Neuronal serotonin in the regulation of maternal behavior in rodents

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Maternal behavior is probably the most important pro-social behavior in female mammals, ensuring both the development and survival of her offspring. Signals driving maternal behaviors are complex and involve several brain areas, most of which are innervated by serotonin. Serotonin transmission influences maternal processes indirectly through release of maternally-relevant hormones such as prolactin, oxytocin and vasopressin, but it can also have more direct effects on survival and the growth rate of offspring, as well as on maternal care, aggression and pup killing. This article aims to examine the basics of the components of maternal behaviors in rodents and the neural systems underpinning these maternal responses with special emphasis on the role of neuronal serotonin in the regulation of these behaviors.

Keywords: serotonin; maternal behavior; TPH2; TPH2 knockout; rats; mice

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Introduction

Maternal behavior is probably the most important pro-social behavior of the mammalian mother, ensuring both the physical and mental well-being [1] and development of her offspring [2].

Most rodents belong to the so-called “altricial” species (immobile at birth), where mothers build a nest in which they give birth to a large number of young that have very limited sensory and locomotor abilities [3]. Newborn pups of rats and mice are born hairless, incapable of temperature regulation, with their eyelids and ear holes sealed, and with underdeveloped motor skills. In these conditions they are dependent upon the mother for thermoregulation, nutrition and protection from harm until weaning at around three weeks after delivery [4].

Maternal behavior is defined as the collection of behaviors by the mother (dam), that promotes offspring growth and survival [4, 5]. Signals driving maternal behaviors are complex and involve several brain areas. Interestingly, many of these areas involved in the regulation of maternal behavior are innervated by serotonin. Although the role of serotonin in influencing maternal processes has been primarily associated with increases in the release of maternally-relevant hormones such as prolactin and oxytocin [6, 7] more recent studies suggest that serotonin signaling surpasses an indirect regulation [8-10]. Studies have associated reductions in central serotonin transmission with significant deficits in survival and the growth rate of offspring, as well as with disruptions in maternal care and increases in pup killing [8-11].

This article aims to examine the basics of the components of maternal behaviors in rodents and the neural systems underpinning these maternal responses with special emphasis
on the role of neural serotonin in the regulation of these behaviors.

**Components of the maternal behavior repertoire in rodents**

**Recognition of their biological offspring**

In animal species, recognition between individuals is an essential requirement for any kind of further interaction. Recognition between mother and newborn is a fundamental necessity that begins with mutual interaction. This interaction starts during gestation and continues through birth, augmented by body contact and lactation [12]. Adult mice are able to discriminate between their own and alien offspring based upon olfactory, gustatory [13] and auditory cues [14]. Mice and rats under laboratory conditions do not selectively care their own young, but also retrieve alien young at a comparable age. It is possible that ready acceptance of foster young is a relic of domestication or of highly artificial laboratory breeding conditions [15]. In field conditions, these care-taking activities are shared with other females and may be related to the trait of communal nesting and nursing in feral species of mice [4]. Nevertheless, when given a choice, rat and mouse dams may retrieve their own young faster than alien pups, a preference eliminated by olfactory bulbectomy [4, 15]. Pup retrieval and huddling

Retrieving the pups into the nest is a pro-active behavior of the dam and is indicative of maternal motivation [2] and an index of maternal responsivity [5]. *Pup-retrieval behavior* occurs when a pup becomes displaced from the nest or when the dam changes the location of her nest. To retrieve, the dam moves toward the pup, often sniffing the pup before gently picking it up with her incisors, carrying it to the nest, and finally placing it there [16]. This behavior is optimally evoked by hairless pups within the first week of age [4]. Huddling pups after retrieval ensures pup covering and reduces the loss of heat during frequent periods of mother-infant separation [5].

