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Serotonin, motivation, and playfulness in the juvenile rat

Stephen M. Siviy*, Loren M. Deron, Chelsea R. Kasten

Department of Psychology, Gettysburg College, Gettysburg, PA 17325, USA

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ABSTRACT

The effects of the selective $5HT_{1A}$ agonist 8-OH-DPAT were assessed on the play behavior of juvenile rats. When both rats of the test pair were comparably motivated to play, the only significant effect of 8-OH-DPAT was for play to be reduced at higher doses. When there was a baseline asymmetry in playful solicitation due to a differential motivation to play and only one rat of the pair was treated, low doses of 8-OH-DPAT resulted in a collapse of asymmetry in playful solicitations. It did not matter whether the rat that was treated initially accounted for more nape contacts or fewer nape contacts, the net effect of 8-OH-DPAT in this model was for low doses of 8-OH-DPAT to decrease a pre-established asymmetry in play solicitation. It is concluded that selective stimulation of $5HT_{1A}$ receptors changes the dynamic of a playful interaction between two participants that are differentially motivated to play. These results are discussed within a broader framework of serotonergic involvement in mammalian playfulness.

1. Introduction

Play is a fundamental neurobehavioral process that is shared widely among the juveniles of most mammalian species, several avian and reptilian species, and even among some invertebrates (Burghardt, 2005; Fagen, 1981; Pellis and Pellis, 2009). Play has been particularly well characterized in the rat (Panksepp, 1998; Panksepp et al., 1984; Pellis and Pellis, 2009; Trezza et al., 2010; Vanderschuren et al., 1997) and shows a distinctive ontogenetic trajectory, appearing in the behavioral repertoire shortly after independent locomotion begins, peaking at around 35 days of age and then steadily decreasing as puberty approaches (Meaney and Stewart, 1981; Panksepp, 1981; Small, 1899). At its peak, play in the rat accounts for about 3–6% of the daily energy budget and about 3% of the time budget (Siviy and Atrens, 1992; Thiels et al., 1990). There is good evidence that a playful phenotype is heritable as robust differences have been reported between different strains of rats (Ferguson and Cada, 2004; Siviy et al., 1997, 2003, 2011) and between rats that have been selectively bred on other related components such as affective vocalizations (Brunelli et al., 2006) and susceptibility to amygdala kindling (Reinhart et al., 2004, 2006).

Play is a highly regulated behavior and, in rats, levels of play are exquisitely sensitive to how long it has been since a previous opportunity to play (Panksepp and Beatty, 1980). Rats that have been isolated for 4 h will play more than rats that have not been isolated, while rats that have been isolated for 24 h will play more than rats that have been isolated for 4 h. Play is also affectively positive (i.e., it is fun for the participants). For example, rats will readily learn to navigate a maze where an opportunity to play is the reward (Humphreys and Einon, 1981; Normansell and Panksepp, 1990) and will show a clear preference for a context previously associated with play (Calcagnetti and Schechter, 1992; Douglas et al., 2004; Trezza et al., 2009b). Rats will also emit short (<0.5 s) bursts of high frequency (~50 kHz) vocalizations when playing and when placed in a context where they have previously played (Knutson et al., 1998a,b) and these types of vocalizations have also been observed in other affectively positive states (Burgdorf et al., 2000, 2001, 2008; Burgdorf and Panksepp, 2001; Knutson et al., 1999; McIntosh and Barfield, 1980). Taken together,

* Corresponding author. Tel.: +1 717 337 6180; fax: +1 717 337 6172.
E-mail address: ssiviy@gettysburg.edu (S.M. Siviy).

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these data suggest that play is a stable behavioral phenotype among most mammals and likely arises from activity in specific neural circuits that are sensitive to motivational and affective processes.

At the neurochemical level, several neurotransmitters have emerged as strong candidates for modulating play. Among these, a specific role for endogenous opioid and cannabinoid systems are particularly prominent. Endogenous opioids are released in many areas of the brain during play (Panksepp and Bishop, 1981; Vanderschuren et al., 1995c) while low doses of morphine increase play and opioid antagonists decrease play (Niesink and Van Ree, 1989; Panksepp et al., 1985; Trezza and Vanderschuren, 2008b; Vanderschuren et al., 1995a,b, 1996). Compounds that prevent the breakdown or reuptake of endogenous cannabinoids once released into the synapse also increase play (Trezza and Vanderschuren, 2008a,b, 2009), suggesting that a subset of cannabinoid synapses are active during play and that prolonging activity in these synapses makes rats more playful. There is also considerable overlap between opioid and cannabinoid involvement in play as increases in play following enhanced endocannabinoid signaling or with morphine can be blocked by either opioid and cannabinoid CB1 antagonists.

