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C. Sue Carter

PNAS 2005;102:18247-18248; originally published online Dec 12, 2005;
doi:10.1073/pnas.0509376102

This information is current as of November 2006.

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The chemistry of child neglect: Do oxytocin and vasopressin mediate the effects of early experience?

C. Sue Carter*

Brain Body Center, Department of Psychiatry, University of Illinois at Chicago, Chicago, IL 60612

Research described in a recent issue of PNAS by Wismer Fries, Ziegler, Kurian, Jacoris, and Pollak (1) reveals significant group differences in two brain-derived neuropeptides, oxytocin and vasopressin, between family- versus orphanage-reared children. These intriguing results may stimulate a new chapter in the ongoing scientific dialogue concerning the neurobiological effects of early experience.

Fascination with the developmental effects of social deprivation is not new. Consider Romulus and Remus, the legendary founders of Rome who were purportedly nursed by a shewolf; or Kasper Hauser, a mysterious 19th century German boy, believed to have been isolated from human contact from early childhood. Modern interest in the impact of maternal separation or neglect on human behavior can be traced to two proteges of Sigmund Freud, Rene Spitz and John Bowlby (2, 3), who described children reared in orphanages or by inconsistent caregivers as at risk for emotional and social disorders. Behavioral studies, including research in nonhuman primates, have documented vulnerabilities in socially deprived infants (4–6). From birth onward, social interactions are essential for normal development. In all human cultures, including nonhuman animals, we find mechanisms for transmitting social experiences from one generation to the next. These experiences may in turn alter future behavior.

Attempts to study the neuroendocrine consequences of early experience have tended to focus on changes in the hypothalamic–pituitary–adrenal (HPA) axis (7, 8). However, adrenal hormones are at best indirect measures of what is happening in the nervous system.

In the Fries *et al.* study (1), some children in both groups had oxytocin and vasopressin in the normal range, and some had low levels of these peptides. However, a significant proportion of the orphanage-reared children exhibited very low levels of peptides. It is important to note that it is too early in our understanding of human neuroendocrinology to conclude that the differences seen here were causally related to behavior. For example, it is possible that differences in oxytocin and vasopressin levels reflect metabolic

differences between children in the two groups. However, at least for oxytocin, the absence of basal differences in this study suggests that this is unlikely.

In Fries *et al.* (1), oxytocin and vasopressin were measured in urine. In theory, these peptides might have originated in tissues other than the brain. However, most of the body's oxytocin and vasopressin is produced in the hypothalamus. In this case, the bladder serves as a convenient and accessible reservoir for centrally produced peptides. The current finding is particularly compelling, because the previously orphaned children had lived in good homes for an average of nearly 3 years and were tested under apparently comparable conditions.

Ontogenetic and epigenetic processes result in variation among individuals.

Fries *et al.* (1) argue, based primarily on studies in other species, that their findings are relevant for understanding the chemistry of human social bonds. Although social bonds and attachments are hypothetical constructs and remain poorly understood, there is no doubt that the physical consequences of social bonds, and especially of their absence, can be real. Although the behavioral patterns of the children in this study were not reported, studies done in other, presumably comparable, populations suggest that some, but not all, adopted children may have problems in social relationships, as well as with emotional regulation (6, 8). Within the lifespan of a single individual, ontogenetic and epigenetic processes, including learning and different forms of cognitive and affective experience, result in variation among individuals. Of particular importance in children orphaned in early life are the age of the child at adoption and the consistency of caretakers. Humans are believed to have evolved as cooperative breeders, under conditions in which caretakers, in addition to the biological mother, were com-

mon (5). But even the resilient and highly flexible human infant needs some social predictability and support to prosper.

The capacity to form social bonds is not limited to humans (9, 10). The mechanisms underlying social bonds are ancient and are based on neural circuitry and endocrine processes rooted deep in mammalian evolution (5). Difficulties with emotional regulation or the management of reactions to stressors also may be associated with atypical rearing experiences (7, 8, 11).

Oxytocin and vasopressin are only two components of broader neural and endocrine systems. However, animal research suggests that these are in fact powerful peptides, with unusually broad consequences for physiology and behavior. Studies in socially monogamous mammals, such as prairie voles, have implicated both oxytocin and vasopressin in the formation of social bonds, including research using behavioral, physiological, and molecular methodologies (12, 13). These same peptides also play a developmental role in the regulation of the HPA axis and could directly or indirectly influence emotionality or social behaviors (14). Oxytocin, in particular, is capable of down-regulating the HPA axis, and this effect applies to both rodents and humans (9, 15, 16). Oxytocin and vasopressin also regulate the autonomic nervous system (17). There is even recent evidence that oxytocin can increase the capacity of individuals to show trust (18).

If availability of either oxytocin or vasopressin is abnormally low, this might plausibly be associated with a reduced capacity to form social bonds and to manage stressful experiences (9). The release of oxytocin and vasopressin and the effects of these peptides on other neural systems are sensitive to the social and endocrine history of the individual (14). Physical states and reactions of the body, including the status of the central and autonomic nervous system, can influence the readiness of an individual

Conflict of interest statement: No conflicts declared.

See companion article on page 17237 in issue 47 of volume 102.

*E-mail: scarcer@psych.uic.edu.

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to engage in social behaviors, form social bonds, and regulate reactivity to social and physical challenges (17). It is possible that atypical social behaviors or a reduced capacity to manage emotional experiences, and even unusually low levels of oxytocin and vasopressin, are related to disturbances in neuroendocrine systems. However, the group differences reported here also may reflect differ-

ences in the capacity of orphaned children to react to novel experiences, such as the presence of a stranger in the home or being the subject of an experiment. These studies reinforce the notion that children with a history of neglect face special challenges and need extra support. Clearly, further research is needed relating individual differences in peptides to differences in behavior,

along with a deeper understanding of the behavioral reactivity of at-risk children.

As with most aspects of human biology, neuropeptides are not destiny. However, documentation of differences, such as those reported by Fries *et al.* (1), moves us one step closer to recognizing the biological substrates underlying human behavior.

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