**Pup licking/grooming**

The mother licks and grooms her pups, not only to keep them clean but to help them urinate/defecate, regulate their body temperature and stimulate their movement to allow them access to nipples and promote more efficient suckling [5]. Licking and grooming have a high impact on pups emotional and social development [2], pups responses to anxiety [5] and it is an important measure of the quality of maternal care [18]. *Pup licking* is subdivided into anogenital licking and body (general) licking. *Anogenital licking* of pups during the first two postnatal weeks is important for induction of urination and defecation [19]. The pups urine ingested by the dam, contributes significantly to her own increasing water needs that result from lactation. Pup licking, together with other forms of body contact, provides pups with *tactile stimulation* and “contact comfort”, which ultimately affect pup growth through growth hormone and corticosteroid secretion [4].

**Nest building**

This behavior consists of transporting bedding materials towards the nest or manipulating the materials to form the enclosed nest edge [4]. Non-pregnant rats and mice produce a flat nest, while females at late pregnancy make a bigger and more complex nest, termed a “brood nest”. Brood nest building starts from one to a few days before parturition, continues for the first two weeks of lactation and then it starts declining [4]. The quality of the nest will contribute to the overall success of the mother-infant interaction. A well-shaped nest that clusters the pups together will prevent the loss of body heat and will help positioning pups to gain access to the dam’s ventrum [5].

**Maternal aggression**

Maternal defense is a behavior exhibited by all dams to defend their litter against a potential threat and it manifests as a dam's aggressive behavior towards an intruder [2]. The function of maternal aggression has been suggested to protect pups from infanticide of non-parental conspecifics or usurpation of the mother’s territory by intruders [20]. In rats, the intensity of maternal aggression changes over the peripartum period: it begins the day before parturition, drops immediately after parturition, increases to a maximum in the
early lactation phase around days 4 to 7, and disappears at weaning \[18\].

**Maternal anxiety**

Changes in emotional state also occur during the postpartum period in female rodents \[21\]. Modifications in the hypothalamic-pituitary-adrenal axis during lactation are thought to reduce fearfulness and anxiety in dams, especially during the early postpartum period \[20\].

A relationship between the patterns of maternal aggression and anxiety may exist in that an increase in maternal aggression and more effective protection of the litter during early lactation might require dams to be less anxious and fearful of intruders. It may also be likely that the neurobiology underlying these two processes is similar \[20\].

**Brain areas pivotal for maternal behaviors**

**Olfactory areas**

Because mice and rats are macrosmic mammals, olfaction is a sensory modality of singular importance in the regulation of mother-infant interactions \[3\]. Rats with anosmia exhibit decreased anogenital licking behavior, maternal aggression as well as minor deficits in retrieving \[4\]. In female mice, olfactory alterations have been related to inhibition of maternal behavior \[5\], increases in pup killing \[22\] as well as decreases in arched-back nursing and licking/grooming of pups \[23\]. Vomeronasal organ (VNO) removal does not affect mouse maternal retrieving, nursing or nest building, but significantly reduces maternal aggression \[4\]. Home-cage observations of dams with a genetic depletion in the VNO channel Trpc2, show specific deficits in nest-building, suggesting a role for pup pheromones in inducing and maintaining pup-directed maternal behaviors as well as maternal aggression \[24\].

**Medial preoptic area**

The medial preoptic area (MPOA) is a well-established centre for the control of maternal behavior \[25\]. It expresses receptors of hormones that enhance parental behaviors and neurons in this area activate when a mouse or rat takes care of her pups \[4\]. An intact MPOA is required for maternal responsiveness because lesions of this area disrupt maternal behaviors such as pup retrieval, nest building, nursing and maternal aggression \[26\]. Neurons in different parts of the MPOA are activated with pup exposure \[25\] and stimulation of this brain area is sufficient to activate maternal responses \[26\]. Different subregions or neuron populations within the MPOA may influence differently specific aspects of maternal behavior \[4\]. Neural models suggest dual outputs from the MPOA that regulate maternal responsiveness: one may depress the aversion and defensive avoidance responses, whereas the other output increases the maternal responsiveness to pups \[4\].

