

PRENATAL BENZYDAMINE EXPOSURE DISRUPTS MATERNAL BEHAVIOR AND POSTNATAL OFFSPRING SURVIVAL IN RATS

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Abstract: Maternal behavior is critical for offspring survival. Used for psychotropic effects, benzydamine may influence maternal behavior through its actions on the central nervous system. In this study, 6 pregnant rats received oral benzydamine every 48 hours throughout gestation, while 6 dams served as untreated controls. Maternal behavior and offspring viability were monitored for seven days postpartum, focusing on nursing, pup retrieval, licking/grooming, absence from the nest, and pup-directed aggression or infanticide. Litter size at birth was unaffected by treatment, however, postnatal survival was markedly reduced in benzydamine-exposed dams, with most mortality occurring within the first 24 hours. Treated dams exhibited impaired maternal care, including prolonged absence from the nest, reduced nursing, delayed pup retrieval, and occasional pup-directed aggression. Prenatal benzydamine exposure can impair maternal caregiving and postnatal offspring survival, highlighting the potential neurobehavioral risks of gestational exposure to compounds with central nervous system activity. These results underscore the need for further mechanistic studies to delineate the pathways underlying disrupted maternal behavior and to inform reproductive safety assessments.

Keywords: benzydamine, rat, prenatal exposure, maternal behavior, postnatal survival

1. Introduction

Postnatal maternal care is a cornerstone of mammalian reproduction, critically influencing offspring survival, growth, and long-term neurobehavioral development. In rodents, maternal behaviors encompass a range of actions, including pup retrieval, nursing, licking and grooming, nest building, and defensive behaviors toward pups. These behaviors serve multiple functions: they maintain pup thermoregulation, ensure

adequate nutrition, stimulate physiological processes such as elimination reflexes, and promote social bonding and neural development (Day and Shea, 2025). Maternal care is instinctive, but it is also shaped by neural circuits that integrate sensory input, motivation, and reward, allowing mothers to respond appropriately to the needs of their offspring (Swain et al., 2014).

During pregnancy, exposure to substances that modulate central neurotransmitter systems (dopamine, serotonin, endocannabinoids, or opioids) may lead to neuroadaptive changes (Hess et al., 2002). Sudden withdrawal after parturition can disrupt these adaptations, resulting in dysregulation of mood-related circuits and stress-response systems. This withdrawal-associated neurochemical imbalance may increase vulnerability to depressive symptoms, anxiety, and impaired maternal motivation during the postpartum period (Whiteman et al., 2014). Such effects are particularly relevant given the critical role of dopaminergic reward pathways, serotonergic regulation, and oxytocin signaling in both mood regulation and maternal behavior. Adaptations in reward-related behaviors and mesolimbic dopamine function during motherhood and the postpartum period (Rincón-Cortés et al., 2020). Consequently, postpartum deprivation from psychoactive substances may represent an underappreciated risk factor for postpartum depression and associated disturbances in maternal care.

Pharmacological exposures during gestation can disrupt neural and neuroendocrine systems potentially leading to long-lasting alterations in maternal care (Franks et al., 2020). Benzydamine is a non-steroidal anti-inflammatory drug with a multimodal pharmacological profile, including anti-inflammatory activity, voltage-gated sodium channel blockade, and modulation of dopaminergic, serotonergic, and endocannabinoid signaling. It has also been reported to exhibit psychotropic effects in humans and animal models, likely due to its ability to influence central neurotransmitter systems (Ősz et al., 2023). Given that maternal behavior relies on the precise balance of these systems, prenatal benzydamine exposure may interfere with the development or function of

maternal neural circuits, thereby altering postnatal caregiving behaviors.

The present study was designed to investigate the impact of prenatal benzydamine exposure on postnatal maternal behavior in rats. A range of maternal behaviors, including nursing, pup retrieval, licking/grooming, nest attendance, and pup-directed aggression, over the first seven days postpartum, a critical period for offspring survival and maternal-infant bonding were assessed. Litter size at birth, pup viability, and postnatal survival were also monitored to distinguish between effects arising from fetal toxicity and those stemming from disrupted maternal care. Understanding how gestational exposure to pharmacologically active compounds such as benzydamine affects maternal behavior is essential for evaluating reproductive and neurobehavioral safety.

