidase regulating proteins. Increased gut permeability/uptake and subsequent peptide increase, which may also be caused by peptidase defects, overwhelm limited break down capacity and make borderline states burst into full blown syndromes. We think that the enzymes involved must be different pairs or more of enzymes (peptidases) in different families, because the opioids found differ in chain length from one patient to the next. The exorphins and other isolated peptides can explain a large part of the symptomatology of the autistic syndromes with its many manifestations. Exposing animals to peptides early during their development can have long lasting effects, and in rats be detectable after 3 months (Gschanes and Windisch, 1999). This could probably be due to trophic effects on the brain and all peptides must therefore be treated with considerable care. This includes also secretin.

With varying chain length of the opioids found as seen for the casomorphins, and varying levels of opioids and bell shaped dose response curves

<p>| TABLE IV | Changes due to dietary intervention (Knivsberg et al., 1995) |</p>
<table>
<thead>
<tr>
<th>Test</th>
<th>Initial score</th>
<th>1 year change</th>
<th>4 years change</th>
<th>N</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-Raven:</td>
<td>6.8 ± 2.8</td>
<td>+8.6 ± 2.8</td>
<td>+8.6 ± 3.2</td>
<td>12</td>
<td>0.005</td>
</tr>
<tr>
<td>ITPA:</td>
<td>25.7 ± 5.5</td>
<td>+2.7 ± 2.5</td>
<td>+6.1 ± 2.8</td>
<td>10</td>
<td>0.005</td>
</tr>
<tr>
<td>Tafjord scheme:</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1: Social interaction</td>
<td>53.7 ± 15.2</td>
<td>+12.1 ± 5.9</td>
<td></td>
<td>14</td>
<td>0.005</td>
</tr>
<tr>
<td>2: Language</td>
<td>71.0 ± 15.2</td>
<td>+8.7 ± 6.5</td>
<td></td>
<td>14</td>
<td>0.005</td>
</tr>
<tr>
<td>3: Structure ability</td>
<td>56.7 ± 17.1</td>
<td>+9.1 ± 5.4</td>
<td></td>
<td>14</td>
<td>0.001</td>
</tr>
<tr>
<td>4: Sensory/Motor</td>
<td>72.9 ± 12.3</td>
<td>+7.2 ± 4.5</td>
<td></td>
<td>14</td>
<td>0.001</td>
</tr>
<tr>
<td>DIPAB:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A: Social isolation</td>
<td>8.5 ± 3.3</td>
<td>−6.1 ± 2.7</td>
<td></td>
<td>14</td>
<td>0.005</td>
</tr>
<tr>
<td>B: Bizarre traits</td>
<td>5.3 ± 2.2</td>
<td>−5.3 ± 1.22</td>
<td></td>
<td>14</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Notice that Raven C reaches a maximum level after 1 year while Illinois test of psycholinguistic ability (ITPA) improves even more after 4 years, probably reflecting the more complex nature of advanced learning (language). DIPAB = Haracopos scheme: “Diagnosis of Psychotic Behaviour in Children”. Peptide levels decrease and followed the decrease in symptoms. Tafjord is a Norwegian scheme for registering play, interaction, structural ability and sensory motor behaviour during play. For details see Knivsberg et al. (1995). Change is measured as delta increase or decrease.
(Reichelt and Reichelt, 1997), it is not surprising that symptoms, abilities, morphology and EEG data are so varied in the autistic syndromes.

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