Developmental Cognitive Neuroscience 1 (2011) 77–87

Contents lists available at ScienceDirect

Developmental Cognitive Neuroscience

journal homepage: http://www.elsevier.com/locate/dcn

Adult depression-like behavior, amygdala and olfactory cortex functions are restored by odor previously paired with shock during infant's sensitive period attachment learning

Yannick Sevelinges[a,b], Anne-Marie Mouly[a], Charlis Raineki[b,c,d,e], Stéphanie Moriceau[b,c,d,e], Christina Forest[b], Regina M. Sullivan[b,c,d,e,*]

[a] Laboratoire Neurosciences Sensorielles, Comportement, Cognition, UMR 5020, CNRS-Université Lyon 1, Lyon, France
[b] The University of Oklahoma, Zoology Department, Norman, OK, USA
[c] Emotional Brain Institute, Nathan Kline Institute, Orangeburg, NY, USA
[d] Child and Adolescent Psychiatry, New York University School of Medicine, New York, NY, USA
[e] Center for Neural Science, New York University, New York, NY, USA

ARTICLE INFO

Article history:
Received 28 May 2010
Received in revised form 28 July 2010
Accepted 29 July 2010

Keywords:
Amygdala
Infant experiences
Depression
Odor–shock pairing
Plasticity
Safety signal

ABSTRACT

Maltreatment from the caregiver induces vulnerability to later life psychopathologies, yet attraction and comfort is sometimes provided by cues associated with early life maltreatment. We used a rat model of early life maltreatment with odor–0.5 mA shock conditioning to produce depressive-like behaviors and questioned whether stimuli associated with maltreatment would restore emotional neurobehavioral function to control levels. Pups received daily novel odor–0.5 mA shock conditioning from postnatal day 8 to 12. This procedure produces a new maternal odor that controls pups' attachment behaviors. In adulthood, either with or without the infant odor, animals received a Forced Swim Test, Sucrose Preference Test or assessment of amygdala and olfactory system functioning using field potential signal evoked by olfactory bulb paired-pulse electrical stimulation. Following neonatal odor–shock pairings, but not unpaired controls, adults without the odor present showed increased depression-like behavior in the Forced Swim Test and Sucrose Preference Test and a deficit in paired-pulse inhibition in amygdala and piriform (olfactory) cortex. All effects were brought to control levels when the infant conditioned odor was presented during behavioral and neural tests. The ability of cues associated with early life maltreatment to normalize behavior and amygdala activity suggests these cues provide adaptive value in adulthood.

1. Introduction

Childhood maltreatment is associated with later life psychiatric disorders and adverse brain development (Cicchetti and Toth, 2005; Connor et al., 2003; Gunnar, 2003; Heim et al., 2009; Pollak, 2003; Rutter et al., 2006; Stovall-McClough and Cloitre, 2006; Teicher et al., 2003; Zeanah et al., 2003) and has been replicated in animal models (Cameron et al., 2005; Cirulli et al., 2009; McEwen, 2008; Sanchez et al., 2001). While this relationship is not entirely clear, maltreatment from the caregiver appears to impart

Abbreviations: aPC, anterior piriform cortex; BLA, basolateral amygdala; CoA, cortical nucleus of the amygdala; CS, conditioned stimulus; FST, Forced Swim Test; pPC, posterior piriform cortex; PN, postnatal day.

* Corresponding author. Current address: Child and Adolescent Psychiatry, New York University School of Medicine, USA.
Tel.: +1 845 398 5511.
E-mail address: Regina.Sullivan@nyumc.org (R.M. Sullivan).

1878-9293/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.dcn.2010.07.005

particularly strong vulnerability to later life psychiatric disorders, yet a strong attraction and comfort can sometimes be elicited by the cues associated with the early life maltreatment (Freud, 1919 edited in 1997; Haynes-Seman, 1987). To explore the enduring effects of early life maltreatment, we used an olfactory fear conditioning paradigm in infant rats and questioned whether the odor associated with shock is attractive in later life. We also questioned whether the presence of this specific odor could restore depression-like behavior and neurobiological functions in adulthood to control levels.

