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Mouse models of emotional *postpartum* disorders

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Summary. - In women the first days *postpartum* are often associated with the onset of major emotional upheaval. Both the cause and the significance of this emotional vulnerability are largely unexplored. A complex interrelationship of emotional and endocrine factors suggests the possibility of a borderline endocrine/neurotransmitter condition, which can be precipitated to some extent by environmental factors. Increased risks are not limited only to nutritional deficiency, infections, and metabolic disorders, since several surveys have shown that women frequently take psychotherapeutic agents at some time during their pregnancy. In this frame, behavioural analysis in animal models appears to be a valuable and sensitive tool for detecting subtle alterations in CNS function, which can be produced by early exposure to psychotropic agents devoid of major teratogenic potential, be they therapeutic drugs or drugs of abuse. The approach has considerable relevance in view of the fact that all or most of the affected subjects can remain within the limits of normal variation until the time of a particular life event, such as for example, the early *postpartum* period analyzed here, with its enormous physiological and behavioural changes. The emphasis in behavioural teratology should be on naturally occurring species-typical behaviours that form an integral part of the normal behavioural repertoire. So, the series of studies reviewed here was performed with mice to assess the consequences of acute or prenatal benzodiazepine exposure, with focus on the early *postpartum* period. The role of the genotype on the sensitivity to an antiepileptic (phenobarbital) drug exposure has also been investigated. The aim was of providing significant information on the nature of changes in the female emotional repertoire, which characterizes this specific life event.

Key words: female *postpartum* behaviour; social interactions; benzodiazepines; barbiturates; GABA/benzodiazepine receptor complex; steroid hormones; mouse.

Riassunto *(Vulnerabilità emozionale postparto: modelli sperimentali nel topo)*. - I primi giorni *postpartum* sono caratterizzati nella donna da una elevata vulnerabilità emotiva, di cui sono stati tuttavia scarsamente investigati sia i fattori causali che il significato funzionale. La stretta relazione esistente tra la funzionalità endocrina e i livelli emozionali suggerirebbe la presenza di una condizione fisiopatologica psico-endocrina di tipo borderline, che verrebbe precipitata da alcune variabili contingenti associate al particolare stato fisiologico del soggetto. Tali fattori "di rischio" non si limiterebbero a possibili deficenze nutrizionali, infezioni o alterazioni del metabolismo generale, ma comprenderebbero anche l'assunzione (evento non così raro in gravidanza) di farmaci psicoattivi ad azione ansiolitico-sedativa. In questo quadro, l'analisi comportamentale su modelli animali costituisce uno strumento insieme sensibile e insostituibile per la rilevazione di alterazioni di tipo lieve a carico del sistema nervoso centrale in seguito all'esposizione durante lo sviluppo precoce ad agenti psicoattivi, a dosaggi di per sé privi di un reale potenziale teratogeno, e che sono rappresentati a seconda dei casi da farmaci terapeutici o da sostanze d'abuso. Tale approccio ha una rilevanza considerevole se si tiene conto del fatto che la maggior parte dei soggetti colpiti rientra nei limiti della normale variabilità, almeno sino all'insorgere di un quadro di eventi ad azione scatenante, quali ad es. quelli che accompagnano il periodo immediatamente postparto (con i complessi cambiamenti fisiologici e comportamentali, che gli sono propri). Partendo dalla convinzione che nell'ambito della teratologia comportamentale, le ricerche dovrebbero generalmente basarsi sull'analisi di comportamenti facenti parte del repertorio tipico della specie, la serie di studi sul topo di cui si offre qui una rassegna, è stata effettuata al fine di verifica degli effetti di trattamenti acuti o prenatali cronici con farmaci benzodiazepinici. Tali studi hanno incluso anche l'analisi del ruolo di differenze fra genotipi nella sensibilità a farmaci antiepilettici (fenobarbitale). In generale, l'enfasi è stata posta sul repertorio comportamentale della femmina che veniva analizzato durante il periodo immediatamente dopo il parto. Lo scopo finale era quello di fornire un modello sperimentale di alterazioni del livello emozionale e della socialità che caratterizzano questa particolare fase del ciclo di vita delle femmine dei mammiferi.

Parole chiave: comportamento postparto; interazioni sociali; benzodiazepine; barbiturici; complesso recettoriale GABA/benzodiazepine; ormoni steroidei; topo.

