aspects of its function and location are understood.

A behavioural paradigm?

Another group of scientists who have become interested in the possibilities of the insect are the neurobiologists, who see in the insect, as in other simple systems, a suitable system for investigating the molecular and cellular springs of behaviour. In this context the large orthopterans, cockroach and locust, have their stoutest advocate in Hoyle[4], who considers that they have the correct balance of behavioural complexity and anatomical simplicity. The argument for the use of the insect for behavioural studies rests to a great extent upon two pillars of wisdom: complex, but genetically predetermined, patterns of behaviour, and large and identifiable cells, whose location is very consistent.

Fabre, the nineteenth century entomologist, to whose painstaking observations scientific entomology owes a great debt, was well aware of the rigidity of even the most complex and seemingly thoughtful of insect behavioural patterns. With the advent of the cobalt chloride staining techniques, it has become clear that not only is the positioning of the cell bodies very consistent, but, more important, so is the pattern of their dendritic branching. While the mapping of cell bodies by electrophysiological means, especially in the ganglia of the locust, has gone on apace, biochemical studies have lagged far behind. Certainly such studies at the single-cell level are no longer a daring prospect since the heroic efforts of O. H. Lowry and E. Giacobini. (One advantage which insect neuronal cell bodies have over mammalian, is that they are free of the contamination of terminal boutons. It seems that no nerve cell terminates on other cell bodies.) The studies of Evans[3] with octopamine are a good example of single-cell work which also combines electrophysiological and biochemical studies. Many of the cells mapped by the electrophysiologists are motoneurones, and it is likely that biochemists might be more interested in intermediary neurones, with other neurotransmitters whose action is likely to be modulatory, and which might not be so easily identified.

The fact that much insect behaviour is genetically based opens the possibility of behavioural mutants. The most obvious prospect in this respect, Drosophila, is rather small for precise electrophysiological studies. It is a pity that the system about which Hoyle[4] is most scathing, a temperature-sensitive mutant of the fruit fly in which the pharmacological evidence suggests some lesion of GABA metabolism or action, is the very one in which a biochemical approach might prove most fruitful[12].

A corollary of a fixed pattern of behaviour is the fact that hormonal signals may trigger off whole sequences of activity whose cellular locations may be identified. The clearest cut example is the effect of the phallic nerve stimulating hormone in the cockroach whose action seems to be limited to one cell, and which has its effect even in the isolated ganglion. It is a reasonable assumption that many of these hormones cause changes in the concentrations of cAMP in target cells, and this opens the possibility of locating these cells by immunohistochemical means, as has been used on the neurosecretory cells themselves[7].

In its present state of development, the insect nervous system represents what Lancelot Brown might have called "a system of great capabilities". At the moment, the gardeners from the different disciplines all tend to work their own little plots, with studious disregard to each other. It remains to be seen how much their efforts, separate or concerted, will change the landscape of neurochemistry.

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Point of View

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

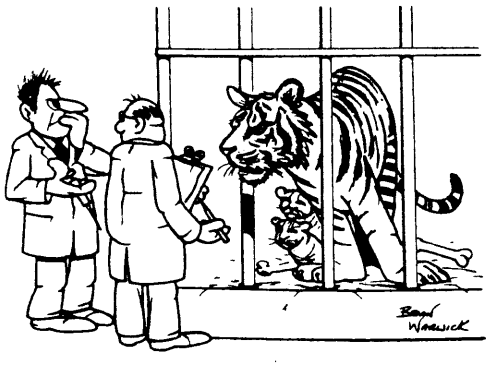
autism may be caused by endogenous overactivity of the child's own brain opiate system.

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[5,8,9]. 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[9]. 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.



The opiates may calm the kittens, but what do you plan to do with the mother?

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[7]. Specifically, opiate-elicited symptoms corresponding to those observed in autistic children are as follows[10]: (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 spurts 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[11].

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[6] 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)[1], 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[12].

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

crying the next. We believe that the brain opiate system can rapidly turn on or off, depending on environmental circumstances. The autistic child may be still sensitive to this 'switch' process. However, the autistic child would be expected to fall to greater emotional depths when environmental circumstances prevail which can normally turn off brain opiate activity. If the autistic child's brain is over-opiated, then 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 insistence to be reunited with the comfort of the familiar. In this way, some autistic children may be caught in an inexorable conflict. To sustain psychological comfort, they must sustain the constancy of env ment which permits their high opiate activity to continue.

Since the autistic child's opiate systems 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 these sensory modalities – auditory, somatosensory, 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 sho be found in brain areas which orga...ze these sensory experiences[6], and that opiates should induce milk to drop in nursing mothers and promote feeding in the young.

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 naloxone can open the mind of the autistic child to more normal social feelings and perceptions. 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 suggests that any agent which will increase crying (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 α-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-antagonists in normal adults[4] indicates that such agents would not be helpful in the autistic disorders of children. However, 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 symptoms 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 carefully selected to consist primarily of children with the full spectrum of symptoms originally described by Kanner[7]. Drug therapy would have to be supported by intensive and long-term humanistic therapy, or theraplay, with full involvement 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 resocializaton 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 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 behaviours, 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 endorphins and enkephalins in austistic 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, acetylcholine, and MSH/ACTH, need to be considered. For instance, autistic children have a higher efflux of serotonin from blood platelets than normal children[2], 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[3] 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 at a very basic level. Most of all, I hope these ideas will encourage sensitive clinicians to institute trials with naloxone within a long-term psychotherapeutic context. Parents of autistic children know that there is some constitutional infirmity within their children's minds that eventually must be addressed in neurophysiological and neurochemical terms. To what extent I have woven a tapestry of logic or fantasy is to be seen. At the present time, we can share little more than a collage of suggestive results. But new avenues of thought have also been opened, and only through our willingness to follow such paths can there be any hope for autistic children.

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Neuroplasticity

Opiates and memory

Bruce S. Kapp and Michela Gallagher

A painful stimulus readily enters into our memory systems, such that the possibility of receiving a repeat of the stimulus invokes a 'fearful' apprehensive reaction, including, often, avoidance. As described by Bruce Kapp and Michela Gallagher in this article, the site of this memory system is probably based in the amygdala, and at least for 'painful memories' seems to involve an opiate mediation.

Since the discovery of endogenous opiate peptides and receptors in the nervous system, intense research has focused on their role in the modulation of pain. It is becoming increasingly clear, however, that these opiate systems may influence a variety of behaviours. Our concern is to review recent evidence which indicates that opiate systems are involved in memory processes, and then speculate on the manner by which one specific opiate system might influence the establishment of an enduring memory for an aversive experience. We begin with a discussion of an experimental approach commonly used to investigate the neural substrates of memory.

Memory – an experimental approach to its neural substrates

Clearly, one of the most interesting human memory observations is retrograde amnesia, the amnesia for events preceding head injury. While this amnesia generally prevails for events occurring shortly before injury, events occurring at longer intervals before injury are readily recalled. Frequently, a retrograde design is used in animal research to study further this selective loss of recent memory. Specifically, an amnesic agent is introduced after a conditioning experience, and retention is measured at some later time. This design permits selective interference with memory processes, because presentation of the agent following conditioning eliminates the possibility of agent-induced interference with sensory processing. Furthermore, testing for retention at a sufficient interval after the introduction of the agent allows for the effects of the agent to dissipate, thereby presumably eliminating agent-induced interference with the ability of the animal to perform during the retention test.

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[1,3,5]. These data indicate a function for opiate-sensitive systems in memory processes.

Systemic opiate administration and memory

Using a retrograde design, Castellano[1] reported that, when compared with