Previous work has shown that, while shock is painful to pups (Barr, 1995; Collier and Bolles, 1980; Emerich et al., 1985; Fitzgerald, 2005), early life odor–shock learning produces an odor that has similar qualities to maternal odor. Indeed, this learned odor (i) induces approach responses in pups, (ii) can support nipple attachment and (iii) attenuates both amygdala activity and fear (Barr, 1995; Camp and Rudy, 1988; Haroutunian and Campbell, 1979; Moriceau and Sullivan, 2006; Raineki et al., 2010; Roth and Sullivan, 2005; Sullivan et al., 1990, 2000). The ecological relevance of this odor pain learning has been demonstrated within the nest. Specifically, rearing pups with a mother treated with a novel peppermint odor results in pups responding to peppermint as a new maternal odor, and peppermint activates olfactory structures normally responsive to natural maternal odor (Sullivan et al., 1990). Furthermore, the natural maternal odor loses its behavioral effect on pups and no longer enhances olfactory bulb activity. This natural learning paradigm is capable of producing a new maternal odor and its neural correlates even when the mother handles her pups roughly and fails to nurse (Raineki et al., 2010; Roth and Sullivan, 2005). This attachment learning is observed throughout the vertebrate kingdom when infants are totally dependent on their parents to survive, including chicks, infant dogs, nonhuman primates and humans (Harlow and Harlow, 1965; Helfer et al., 1997; Rajecki et al., 1978; Salzen, 1979; Sanchez et al., 2001). We suggest that this attachment system permits altricial animals to easily form a repertoire of proximity-seeking behaviors to the primary caregiver, regardless of the quality of the care they receive (Hofer and Sullivan, 2008). This early life maternal odor retains its value in pups as they mature. Specifically, the odor enhances sexual (Fillion and Blass, 1986; Mainardi et al., 1965; Marr and Gardner, 1965) and maternal behavior (Shah et al., 2002), influences mate choice (Moore et al., 1996) and can attenuate fear learning and amygdala activity (Sevelinges et al., 2007, 2008). Thus, the odor appears to retain value into adulthood, although the behaviors it controls change from mother–infant interactions to behaviors important in adulthood.

While this early life shock conditioning appears beneficial by producing an odor that enhances interaction with the mother, other work suggests that early life stressors and shock have detrimental effects later in life and impact many brain areas, including the amygdala (Anisman et al., 1998; McEwen, 2003; Ressler and Mayberg, 2007). Specifically, a myriad of early life stress paradigms produce depressive-like behaviors as measured by increased time spent immobile in the Forced Swim Test (FST; Porsolt et al., 1977) and decreased sucrose consumption (Papp et al., 1991). Therefore, we next questioned whether early life odor–shock pairing, similar to other early life stressors (Cirulli et al., 2009; Ladd et al., 2000; Pryce et al., 2005), would induce depressive-like behaviors and disrupt amygdala function.

Furthermore, recent work has shown that depressive-like behaviors and related abnormal amygdala activity could be normalized with the presentation of a safety signal at levels comparable to the administration of the antidepressant fluoxetine (Muigg et al., 2007; Pollak et al., 2008; Roche et al., 2007). Interestingly, safety signals have also been shown to attenuate amygdala activity (Rogan et al., 2005). Here, we capitalized on these recent findings and questioned whether the odor paired with shock in infancy, which took on characteristics of the maternal odor (Raineki et al., 2010), might later function as a safety signal to normalize depressive-like behavior and amygdala activity in adulthood. In support of this hypothesis, we recently reported that this infant odor paired with shock retains its value with maturation and can attenuate fear learning and its related amygdala activity (Sevelinges et al., 2007, 2008).

In summary, we hypothesized that early life paired odor–shock results not only in later life depressive-like behaviors and amygdala dysfunction, but also supports positive associations to cues (i.e. odor) paired with adversity (i.e. the shock) because of the infant's unique learning attachment system. We test this hypothesis by pairing shock with a novel odor in infancy and assessing the ability of the odor to normalize adult depressive-like behavior, amygdala function and olfactory structures.

2. Material and methods

2.1. Subjects and husbandry

Male Long Evans rats ($n = 166$) were born in the respective institutions' animal care facilities from dams housed in polypropylene cages (34 cm × 29 cm × 17 cm) lined with abundant pine shavings, ad libitum food and water, and kept in a temperature (23 °C) and light (from 7:00 am to 7:00 pm) controlled room. Mothers were either purchased pregnant (France) or bred (USA) in the facilities. The day of parturition was considered postnatal day (PN) 0 and culling of litters to 12 pups occurred on PN0–1. To prevent litter effects on statistical analysis, no more than one male from a litter was used in an experimental conditioning/testing condition. Institutional approval was received for all procedures, which followed the National Institute of Health (USA) and European guidelines (France). An overlap in personnel conditioning/testing both infant and adult rats in both France and the USA ensured consistency of conditioning and testing of infant and adult animals between labs.

2.2. Infant odor–shock conditioning with peppermint

PN8 pups were assigned to one of the following experimental groups: Paired odor–shock ($n = 66$), Unpaired