Introduction

In women the first ten days *postpartum* are often associated with the onset of major emotional upheaval. This critical phase in the life cycle is popularly identified as "*postpartum* blues" or "milk blues". The use of these terms derives from an assumed relationship between the onset of lactation (on approximately the third day) and *postpartum* depression [1]. Clinical observations also suggest that the most frequent experiential state in the puerperium is one of great vulnerability. In fact, measures of affectivity in women (i.e., self-ratings of affect) suggest a great dysphoria, and thresholds for mild depression and crying appear lower. Other specific symptoms such as fatigue, irritability, and exaggerated empathy may occur. Both the cause and the significance of the described *postpartum* emotional vulnerability are largely unexplored.

In female mammal, the study of emotional disorders in the life cycle demands attention to endocrine-behavioural interaction, since some of the most stressful events in life (i.e., pregnancy, labor or lactation) occur simultaneously with marked fluctuations in the level of circulating steroid hormones. A complex interrelationship of emotional and endocrine factors suggests the possibility that these subjects may have disturbances in steroid hormone secretion or metabolism. The rapid shifts in the levels of such hormone levels, as progesterone and estrogen, occurring at the puerperium may accentuate the metabolic abnormalities. There is evidence to suggest that progesterone is a central nervous system depressant [2, 3] and excessively high levels, unusually step gradients, abnormal progesterone metabolites, or an abnormal estrogen-progesterone ratio may produce an altered mood state. The cause could also be a borderline endocrine/neurotransmitter precipitated to some extent by environmental factors, and resulting in a phase in the female life span of functional vulnerability.

Increased risks are not limited only to medications but can also be related to other factors such as the use of alcohol, nutritional deficiency, infections and metabolic disorders. In addition to dietary supplements, psychotropic medications are commonly prescribed for women of childbearing age. Several surveys have shown that women frequently take psychotherapeutic agents such as sedatives, tranquilizers, or antidepressants at some time during their pregnancy [4].

Animal models

In the literature concerned with animal models, lactating females are reported to show altered emotional responses that are in many ways similar to those produced by acute benzodiazepine (BDZ) treatment [5], and the latter can further amplify some of these changes [6, 7]. Specifically, female rats eat more, are less fearful or anxious (see e.g. [8]), appear more reactive and freeze less in response to a sudden environmental change (i.e., an auditory signal) during lactation than during other stages of the reproductive cycle [9]. Such a profile suggests a functional shift in affective patterns to less fear-emotionality responses.

There is also evidence, on the basis of psycho-pharmacological observations in animal models (mostly rats and mice) that activity in the GABA/benzodiazepine receptor complex in specific brain areas might be enhanced during rat motherhood [10, 11]. This central neurochemical system is believed to subserve the principal behavioural effects of drugs such as benzodiazepines (BDZ) and barbiturates (PHB) that are prescribed regularly and often chronically during pregnancy and early neonatal life to prevent epileptic seizures, febrile seizures, hyperbilirubinemia, and the stressful effects of labor [4]. In addition, they have been shown to readily cross the placenta and to be secreted in the mother's milk [12] producing a well-documented series of medium- and long-term effects in the offspring (for studies of subtle behavioural changes in animal models see [13-16]).

It has been also shown that mother-pup interactions in the rat may modulate the brain GABAergic activity of lactating dams [10]. In fact, cerebrospinal fluid concentration of GABA in the mother, which profoundly influences the behaviour and the neuroendocrine phenomena associated with lactation, is markedly increased by pup-related stimuli, reaching very high levels while the mother is nursing her pups, and very low levels following pup removal [11]. Moreover, the activity of glutamic acid decarboxylase (a GABA biosynthesis enzyme) is increased in the mediobasal hypothalamus of lactating rats [17].

As concerns hormonal factors that may be involved in the changes in GABA/BDZ mechanisms during lactation, the ovarian sex steroids estradiol and progesterone are known to affect GABA/BDZ receptors in several brain areas [18]. Moreover, progesterone metabolites have been shown to increase the binding of the BDZ flunitrazepam to benzodiazepine sites, and to be potent barbiturate-like ligands of the GABA receptor complex [2, 3, 19], while progesterone produces anxiolytic effects in the female, but not in the male rat [3]. On the other hand, it is known that acute stress rapidly and reversibly affects both BDZ [20] and GABA [21] binding in the brain. Since fear/anxiety patterns are a function of the whole adaptive response displayed by animal subjects in a social interaction for example, between offspring and dam, the various physiological changes apparently fit well with the behavioural adaptations that occur during parental care.