2. Materials and Methods

The experiment was performed on white female Wistar rats ($n = 12$), aged 10-12 weeks at the time of mating. The animals were housed under standard laboratory conditions (temperature $21 \pm 2^\circ\text{C}$, relative humidity $50 \pm 10\%$, 12 h light/12 h dark cycle), with free access to food and water. Following confirmation of pregnancy, the females were randomly assigned to two experimental groups: a treated group ($n = 6$), which received benzydamine (B1-B6), and a control group ($n = 6$), which received the vehicle (C1-C6). All experimental procedures were approved by the Scientific Research Ethics Committee of UMFST “G.E. Palade” Târgu Mureş (Approval no. 2073 / 15.02.2023) and were conducted in accordance with Directive 2010/63/EU on the protection of animals used for scientific purposes.

Benzodiazepine was administered orally by gavage every other day throughout gestation at a dose of 261 mg/kg, calculated based on doses

reportedly used for recreational purposes in humans and calculated using the dose conversion method described by Nair and Jacob, 2016. The control group received an equivalent volume of vehicle.

After parturition, each dam was housed individually with her litter. For each female, the total number of pups at birth and the survival rate of the offspring up to postnatal day 7 were recorded.

Maternal behavior was observed and analyzed over a 7-day postpartum period, corresponding to the phase of maximal parental activity. All observations were conducted under quiet conditions and at the same time each day to minimize circadian influences.

Maternal behavior was assessed by direct observation (2 hours / day, same time) during the first 7 postpartum days. Instances of maternal neglect, offspring rejection (e.g., active pushing away or absence of nursing), and potential episodes of infanticide (defined as active attacks on the offspring) were recorded. Throughout the observation period, the nests were not disturbed to avoid interference with maternal behavior.

On postnatal day 7 (PND7), pup retrieval behavior was assessed. Each dam was briefly removed from the nest, after which the pups were evenly distributed throughout the home cage. The dam was then returned to the cage, and the number of pups retrieved to the nest as well as the latency to retrieve each pup were recorded during a 15-minute observation period.

3. Results and Discussions

Litter size at birth, offspring viability and postnatal survival

As seen in **table 1**, there were no meaningful difference in litter size at birth, suggesting benzydamine did not affect prenatal gestation outcome.

In the benzydamine-treated group, a marked reduction in offspring viability was observed. Complete postnatal loss of all live-born pups within 24 h of birth occurred in 3 out of 6 litters. Consequently, the postnatal viability index (PND0–PND1) showed high inter-litter variability and was substantially lower compared with the control group.

Table 1. Neonatal viability and survival in relation to litter size at birth

Groups	Animals	Total no. of live fetuses	Litter size at birth		No. of pups after day 1	Survival (%)	No. of pups after 7 days	Survival (%)
			Total live pups	Mean \pm SD per dam				
Benzydamine	1	10	65	10.8 \pm 1.7	0	49.2 %	0	47.7%
	2	11			1		1	
	3	12			12		12	
	4	13			13		13	
	5	11			0		0	
	6	8			6		5	
Control	1	9	63	10.5 \pm 1.3	9	98.4%	8	98.4%
	2	11			10		10	
	3	9			9		9	
	4	12			12		12	
	5	12			12		12	
	6	10			10		10	

The postnatal survival index (PND0–PND7) was markedly reduced in the benzydamine-treated group relative to controls. Only minimal additional pup loss was recorded between postnatal Day 1 and Day 7, indicating that most postnatal mortality occurred during the first 24 h after parturition.

Maternal behaviour during the postnatal period

Females exposed to benzydamine during gestation exhibited abnormal maternal behavior in the postpartum period compared with controls. A marked reduction in maternal care behaviors was observed, including a decreased frequency of nursing, reduced time spent in direct contact with the pups, and limited engagement in maternal grooming. In addition, prolonged periods of absence from the nest were noted, suggesting diminished maternal interest and impaired motivation to protect the offspring. In some cases, these behavioral alterations were accompanied by aggressive responses toward the pups, culminating in episodes of infanticide (**Table 2**).

Overall, these findings indicate a significant disruption of post-gestational maternal behavior in females prenatally exposed to benzydamine.

