The appreciation of the existence of a brain disorder as encapsulated in early childhood autism has only come to the fore in recent years. Possibly for this reason, there is no apparent agreement as to which of the symptoms of the disorder, namely emotional disturbances or cognitive defects, are primary, and which are secondary. Nor is there yet either a generally accepted medical treatment or a coherent neurochemical theory of autism. In this article, Jaak Panksepp puts forward the idea that autism is an emotional disturbance arising from an upset in the opiate systems in the brain, and hence proposes, as a possibility, opiate antagonist therapy for the autistic syndrome.

We have approached the possible neurochemical causes of autism by assuming that the fundamental problem of the autistic child is emotional. Some of the earliest observed symptoms of autism include a lack of crying during infancy, a failure to cling to parents, and a generally low desire for social companionship, which, we believe, shows that the autistic child is constitutionally unable to feel properly the emotions arising from social relationships. Injections of low doses of morphine can generate such behaviour patterns in animals; extrapolating from these observations, I should like to propose the hypothesis that childhood

A neurochemical theory of autism

Jaak Panksepp

The appreciation of the existence of a brain disorder as encapsulated in early childhood autism has only come to the fore in recent years. Possibly for this reason, there is no apparent agreement as to which of the symptoms of the disorder, namely emotional disturbances or cognitive defects, are primary, and which are secondary. Nor is there yet either a generally accepted medical treatment or a coherent neurochemical theory of autism. In this article, Jaak Panksepp puts forward the idea that autism is an emotional disturbance arising from an upset in the opiate systems in the brain, and hence proposes, as a possibility, opiate antagonist therapy for the autistic syndrome.

We have approached the possible neurochemical causes of autism by assuming that the fundamental problem of the autistic child is emotional. Some of the earliest observed symptoms of autism include a lack of crying during infancy, a failure to cling to parents, and a generally low desire for social companionship, which, we believe, shows that the autistic child is constitutionally unable to feel properly the emotions arising from social relationships. Injections of low doses of morphine can generate such behaviour patterns in animals; extrapolating from these observations, I should like to propose the hypothesis that childhood
autism may be caused by endogenous overactivity of the child's own brain opiate system.

At the outset, I must emphasize that our work has been done exclusively with laboratory animals, so these are only suggestions as to what may be wrong in the brain of the autistic child. Further, there is no direct evidence that the therapeutic interventions which we suggest will be effective. Conversely, to my knowledge there is no evidence that they might be ineffective.

Opiates and social affect

Our thinking about autism evolved from an interest in understanding the emotions which mediate positive social feelings between animals. Our basic assumption has been that distinct mechanisms in the brain lead animals to seek the company of others. The central idea which guided the work was that there may be basic similarities between the underlying processes of narcotic addiction and the brain mechanisms which mediate social dependence. Perhaps brain opiate systems can create feelings of belonging, so people who are lonely and isolated can use narcotics as a substitute for the interpersonal bonds that normally exist, for example, between parent and child.

In our initial experiments, we found in many species that low doses of opiate drugs were very effective in reducing the crying of young animals when separated from their mothers or siblings for 10-15 min, almost as if opiates are neurochemically equivalent to the presence of the mother. The doses were low by traditional experimental standards—ranging from 0.25 to 1 mg/kg injected peripherally, or as low as 100 picomoles (either as morphine or as one of the many known opiate peptides) when injected into the fourth ventricle. Of 20 other psychoactive drugs and 10 other CNS peptides we have tested, none has been as effective as the opiates in decreasing crying (though somatostatin and clonidine were close). However, blockade of serotonin and acetylcholine systems and intraventricular α-MSH treatment have been as effective in increasing crying as opiate blockade with naloxone.