Experimental section

In this frame, we have performed over the past years a series of experiments with mice aimed at assessing the short-, medium-, and long-term consequences in the offspring of prenatal benzodiazepine (oxazepam) exposure. The role of the genotype on the sensitivity to an antiepileptic (phenobarbital) drug exposure has also been investigated. A substantial part of the data has already been published [14, 15]. Therefore, the main purpose of the present paper is to address some interesting issues which have emerged in the course of these studies such as the finding of an altered *postpartum* emotional profile as a joint function of a history of anxiolytic drug exposure and changes in pup stimuli (fostering procedure), respectively.

The series of studies reviewed here was designed with the conviction, as suggested by Bignami *et al.* [15], that emphasis in the search for teratogenic effects should be on naturally occurring species-typical behaviour that

forms an integral part of the normal behavioural repertoire. From this viewpoint, it appears that the study of behaviour of females of altricial rodents, such as mice and rats during a specific reproductive stage (i.e., the early *postpartum* period), can contribute significant information on the nature of changes in the emotional repertoire often characterizing this specific phase in life cycle.

Female rats and mice display following parturition an organized pattern of maternal care, which includes nest building, general body and genital licking of the young, retrieval of the young to the nest, and adoption of the lactating posture over the young [22]. The display of this spectrum of maternal responses can be disrupted by dam exposure to drugs or toxicants [23, 24]. These deficits are generally attributed to the female's inability to respond maternally to the young, possibly because of a direct alteration in central nervous system mechanisms underlying maternal behaviour. However, the possible role of changes in mother-pup interactions in the production of such effects has not received much attention.

Maternal behaviour as a joint function of genotype and a history of drug exposure

Pharmacogenetic differences are known to be manifested both between and within species in the rate of metabolism of many drugs, and these pharmacogenetic factors affect their teratogenic potential. Accordingly, we used two genetically unrelated strains of mice - C57BL/6J and CBA - which are known to differ markedly in behavioural patterns (e.g. [23, 25]), in some neurochemical parameters and also in the way prenatal phenobarbital exposure affects the development of different neurochemical systems [25]. To this end, an assessment of the effects of phenobarbital (PHB) administration to the mother during gestation on the *postpartum* behaviour of the mother was carried out in both CBA and C57BL/6J mice. Dams reared litters of their own strain, composed of both treated and untreated pups, in order to provide the same amount of stimulation to the mother. This was to distinguish between the effects on the mother of previous treatment and her responses to stimuli produced by the pups. In fact, the display of maternal behaviour has also been shown to be dependent upon eliciting sensory cues provided by the pups [22, 26].

The aim of this report was a) to characterize nest-building activities (nest quality score) and maternal care in lactating C57 and CBA mouse strains and b) to examine the extent to which any differences could be attributed to strain-dependent alterations in the sensitivity to gestational phenobarbital exposure (Figs 1, 2).

Maternal behaviour of mice depends both on the age of the pups and on the previous treatment of the mother. Maternal care declined as the pups developed, but quite interestingly PHB treated dams of the CBA strain cared for their offspring for longer periods of time than untreated dams of the same strain. In particular, CBA pups received more nursing, than their counterparts, reared by control dams. PHB females of the CBA strain were also significantly less involved in activities not directly related to caring for the pups. This profile is further confirmed by the finding that maternal treatment has a significant influence even on the quality of the nest. In particular, PHB females of the CBA strain build larger, more fully enclosed, maternal nests than controls, and than PHB treated and control C57 dams (Fig. 3).

With respect to the behaviour of the C57 strain, PHB dams were on the whole less involved in maternal care. In fact, pups reared by PHB treated females received a smaller amount of nursing, licking, and nest-building activities than their corresponding control group. In this strain, the quality of the nest was not significantly affected by gestational PHB exposure.

Dam parental behaviour during the *postpartum* period as a joint function of fostering procedure and history of drug exposure

The *postpartum* period is the time of maximal interaction between the mother and her offspring, a time in which pup care is known to exert substantial and long-lasting influences on the behaviour and neuroendocrine regulations of the offspring [26, 27]. For these reasons, the usual procedure is to eliminate postnatal maternal effects by assigning at birth both treated and control litters to untreated-unhandled dams.

