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Neuropeptides and non-human primate social deficits associated with pathogenic rearing experience

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Abstract

There is a persuasive evidence that autism is highly heritable and likely to be substantially determined by polygenic mechanisms. Nevertheless, some intriguing findings in children raised in conditions of extreme social deprivation suggest that an autistic-like syndrome may occur as a consequence of environmental conditions. A particularly close model of this human syndrome has been studied in rhesus monkeys for almost half a century. Monkeys reared in pathogenic rearing conditions manifest considerable deficits in social interaction and increased self-directed behaviors. We have been interested in the possibility that disruptions in normal social development in non-human primates might be expressed in neuropeptide systems which have emerged in rodent studies as important candidates for a unique social biology. In recent studies, we have described persistently reduced CSF OT levels in male rhesus monkeys with significant social deficits. We also found that OT levels were positively related to the expression of affiliative social behaviors. Alterations were also detected in both CRH and AVP receptor binding patterns in limbic structures likely to influence social and emotional development. Taken together, these data suggest that abnormal rearing influences the development of brain systems critical to normal social and emotional competence in rhesus monkeys and may contribute to the development of autistic-like symptomatology associated with pathogenic rearing histories.

Keywords: Autism; Disorders; Social deficits

1. Autism and social deficit syndromes

There is a persuasive evidence that autism is highly heritable and consequently, likely to be substantially determined by genetic, albeit complex, and polygenic mechanisms (Folstein et al., 2003; Korvatska et al., 2002). Nevertheless, some intriguing findings in children raised in conditions of extreme social deprivation suggest that an autistic-like syndrome may occur as a consequence of substantially environmental influences.

A significant proportion (approximately 12%) of 111 human infants raised in the infamous Romanian orphanages during the reign of Nicolae Ceausescu showed decreased social interaction as children, exhibiting syndromes of social deficits and stereotypy remarkably similar to autism (Rutter et al., 1999). Deficits in the capacity to form social relationships, social communication and eye-contact, and language deficits were prominent in the most severely affected (6%) and evident in somewhat milder forms in the remaining 6%. Social deficits did not depend on the presence of broader cognitive impairments. These findings have raised interest in the potential role of social stimulation during critical periods of development as necessary to normal social and emotional development and potentially to the biology of social behavior, social attachment, and social deficit syndromes such as autism (Rutter and O'Connor, 2004).

While it is unlikely that non-human primate models of social deficit currently available will reveal significant insights about genetic causes of autism, they may nevertheless provide very important insights about neural systems involved in the normal development of social behavior.

2. Why is research on primate social attachment necessary?

Although much has been learned about neural regulation of social attachment from rodents, comparative studies of rodents and monkeys provide an opportunity to extend

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these findings to studies of higher order social and cognitive behaviors. Non-human primates, like their human relatives, are largely visual rather than olfactory. Although they lack human language, monkeys produce categorical vocalizations (Gouzoules and Gouzoules, 1990a,b, 1995; Gouzoules et al., 1984), they form clear social preferences with reciprocal interaction and alliances (Altmann, 1962), and they are capable of performing complex cognitive tasks similar to those used in clinical assessments of human patients (e.g. Wisconsin Card Sort, face recognition, and computer maze tasks) (Jorgensen et al., 1995; Parr et al., 2000). The monkey brain has a well-developed temporal lobe and an extensive prefrontal cortex, regions that are largely undeveloped in the rodent. These areas, which may be important for social and communicative disturbances in human psychopathology (Davidson, 2003; Willick, 1993), can be studied with invasive in vivo and ex vivo techniques in monkeys.

3. Chronic social attachment deficits in non-human primates: two approaches

3.1. Lesion models

Two neonatal manipulations produce chronic social deficits in monkeys. The first is a lesion approach—both social and cognitive deficits emerge as a consequence of neonatal ablations of medial temporal structures (Bachevalier, 1994, 1996; Bachevalier et al., 2001; Prather et al., 2001). These important studies implicate medial temporal structures in social behavior, but the lesion method is an awkward experimental approach. Each animal can be used for only one experiment, the lesion is irreversible, and the results are difficult to interpret. Interpretation is confounded by the fact that evaluation occurs months, sometime years, after the lesioning, and ablations involve destruction of many kinds of cells as well as fibers of passage. It is also difficult to know whether the social deficits are secondary to cognitive or emotional impairments (Amaral et al., 2003; Prather et al., 2001). Most important, the lesion method does not provide cellular or molecular information, which is the level at which we can now investigate neural function.

4. Primate pathogenic rearing protocols

A particularly close model of the human syndrome described by Rutter has been studied in rhesus monkeys for almost half a century. Monkeys reared in social isolation manifest severe deficits in social interaction and increased self-directed behaviors. First described by Harlow (Harlow and Schiltz, 1967; Harlow et al., 1955; Harlow and Harlow, 1971), many laboratories have since replicated the emergence of social behavior deficits in rhesus monkeys raised in nurseries with a range of deficits related to the availability of social companions (Sackett, 1984; Suomi, 1997; Suomi et al., 1971). In the early protocols, rhesus infants were removed from mothers shortly after birth. Infants were then raised by human caretakers in individual cages for the first 9–12 months of life (Harlow et al., 1964). When these animals were subsequently introduced into group social environments they exhibited a pattern of social withdrawal and hostility (McKinney et al., 1971; Sackett, 1967b) combined with a high frequency of self-stimulation and repetitive, stereotypic behavior (Gluck and Sackett, 1974; Goosen, 1981). In additional groupings, these animals exhibited abnormal responses to play solicitation, continued aggression, or withdrawal (Chamove, 1984; Chamove et al., 1973; Mitchell, 1968; Mitchell and Clark, 1968). Depending on the duration of the initial deprivation, some social deficits could be reversed (Suomi et al., 1972), while others persisted (Cummins and Suomi, 1976). Deficiencies in the development of social skills have been associated with apparent problems in communication including abnormal response to conspecific facial and vocal displays, as well as measurable anomalies in vocalizations produced by socially deprived monkeys (Brandt and Stevens, 1971; Newman and Symmes, 1974).

The pattern of deficits which emerged in these monkeys is in many ways similar to the behavior of subtypes of children raised in the catastrophically abnormal rearing environments described by Rutter (Rutter et al., 1999), and appears to provide an animal model of DSM III's reactive attachment disorder with strong construct and face validity (see also Table 1).

The pathogenic rearing model has received scant attention in monkeys in recent years because there has been confusion about the mechanism for the social deficits. Does the abnormal behavior result from a lack of social stimulation, from decreased sensory input, or from a perceived lack of control or predictability? Although nursery-reared animals permitted daily social interactions exhibit less severe behavioral abnormalities, many of these animals fail to fully develop species typical social skills. Recent studies in rats demonstrate that differences in maternal rearing patterns produce significant and persistent differences measured in the adult offspring's emotionality (Caldji et al., 2003; Caldji et al., 1998), cognition (Zaharia et al., 1996), and brain receptor binding of $GABA_A$, CRH and α_2-adrenergic ligands (Caldji et al., 1998; Caldji et al., 2003), glucocorticoids (Sutanto et al., 1996), as well as CRH and AVP mRNA expression (Liu et al., 1997). Noonan (Noonan et al., 1994) has also described transient changes in oxytocin binding associated with brief, repeated mother–infant separations.

We have been interested in the possibility that disruptions in normal social development in non-human primates might be expressed in neuropeptide systems which have emerged in rodent studies as important candidates for a unique social biology—oxytocin and vasopressin.