**Bed nucleus of the stria terminalis**

The limbic bed nucleus of the stria terminalis (BNST) is considered a “super-region” for maternal behavior together with the adjacent MPOA \[2\]. Disruption in the connections of the BNST region alters maternal care \[23\] and electrical lesions in the same brain area caused virgin female rats become paternal more rapidly than control animals \[4\]. In contrast to maternal care, maternal aggression is more likely to be mediated via the BNST through oxytocin and vasopressin \[2\].

**Amygdalar complex**

In laboratory rats, lesions or suppression of the amygdala cause deficits in pup retrieval and nursing behavior \[4\]. The medial amygdala, which receives pheromonal information from the accessory olfactory bulb, appears to be a crucial component for normal activation of the maternal aggression circuitry \[26\] and was shown to mediate the suppression of maternal care and the initial avoidance responses in virgin female rats \[1\]. A number of other brain areas, many of them interconnected and involved in defensive social encounters, were also shown to inhibit maternal responses, suggesting that pup aversion may share common circuitry with defensive behavior \[1\].

**Nucleus accumbens and ventral tegmental area**

Both the nucleus accumbens (NA) and the ventral tegmental area (VTA) play a positive role in regulating the attraction related to pup stimuli and are involved in the onset of maternal behavior and maternal retrieving behavior \[4\]. Lesions in the NA have been shown to disrupt pup retrieval but not nursing pup licking or nest building \[26\]. Although these two areas are considered mostly of dopaminergic content, there is considerable evidence demonstrating that moderate to high levels of 5HT_{2A/C} receptors are expressed in the NA and VTA such that the administration of these receptor agonists were able to reverse maternal behavior deficits by possibly activating the 5-HT_{2A/C} receptors localized in these two brain areas \[27\].

**Serotonin as a fundamental regulator of maternal behavior**

**Indirect actions**

Brain areas critical for maternal behaviors in rodents include the MPOA, the BNST, the olfactory bulb and
amgydala, all of which are directly innervated by serotonergic afferents arising in the raphe nuclei of the mesencephalon [8]. This is one of the main elements suggestive of an involvement of this neurotransmitter in maternal processes.

The role of serotonin in the modulation of maternal responses has been primarily associated with increased secretion of maternally-related hormones [6, 28, 29]. Among the multiple serotonin receptors that exist in brain, at least 5HT1A, 5HT2A and 5HT2C receptors seem to mediate activation of hypothalamic-pituitary-adrenocortical function and studies have demonstrated that direct stimulation of at least these types of receptors mediate the release of oxytocin [29], prolactin and adrenocorticotropic hormone [7]. Besides the regulation of these molecules fundamental for maternal behaviors, serotonin also can influence other important parameters such as the expression of estrogen receptors [30] and the secretion of vasopressin [29]. The modulation of maternal processes by serotonin is also supported by studies of mice overexpressing the Rai1 (retinoic acid-induced) gene. These mice display growth retardation, reduced reproductive fitness and most importantly, abnormal maternal behaviors [31]. Whole-brain analyses identified a significantly impaired metabolism of serotonin in these mice, suggesting a neuronal basis for the behavioral modifications observed [31] (see Figure 1).

Direct actions

In addition to the indirect regulation of maternal processes by the serotonin system, recent studies suggest that its signaling goes beyond indirect regulation [9, 10].

TPH2 is the enzyme responsible for the synthesis of serotonin in the brain. Pups born to mothers with a genetic depletion of TPH2 have deficits in survival and body weights [8, 9]. In addition, TPH2 knockout mothers display increases in pup killing and disruptions in pup retrieval/huddling, nest building and high arched-back nursing, whereas they did not exhibit maternal aggression [8]. Strikingly, most of the behaviors used to assess maternal performance, if not all, are altered in females without brain serotonin.