Our analysis focussed on the evaluation of the possible role of maternal changes or changes in mother-pup interactions in producing the effects of prenatal BDZ exposure (see review by Bignami *et al.* [15]).

The aim of this report was a) to characterize maternal care in lactating outbred CD1 mice; b) to directly assess possible effects on maternal behaviour of oxazepam (OX) administration to the mother during late gestation; and c) to verify the influence of the fostering variable by manipulation of the quality of pup-stimulation provided to the mother. In fact, the maternal behaviour of rodents is reportedly dependent upon specific sensory cues provided by the pups [26].

After parturition, entire litters were exchanged either within treatments (in-fostered groups, IF) or between treatments (cross-fostered groups, CF), while additional litters were left undisturbed (un-fostered groups, UF) (Fig. 4).

As a result, with respect to nursing responses, pups raised by oxazepam females in the UF and CF conditions (treated and control offspring, respectively) received less maternal care than those reared by control females; by contrast, treated-IF dams tended to provide a normal or even "supranormal" amount of care to treated offspring. Quite interestingly, the assignment of treated offspring

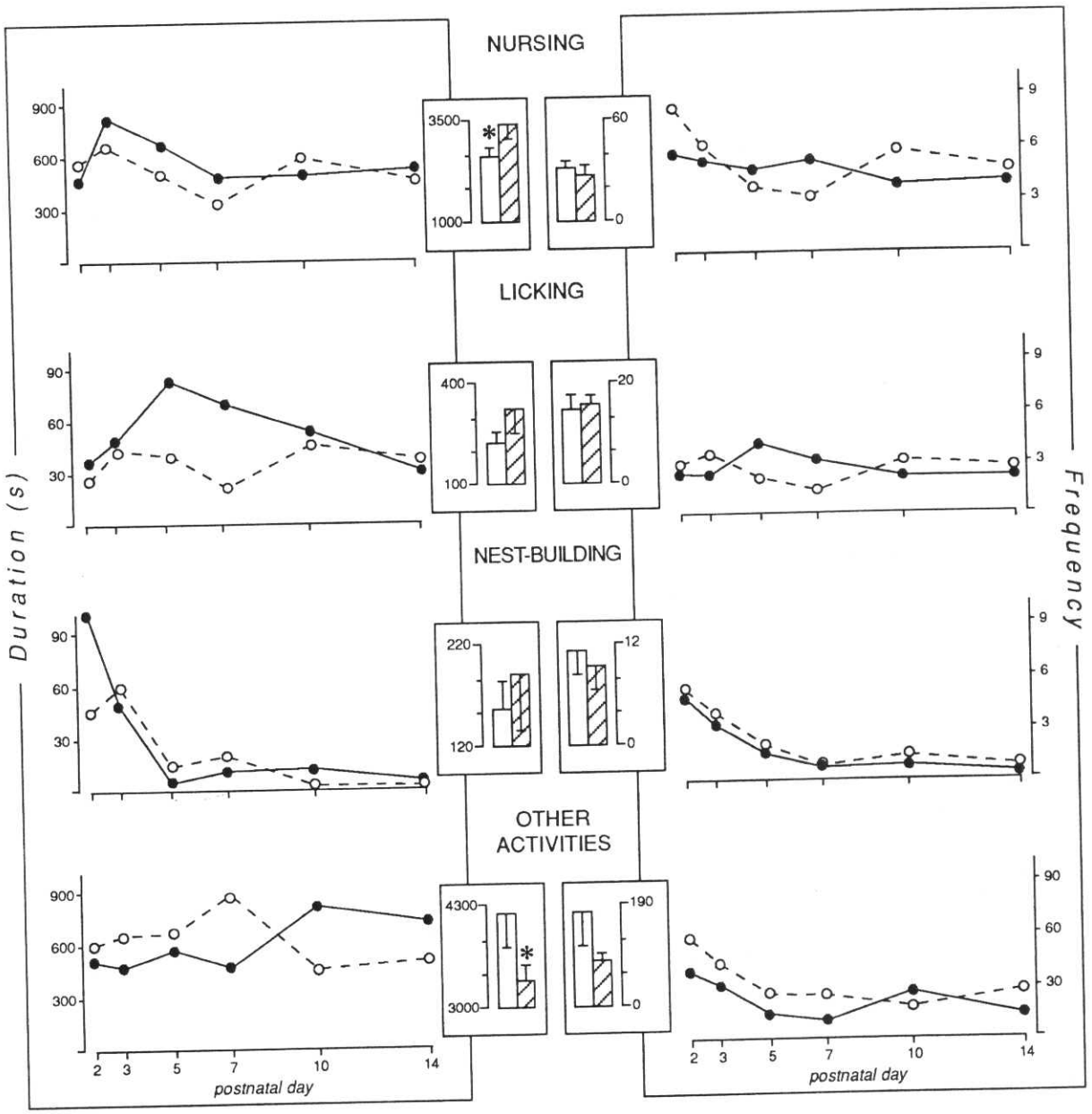