Opiate-induced symptoms of autism

We recognized that much of the behaviour induced by low doses of narcotics was similar to the major symptoms of those autistic children who suffered disturbances of affective contact, as described by Kanner. Specifically, opiate-elicited symptoms corresponding to those observed in autistic children are as follows: (1) the opiate-treated animal does not appear to appreciate fully physical pain; (2) it does not cry as readily and spontaneously as normal animals; (3) it clings poorly; (4) it does not have a strong desire for social companionship; (5) it can show unusual learning effects characterized by extreme persistence of behaviour in the absence of external rewards (akin to the insistence on sameness by autistic children). The list of similarities suggests that the underlying neurochemical imbalance in autistic children may be excessive, or unusual, activity in their own endogenous brain opiate systems. Such a brain disturbance may block psychosocial development at its earliest stages—leading to failures in language acquisition and other idiosyncracies in learning.

Other incidental observations support an opiate excess hypothesis of autism: in some circumstances, opiate-treated animals exhibit unusual motor flurries such as spurs of high activity interspersed with quiescence, as do some autistic children. Young animals treated with morphine exhibit unusual body postures, such as walking on toes—a symptom often observed in autistic children. Autistic children also exhibit a relatively high incidence of seizure disorders, and recent evidence from a number of laboratories indicates that brain opiate peptides—especially β-endorphin—are very effective in promoting convulsive activity in the brain.

Possible aetiology of autism

Contrary to most prevailing professional opinions, we have sided with the idea that the primary disorder of autism is an emotional rather than a cognitive one. We feel that the language difficulties of an autistic child do not reflect a primary cognitive disorder. One of the major infantile functions of language may be to convey emotive states. Unless the child has a normal desire for social interaction, the resulting failure of early language development may abort the construction of more mature linguistic skills. In any case, if autistic symptoms are due to excess opiate activity, the localization of opiate systems in brainstem areas where sensory information enters the brain readily provides a substrate whence both types of processes could be directly influenced.

Why might certain children have excessive brain opiate activity? Although our experimental work has not yet addressed this question, a few possibilities arise from other recent work. Certain areas of the prenatal rat brain (e.g. the striatum) are rich in the most potent of the endogenous opiates (i.e. β-endorphin), but, with maturation, the manufacture of opioid peptides may shift towards the weaker and shorter acting ones (i.e. the enkephalins). Although the reasons for the reduction of β-endorphin levels with age are not yet known, autism may reflect a failure of brain systems to exhibit this maturational decline (perhaps because of the failure of certain cleavage enzymes to appear). Accordingly, early childhood autism may be caused by a profound maturational lag in which certain brain chemistries tend to remain at an infantile stage of development, leaving the autistic child in the opiate 'bondage' which perhaps all young animals experience, but from which most are gradually liberated. This maturational lag may prevent the brain from becoming appropriately responsive to the sensory and social environment.

Furthermore, why should normal infants have high opiate activity? Perhaps the capacity of opiates to cause catalepsy provides a clue. Opiate-induced motor 'bondage' may restrain the visceral and motor activity of the foetus in the womb, and, in the newborn, may quell the urge to be active before muscular strength and co-ordination have matured. From our own research, we know that young infant animals are especially sensitive to the cataleptic effects of opioids, and that the opiate-antagonist naloxone can increase the young animal's motor activity, although it reduces activity in adults.