Rodents have become a widely used laboratory model for the study of parental care, with maternal behaviors commonly including pup retrieval, nursing, licking and grooming, and defensive responses toward offspring (Rilling and Young, 2014). One of the core maternal behaviors in rodents is pup retrieval, whereby the dam detects the distress vocalizations and locations of displaced pups, retrieves them, and transports them back to the nest. This behavior consists of a sequence of actions requiring intact sensory processing, motor coordination, and motivational drive. Following retrieval, the dam engages in close-contact caregiving behaviors, including nursing and licking/grooming, which serve critical functions such as thermoregulation, maternal-offspring bonding, and stimulation of pup physiological processes, including elimination reflexes (Numan et al., 2009).

Table 2. Maternal behavior parameters during the first 7 days postpartum in rats

Maternal behavior parameter	Observation window	Control	Benzydamine-treated dams during the observation period
Time spent nursing (% of observation time)	PND 0–7	80%	0–68%**
Time absent from nest	PND 0–7	<10–15% vs 35%	20–35%
Active pup rejection (pushing away, refusal to nurse)	PND 0–7	Rare to absent	1–7 events
Pup retrieval deficits	PND 7	0–1 delayed retrieval/day	Frequent delays or failure
Infanticidal behavior (active attacks)	PND 0–7	Absent*	50% dams
Complete litter loss due to maternal behavior	PND 0–7	0%	33 %

*One control dam exhibited infanticidal behavior, resulting in the death of one pup.

**dams that exhibited infanticidal behavior spent 0% of the observation period nursing their pups. In contrast, the two dams that did not display infanticide spent, on average, 68% of the observation period engaged in nursing and other pup-directed maternal behaviors.

Prenatal pharmacological disruption of any of these systems has the potential to alter maternal motivation, bonding, and defensive or agonistic behaviors toward offspring (Fuentes et al., 2022).

Benzydamine exhibits a multimodal pharmacological profile, including anti-inflammatory activity, blockade of voltage-gated sodium channels, and modulatory effects on the endocannabinoid, dopaminergic, and serotonergic systems (Ösz et al., 2023). During the peri- and postnatal periods, the neural circuits that regulate maternal behavior, such as the medial preoptic area (MPOA), ventral tegmental area (VTA), nucleus accumbens, and the hypothalamic paraventricular nucleus (PVN), critically depend on the coordinated regulation of oxytocin and prolactin signaling and dopaminergic tone.

In the following section, we outline mechanistic considerations that may underlie the altered maternal postnatal behavior observed following prenatal benzydamine exposure and that could inform future research directions.

Our findings indicate that prenatal exposure to benzydamine is associated with alterations in maternal postnatal behavior, including impaired caregiving, prolonged absence from the nest, and, in some cases, infanticide. Given that litter size at birth was not affected, the observed postnatal offspring loss is unlikely to reflect prenatal toxicity or impaired fetal viability; however, assessment of neonatal viability at birth was limited in dams that exhibited immediate pup-directed cannibalism, as offspring were killed shortly after parturition. Instead, the pattern of early, litter-specific mortality suggests a disruption of maternal neurobehavioral regulation. Several interacting neurochemical and neuroendocrine mechanisms may contribute to this phenotype.

Based on its chemical structure and similarities to lysergic acid diethylamide

(LSD), benzydamine has been proposed to exhibit agonistic activity at serotonergic 5-HT2A receptors (Balaban et al., 2013), which has been suggested to potentially enhance dopaminergic neurotransmission in the central nervous system (Howell et al., 2015).

Dopamine signaling within the mesolimbic pathway, particularly the VTA to nucleus accumbens (NAc) circuit, is essential to maternal motivation and the rewarding properties of pup-directed behaviors. Activation of this pathway promotes pup retrieval, nursing, and sustained maternal engagement (Day and Shea, 2025). Prenatal exposure to benzydamine may induce transient dopaminergic hyperstimulation (Ösz et al., 2023) that could disrupt the finely tuned dopaminergic balance required for normal maternal motivation, resulting in either diminished caregiving behavior consistent with an anhedonia-like state or maladaptive responses such as hyperactivity or aggression. Behaviorally, this may manifest as reduced nursing postures, delayed pup retrieval, and decreased time spent in contact with offspring (Rincón-Cortés and Grace, 2020).

Moreover, 5-HT2A receptors, plays an important role in the regulation of anxiety, impulsivity, and aggressive behavior. Dysregulation of serotonergic tone can lead to behavioral instability and impaired control of emotionally salient responses (Rosell et al., 2010). Prenatal benzydamine exposure may result in abnormal activation of 5-HT2A-mediated signaling, either directly or indirectly, leading to persistent alterations in serotonergic function during the postnatal period. Such dysregulation may increase irritability, behavioral disorganization, and stress reactivity (Jagtap et al., 2023), thereby promoting inappropriate responses to pup-related cues, including neglect or directed aggression.