Fig. 1. - Mean duration and frequency (+SE) of nursing, licking, nest-building, and other activities observed in control CBA or C57 dams. Bar graphs (insets) represent aggregated behavioural scores (+1 SE) from six observation days (N=8). * $p < 0.05$; ** $p < 0.01$ (see text). Open (or white bars) and closed circles (or shaded bars) represent respectively mothers receiving vehicle or phenobarbital (60 mg/kg) during pregnancy (GD10-GD16).
(Reprinted from: *Psychopharmacology* **102**, by G. Laviola, K. Sedowofia, J. Innes, R. Clayton and A. Manning. "Genetic differences in maternal behaviour patterns following phenobarbital administration to mice during pregnancy", pp. 283-290, 1990, with permission from Springer-Verlag, Heidelberg, Germany).

(CF), instead of untreated offspring (IF), to control dams prevented the reduction of nursing duration observed in the IF condition. In other words, all combinations of treatment and fostering procedures of oxazepam dams and oxazepam pups showed the maximal level of maternal care or capacity to elicit maternal care. By contrast, substantial reductions of such capacities can occur with other combinations of treated and control animals.

The relation between CNS changes after BDZ exposure and changes in maternal behaviour is not simple, what needs to be explained is the nature of the interaction between behavioural and CNS variables allowing BDZ treatment in late pregnancy exert an enhancing rather than a depressing effect on maternal care when two additional conditions are satisfied: The first is the extra stimulation produced by an exchange of pups, which