The theory still has to explain other symptoms of autism. Autistic children exhibit dramatic shifts from dreamy, detached states to uncontrollable panic, crying, and general emotional turmoil, which could be an amplification of the normal child's rapid changes between laughing with delight one moment, and...
opiates. We believe that the brain
is normally capable of maintaining
au2 to normal activity through environmental circumstances. The autistic child may also be
responsive to this 'switch' process. How-
ever, the autistic child's brain is
over-opiated, and any condition which
shuts down this system (i.e., separation
from familiar objects) would produce
symptoms like withdrawal in the narcotic
addict – intense panic, crying, and an
inability to resume normal activity. This may be relatively
freerunning, the child would respond less to those social acts
which normally provide comfort – the
soothing voice, the gentle touch, the
comfort of being rocked. Is it mere chance
that autistic children have been found to
respond abnormally, especially in those
domains – auditory, somato-sensory, and vestibular – which are
essential to social experience? In the
present theory, we assume that the social
signals – of being touched, of being spoken to,
of being rocked – enter the mind to some extent through an opiate gate or an
opiate messenger. Thus it seems reasonable
to us that high levels of opiate activity
shift brain opiate systems to respond creatively to the social
environment is lost to the autistic children,
and thus the major neurochemical avenues through which primitive socialization may be elaborated (i.e., activation of brain opiate systems) is pharmacologically blocked? Since opiates may merely act by gating socialization processes, we hope many of the other influences which contribute to socialization will still be operative. A specific dilemma is that opiate-blockade might facilitate the occurrence of panic attacks in autistic children. Also, long-
term opiate-blockade could induce compensatory over-production of endorphins and enkephalins so that after the drug wore off, autistic symptoms would be intensified. Still, preliminary studies with dogs have shown that naloxone increases solicitive behaviors, such as face-licking and tail-wagging toward humans, without any expression of emotional distress. We have also kept puppies on high doses of naltrexone (10 mg/kg per day) for 6 weeks with no untoward effects. From preliminary attempts to provide drug and psychotherapy to unsocialized dogs, we suspect that the occasional use of short-acting opiate antagonists, such as naloxone, might be more beneficial than the continued use of such drugs during all therapeutic sessions.

Proposed therapy

Although the paucity of data relevant to
this proposal casts uncertainty over it, the
reasoning does suggest relatively safe
medical interventions which can be tried
now. If the key which allows brain opiate
systems to respond creatively to the social
environment is lost to the autistic children, can we unlock the door, even a little, by pharmacological blockade of brain opiate systems? Perhaps drugs such as naltrexone can open the mind of the autistic child to
more normal social feelings and percep-
tions. Fortunately, naloxone is a 'safe'
drug with no major contraindications.
Perhaps the major shortcoming of the
drug is its ineffectiveness when given
orally, and its relatively brief time-course
of biological activity, which apparently
does not exceed several hours in humans.
However, this last characteristic may be
an advantage, if it turns out that the most
effective period of therapeutic entry is
during the period when opiate blockade is
waning. Another promising agent is
available: naltrexone is effective orally and
can yield opiate blockade for up to
several days with a single administration,
but the drug has not yet been approved
for general medical use. On a more general
level, the present conceptualization sug-
gests that any agent which will increase
cri a (and other care-soliciting
behaviours) may be useful in reducing
autistic aloofness. Thus, in addition to
opiate blocking agents, we might anticipate
that serotonergic and cholinergic
blockade, as well as treatment with
a-MSH and related ACTH fragments,
might be beneficial in treatment of autism.

To my knowledge, opiate antagonists
have never been used in the treatment of
autism. Indeed, perhaps the general lack
of psychological effects of opiate-
agonists in normal adults indicates
that such agents would not be helpful in
the autistic disorders of children. How-
ever, in animal research, very few
behavioural effects have been apparent
in mature animals, but quite a few effects
were observed in young animals tested in
a social context – the main effect being
an increase of emotional responses, indicative
of care-seeking behaviour.

Since the prevalence of autistic symp-
toms in childhood emotional disorders
surely exceeds the incidence of early
childhood autism, we believe that the
initial target population for evaluating
opiate-blockade therapy should be care-
fully selected to consist primarily of
children with the full spectrum of symp-
toms originally described by Kanner.
Drug therapy would have to be supported
by intensive and long-term humanistic
therapy, or theraplay, with full involve-
ment of the parents, as the aim is not just to
alleviate a few discrete symptoms, but to
guide the child's life on to a new track.
Perhaps the first group of individuals who
might be offered this treatment are those
few autistic people who have reached
adulthood with exceptional adaptive skills.