Brain monoamines have long been thought to be involved in the modulation of play. Indeed, one of the first pharmacological studies using play as a measure showed that low doses of psychomotor stimulants such as amphetamine and methylphenidate are very potent in reducing play (Beatty et al., 1982). Given the extent to which dopamine is well known to be involved in other motivational and affective processes it is not surprising to find the imprint of dopamine on play behavior as well. Dopamine utilization increases during play bouts (Panksepp, 1993), dopamine antagonists uniformly reduce play (Beatty et al., 1984; Niesink and Van Ree, 1989; Siviy et al., 1996), and neonatal 6-OHDA lesions impair the sequencing of behavioral elements during play bouts (Pellis et al., 1993). While it has been difficult to obtain consistent increases in play with dopamine agonists (Beatty et al., 1984; Field and Pellis, 1994; Siviy et al., 1996) increases in play following alcohol, nicotine, and indirect cannabinoid agonists can all be blocked by silent doses of dopamine antagonists (Trezza et al., 2009a; Trezza and Vanderschuren, 2008a). These data suggest that play is associated with increased release of dopamine (Robinson et al., 2011), and it has been suggested that an optimal level of dopamine functioning is necessary for play to occur (Trezza et al., 2010).

Both norepinephrine and serotonin have fairly extensive and diffuse projections throughout the forebrain and a specific role for norepinephrine was initially indicated from findings that selective alpha-2 noradrenergic antagonists can increase play while alpha-2 agonists reduce play (Normansell and Panksepp, 1985a; Siviy et al., 1990, 1994; Siviy and Baliko, 2000). A specific role for alpha-2 receptors is also indicated by the finding that reductions in play following methylphenidate can be reversed by a silent dose of the alpha-2 antagonist RX821002 but not by either an alpha-1 or beta antagonist (Vanderschuren et al., 2008). Vanderschuren et al. (2008) also reported that the play-disrupting effects of methylphenidate could be mimicked by the selective noradrenergic reuptake inhibitor atomoxetine but not by the selective dopamine reuptake inhibitor GBR12909. These data suggest that increased synaptic availability of NE is incompatible with play and this is apparently due to action at post-synaptic alpha-2 receptors.

Serotonin is thought to have considerable impact on a wide range of neurobehavioral processes including affective regulation (Dayan and Huys, 2009; Hariri and Holmes, 2006), establishing and maintaining dominance (Huber et al., 2001; Raleigh et al., 1991), and defensive behavior (Blanchard et al., 1998; Graeff, 2002), to name just a few, so it is very likely that serotonin may also be involved in at least some aspect of play. Indeed, augmenting serotonin functioning through acute treatment with either fluoxetine or MDMA ("Ecstasy") reduces play (Homberg et al., 2007; Knutson et al., 1996). Homberg et al. (2007) reported less play among serotonin transporter knockout rats as well. Although these data would suggest that enhanced serotonergic functioning is incompatible with play, a more complex pattern emerges when only one rat of a pair is treated and attention is paid to the reciprocal interactions between the two rats of the testing pair. When rats were allowed to establish a dominance relationship such that one rat accounted for more pinning than the other (this being the dominant rat) the effects of either fluoxetine or serotonin depletion depended on the status of the rat that was treated. Augmenting serotonin levels through fluoxetine reduced the pinning asymmetry when the dominant rat was treated (Knutson et al., 1996) while depleting serotonin enhanced the pinning asymmetry (Knutson and Panksepp, 1997). Interestingly, these effects were largely due to changes in the behavior of the untreated partner towards the treated partner. Also, treating the subordinate rat had no effect on the pinning asymmetry and playful solicitations were not affected in this set of experiments. These data suggest a more subtle role for serotonin in modulating play behavior that may be more sensitive to interactive cues between the play partners.

In addition to having extensive projection throughout the forebrain, there is also considerable diversity in the receptor mechanisms associated with serotonergic functioning. There are believed to be at least 14 different receptor subtypes for serotonin (Martin and Humphrey, 1994; Millan et al., 2008) although the $5HT_{1A}$ receptor is the best characterized of these. The $5HT_{1A}$ receptor is located at both pre-synaptic and post-synaptic sites and many of the behavioral effects associated with stimulation of this receptor are generally ascribed to a reduction in 5HT release due to stimulation of somato-dendritic autoreceptors (Carboni and Di Chiara, 1989; Hjorth et al., 1982) although stimulation of post-synaptic $5HT_{1A}$ receptors may also reduce 5HT cell firing and release as well through an indirect feedback pathway (Sharp et al., 2007). In either case, the net effect of stimulating $5HT_{1A}$ receptors is a reduction in serotonin neurotransmission. As the prototypical agonist for the $5HT_{1A}$ receptor (Hjorth et al., 1982), the behavioral effects of 8-OH-DPAT have been studied most extensively, yet the effects of this compound on play have not been well characterized. While the complexity of $5HT_{1A}$ receptor