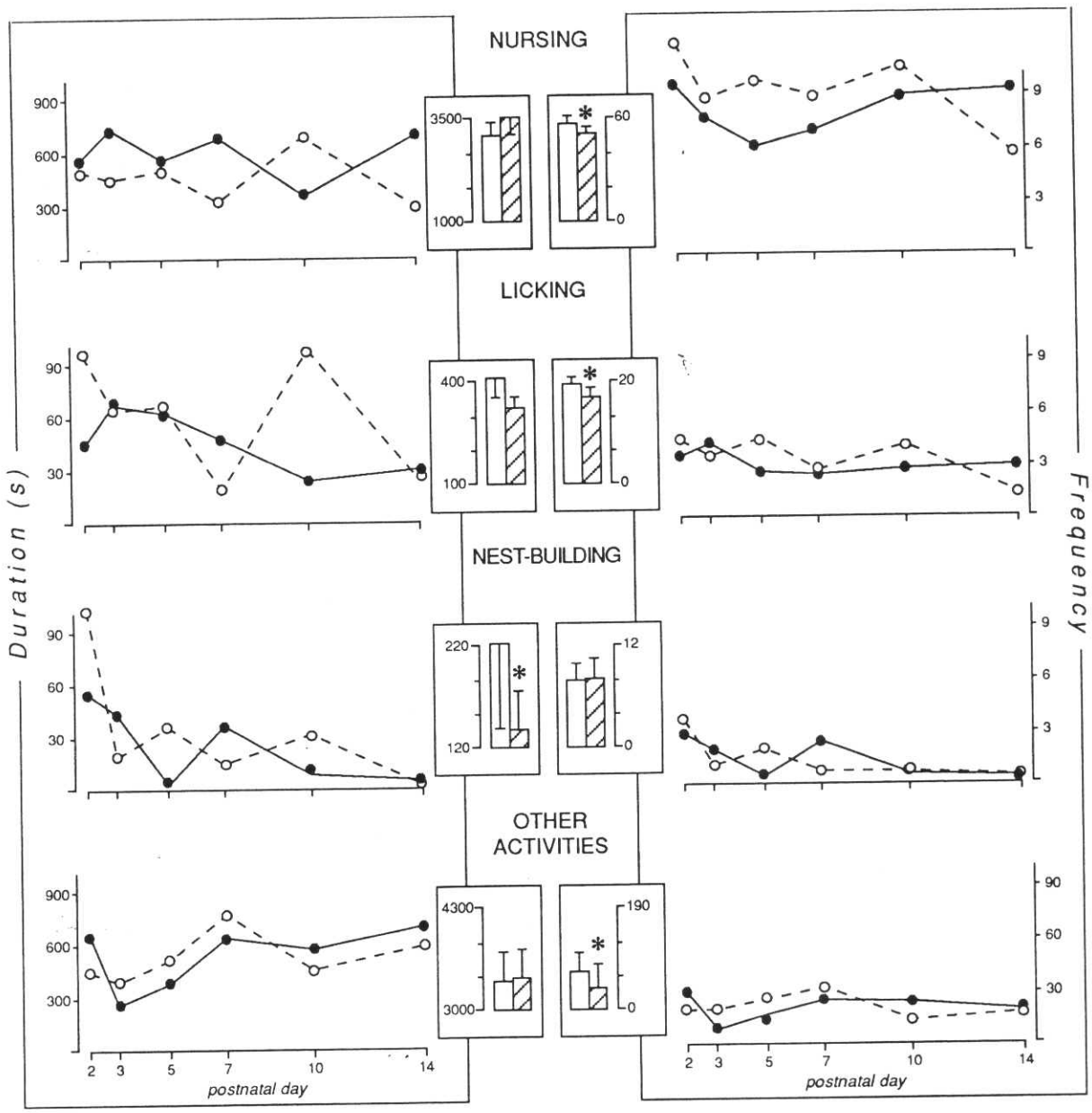

Fig. 2. - Mean duration and frequency (+SE) of nursing, licking, nest-building, and other activities observed in control CBA or C57 dams. Bar graphs (insets) represent aggregated behavioural scores (+1 SE) from six observation days (N=8). * $p < 0.05$; ** $p < 0.01$ (see text). Open (or white bars) and closed circles (or shaded bars) represent respectively mothers receiving vehicle or phenobarbital (60 mg/kg) during pregnancy (GD10-GD16).

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may have been modified by a residual anxiolytic action; the second condition is the stronger stimuli for the elicitation of maternal responses by pups with a mild inpairment in neurobehavioural development [14]; including a prolongation of ultrasonic calls in early BDZ-treated rat pups [28].

These data show that much more emphasis should be placed in behavioural teratological studies on the "experiential" context in which treatment effects acquire an additional role in the modulation of sensory functions and responses to environmental stimuli, for example using different fostering procedures (i.e., manipulation of dam- and pup-related cues). Our findings do stress the importance of the fostering variables in behavioural teratology studies, most notably the interaction between treated pups and mothers. Studies generally use only