Lerch-Haner and colleagues [10] used dams with a specific disruption in serotonin neuron development (Pet-1 knockout mice) and found that nurture and survival of their offspring were profoundly reduced. Furthermore, Pet-1 knockout dams showed maternal neglect accompanied with deficits in pup retrieval/huddling and nest building. However, these alterations were rescued by genetical restitution using the human ortholog of Pet-1 [10].

Both TPH2 and Pet-1 knockout dams appear to be inattentive to their young and alternated between digging/climbing behaviors and alternated traversal of the cage [8, 10]. These outcomes correlate well with the increased compulsivity and impulsivity phenotypes associated to the lack of central serotonin [32].

Pretreatment with agonists for 5HT2 receptors rescued all the maternal behavior deficits induced by antipsychotic drugs in rats. In this study, rats treated with a 5HT2 receptor agonist took a much shorter time to initiate contact with pups and retrieve their pups into the nest sites, retrieved more pups and spent more time licking their pups [27]. Similarly, the administration of agonists for the serotonin 5HT1B receptor caused increased maternal aggression in postpartum rats [33].

Several studies have been carried out to study the influence of serotonin in the regulation of maternal responses, and these include the use of pharmacological manipulations as well as transgenic models designed to target more specific elements within the serotonin system (see table 1).

Conclusion

Maternal responses in rodents include a wide variety of behaviors ranging from nursing, pup retrieval and nest building to maternal aggression. Each of these components
Table 1. Effects of serotonin manipulations on specific components of maternal behavior

<table>
<thead>
<tr>
<th>Serotonin condition</th>
<th>Pup survival</th>
<th>Pup retrieval</th>
<th>Pup huddling</th>
<th>Pup licking</th>
<th>Nursing</th>
<th>Nest building</th>
<th>Pup killing</th>
<th>Aggression</th>
<th>Anxiety-like</th>
<th>Pet-1 knockout</th>
<th>NA</th>
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<tr>
<td>SHT1A agonism</td>
<td>NA</td>
<td>↓</td>
<td>NA</td>
<td>↓</td>
<td>↓</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>[34]</td>
</tr>
<tr>
<td>SHT1A antagonism</td>
<td>NA</td>
<td>⇔</td>
<td>NA</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>NA</td>
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<td>NA</td>
<td>NA</td>
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<td>[27]</td>
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<td>NA</td>
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<td>[33,35]</td>
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<tr>
<td>5,7-DHT (SHT depletion)</td>
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<td>NA</td>
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<td>NA</td>
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<td>[6]</td>
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<tr>
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<td>NA</td>
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<tr>
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<td>↓</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>[10]</td>
</tr>
</tbody>
</table>

NA = Not assessed  ↑ = increased  ↓ = reduced  ⇔ = unchanged

of the maternal repertoire seems to be associated with a unique neuronal circuit, of which serotonin is a main component. Either indirectly or directly, this neurotransmitter has a profound influence in the regulation of this evolutionarily important behavior.

References

11. van Velzen A, Toth M. Role of maternal 5-HT(1A) receptor in programming offspring emotional and physical development. Genes Brain Behav 2010; 9:877-885.
dopaminergic function in nucleus accumbens in mice. Behav Brain Res 2010; 215:141-145.


27. Zhao C, Li M. The receptor mechanisms underlying the disruptive effects of haloperidol and clozapine on rat maternal behavior: a double dissociation between dopamine D(2) and 5-HT(2A/2C) receptors. Pharmacol Biochem Behav 2009; 93:433-442.


33. da Veiga CP, Miczek KA, Lucion AB, de Almeida RM. Social instigation and aggression in postpartum female rats: role of 5-Ht1A and 5-Ht1B receptors in the dorsal raphe nucleus and prefrontal cortex. Psychopharmacology (Berl) 2011; 213:475-487.