Stimulation of cannabinoid receptors has been also proposed as an additional mechanism

underlying benzydamine's effects (Avvisati et al., 2018; Howlett et al., 2021). In the adult maternal brain, CB1 receptor signaling modulates reward processing and anxiety, whereas CB2 receptors contribute to immune and neuroinflammatory regulation (Friuli et al., 2025). Prenatal disruption of endocannabinoid signaling by benzydamine may alter the development and later function of neural circuits underlying maternal reward and motivation. Consequently, maternal responsiveness to pup-derived stimuli may be reduced, leading to diminished caregiving behaviors and increased avoidance or disengagement from the litter (Schechter et al., 2013).

Previous studies have shown that disruption of endocannabinoid signaling can modify oxytocin receptor expression (Schechter et al., 2013). Oxytocin and prolactin are central regulators of maternal bonding, nursing, and the inhibition of offspring-directed aggression (Georgescu et al., 2021). High licking/grooming dams exhibit increased VTA oxytocin projections and greater nucleus accumbens dopamine release in response to pups, which is attenuated by VTA oxytocin antagonism (Stolzenberg et al., 2011). Oxytocin regulates social behaviors, including parenting and bonding. Pharmacological or genetic disruption of central oxytocin signaling impairs maternal care, as seen in CD38 knockout mice, whose deficits are rescued by oxytocin administration. Centrally released oxytocin during parturition and nursing facilitates maternal approach behaviors, and rodent dams typically display indiscriminate caregiving toward pups (Ross and Young, 2009).

Numerous studies have documented disruptions of the oxytocin system in depression, suggesting that investigating its role in maternal depression could inform both research and intervention strategies. Plasma

oxytocin levels are reduced in individuals with major depression and show an inverse correlation with the severity of depressive symptoms (Frasch et al., 1995; Scantamburlo et al., 2007). Third-trimester plasma oxytocin levels have been shown to predict maternal postpartum depression, while lower first-trimester oxytocin is associated with both postpartum depressive symptoms and reduced maternal attachment behaviors (Skrundz et al., 2011; Feldman, 2012).

Prenatal benzydamine exposure may increase dopaminergic activity, reducing prolactin release (Fitzgerald and Dinan, 2008) and impairing lactation and maternal caregiving behaviors (Kraus et al., 2025).

Conclusions

Prenatal benzydamine exposure may disrupt the coordinated neurochemical and neuroendocrine regulation of maternal behavior. Rather than reflecting direct fetal toxicity, the observed postnatal offspring loss appears to arise from altered maternal motivation, stress responsiveness, and social behavior. These findings highlight the importance of considering maternal neurobehavioral endpoints when evaluating the developmental and reproductive toxicity profile of pharmacologically active compounds with central nervous system effects.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

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Camil-Eugen Vari; Formal analysis, Bianca-Eugenia Ősz, George Jîtcă, Andreea Sălcudean, Camil-Eugen Vari; Funding acquisition, Bianca-Eugenia Ősz; Investigation, Bianca-Eugenia Ősz; George Jîtcă, Andreea Sălcudean, Camil-Eugen Vari; Methodology, Bianca-Eugenia Ősz, George Jîtcă; Project administration, Bianca-Eugenia Ősz; Resources, Bianca-Eugenia Ősz, Andreea Sălcudean; Software, George Jîtcă; Supervision, Bianca-Eugenia Ősz, Camil-Eugen Vari; Validation, Bianca-Eugenia Ősz, Camil-Eugen Vari; Visualization, Bianca-Eugenia Ősz, George Jîtcă; Writing – original draft, Bianca-Eugenia Ősz, George Jîtcă; Preparation, Bianca-Eugenia Ősz, George Jîtcă; Writing – review & editing Bianca-Eugenia Ősz, George Jîtcă, Camil-Eugen Vari.

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Generative AI Statement

During the preparation of this work the author(s) used ChatGPT in order to *improve language and grammar*. After using ChatGPT, the author(s) reviewed and edited the content as needed and are fully responsible for the originality and integrity of the content of the manuscript.

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