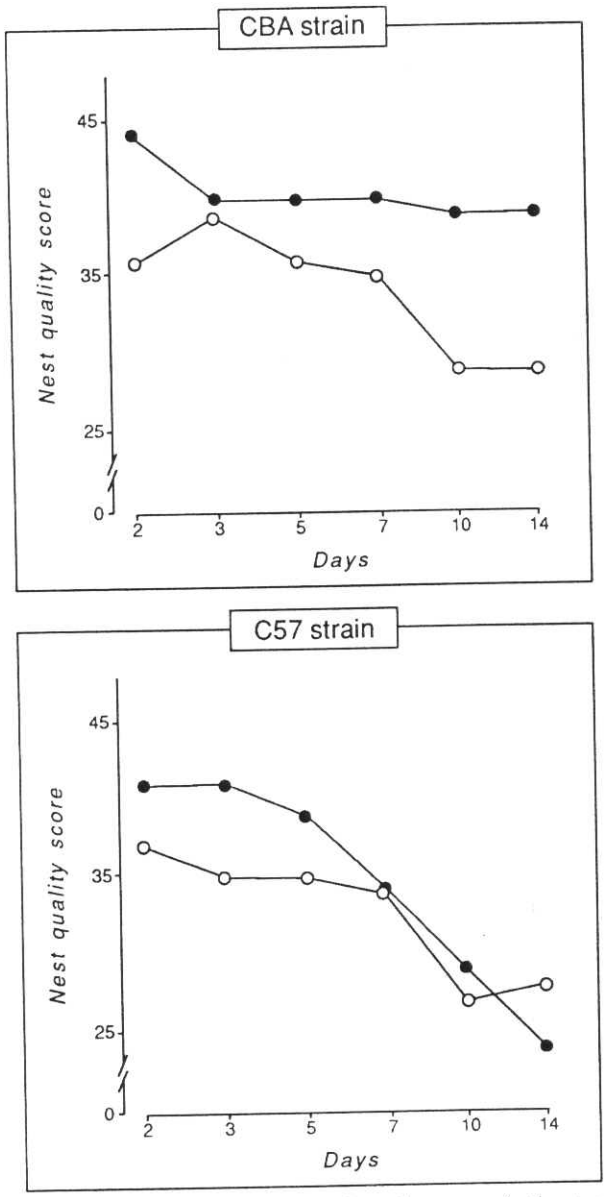

Fig. 3. - Nest rating as a function of pup age in the two mouse strains. Open and closed circles represent respectively mothers receiving vehicle or phenobarbital (60 mg/kg) during pregnancy (GD10-GD16). Data refer to the same animals of Figs 1 and 2. (N=8).
(Reprinted from: *Psychopharmacology* **102**, by G. Laviola, K. Sedowofia, J. Innes, R. Clayton and A. Manning. "Genetic differences in maternal behaviour patterns following phenobarbital administration to mice during pregnancy", pp. 283-290, 1990, with permission from Springer-Verlag, Heidelberg, Germany).

cross-fostering or fostering of both treated and vehicle pups to untreated-unhandled dams, which may also contribute to explain the variation of drug effects. Thus this study stresses the need for a better understanding of dyadic mother/pup interactions in studies aimed at characterizing early drug and toxicant effects on animal and human development.

Dam social competence during the *postpartum* period as a function of developmental BDZ exposure

Another part of our analysis was the assessment of emotional response changes in the early *postpartum* period such as those expected to be expressed in a social interaction test between adult female offspring with a histories of prenatal exposure to BDZ (using the paradigm of maternal aggression towards an unfamiliar male intruder in the nest area), as suggested by previous reports [29] (Fig. 5). In brief, lactating BDZ-mice showed a prominent enhancement of aggressive responses towards the male intruder. On the other hand, the proaggressive effect of BDZ treatment given shortly before testing was not modified in the same females [30].

Overall, the results apparently deny that the enhanced aggression was due to general changes in reactivity such as those which are usually ascribed to "hyperarousal", since the general activity level for example was not significantly modified; the basic change was rather in the relative prepotency of the various responses available within the species-specific aggressive/defensive repertoire. In particular, goal-directed (offspring-protective) responses were favoured at the expense of fear/emotionality responses.

Previous models have postulated subtle modifications in sensory functions (altered auditory temporal resolution, [31,32] in an attempt to explain some remarkable changes in fear expression and goal-directed behaviour after an early history of BDZ exposure; that is, to a modified functional value of the stimuli that contribute to the modulation of aggressive and defensive responses whose relative prepotency shows a marked variation during the animal's lifetime (e.g., in relation to the reproductive cycle).

The long-term effects of early BDZ exposure contribute to the notion that events in early ontogenesis can influence the subsequent mode of reaction at the adult to the joint influences of physiological (i.e., hormone milieu) and environmental (stimulus) variables. Therefore, it appears that an appropriate use of drugs and tests can lead to a better understanding of the mechanisms that mediate such plasticity in the behavioural repertoire, which might have considerable heuristic value and clinical-therapeutical relevance.