Possible shortcomings

Drug therapy is always a cost-benefit
dilemma. At present no evidence exists
concerning the costs, or benefits, of
opiate-blockade therapy for autism. We
can, however, anticipate problems which
may arise. First, there is a logical paradox.

How is resocialization to occur if one of
the major neurochemical avenues through
which primitive socialization may be
elaborated (i.e., activation of brain opiate
systems) is pharmacologically blocked?
Since opiates may merely act by gating
socialization processes, we hope many of
the other influences which contribute to
socialization will still be operative. A
specific dilemma is that opiate-blockade
might facilitate the occurrence of panic
attacks in autistic children. Also, long-
term opiate-blockade could induce com-
ensatory over-production of endorphins
and enkephalins so that after the drug
wore off, autistic symptoms would be
intensified. Still, preliminary studies with
dogs have shown that naloxone increases
solicitive behaviors, such as face-licking
and tail-wagging toward humans, without
any expression of emotional distress. We
have also kept puppies on high doses of
naltrexone (10 mg/kg per day) for 6
weeks with no untoward effects. From
preliminary attempts to provide drug and
psychotherapy to unsocialized dogs, we
suspect that the occasional use of short-acting opiate antagonists, such as
naloxone, might be more beneficial than
the continued use of such drugs during all
therapeutic sessions.

Alternatives

Surely, the above conception of autism
is over-simplified, and primarily points
towards one reasonable neurochemical
system where the problem may lie. I hope
the cerebrospinal fluid levels of endor-
phins and enkephalins in autistic children
will soon be measured. But, even if the
opiate-excess hypothesis of autism is on
the right track, more precise knowledge is
needed before a fully effective medical
therapy can be developed. For example,
the relationship between over- and
under-activity of the opiate systems and
the symptoms of autism needs to be
clarified, and the precise biochemical
lesion identified.

Also, other neurochemical systems
which are closely tied to opiate activity,
especially of brain serotonin, acetyl-
choline, and MSH/ACTH, need to be
considered. For instance, autistic children
have a higher efflux of serotonin from
blood platelets than normal children, so
their difficulties may arise from excessive
brain serotonin activity. This possibility
is nicely compatible with an opiate-excess
hypothesis, since many of the analgesic
and quieting effects of opiates are due to
serotonin release. Perhaps the brief
therapeutic effect that has been observed
in autistic children treated with the serotonin blocking agent methysergide could be prolonged or intensified by concurrent treatment with opiate-blocking agents.

Knowledge in this new area of research, as in any area of science, proceeds by the gradual refinement of oversimplifications. I hope that presentation of these ideas will help continue to broaden our thinking about the problem of autism, and to help clarify how the problem may be attacked.

Acknowledgements

Many students and colleagues have shared their enthusiasm and energies in bringing to life the ideas summarized herein. I would especially like to acknowledge the collaborations of R. Conner, J. P. Scott, R. Meecker, B. Herman, T. Vilberg, P. Bishop, K. Davis, and F. DeEskinazi. Also I thank NIH for supporting this work through their award of a Research Scientist Development Award (MH-00086).

Reading list


The results from investigations using this design demonstrate that various agents administered to animals shortly after a conditioning experience produce retrograde amnesia. However, as the interval between conditioning and administration of the agent increases, the severity of the amnesia decreases until at some prolonged interval no amnesia is observed. This time-dependent effect has led to several assumptions. First, in producing amnesia, the agent is assumed to affect neural processes which are initiated by the experience, and which contribute to the formation of an enduring memory, processes which change with time, as demonstrated by their increased resistance to interference as time passes from the experience. Secondly, given that the agent exerts known effects on specific neural systems, the assumption is made that the system upon which the agent acts may function in memory formation.

Among the variety of agents used to investigate the neural systems which may contribute to memory, opiate compounds administered either systemically or intracranially following aversive conditioning in animals have been reported to produce retrograde amnesia. These data indicate a function for opiate-sensitive systems in memory processes.

Systemic opiate administration and memory

Using a retrograde design, Castellano reported that, when compared with