General discussion

As pointed out in the "Introduction", lactating altricial rodents show changes in CSF GABA levels that must be taken into account when attempting to explain the behavioural changes during the *postpartum* period [11, 17]. While the functional links between the components of the large GABA/BDZ receptor complex are still

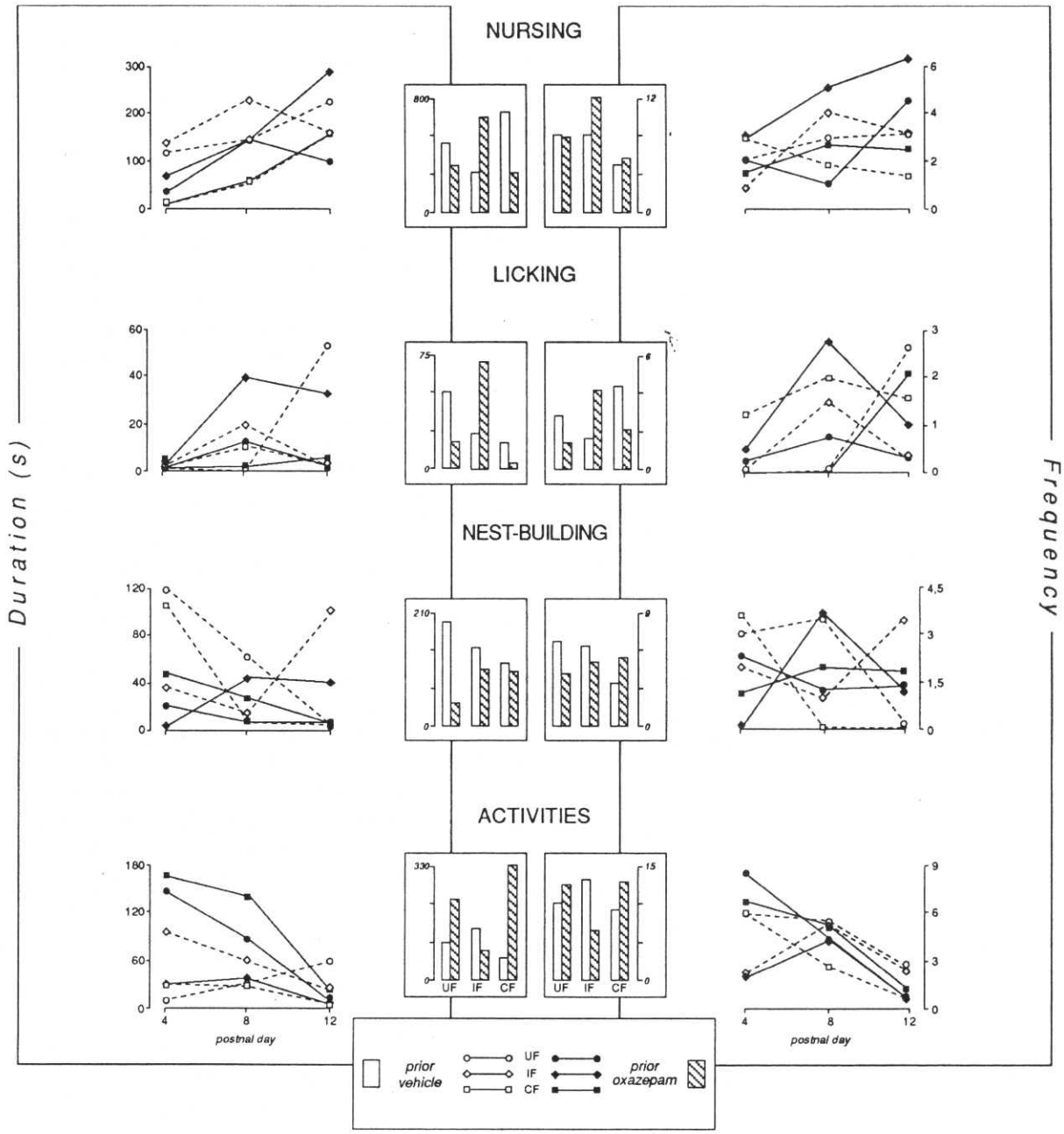

Fig. 4. - Mean duration and frequency of nursing, licking, nest-building, and activity observed in mouse dams assigned to either the un-fostered (UF), the in-fostered (IF), or the cross-fostered (CF) condition, after receiving either vehicle or oxazepam during late gestation (see text). Columns refers to data averaged over the three testing days.
(Reprinted from: *Neurosci. Biobehav. Rev.* **15** by G. Laviola, G. Bignami and E. Alleva. "Interacting effects of oxazepam in late pregnancy and fostering procedure on mouse maternal behaviour", pp. 501-504, 1991, with permission fromPergamon Press Ltd., Headington Hill Hall, Oxford OX3 OBW, UK).

poorly understood, it may have at least heuristic value to focus attention on possible functional alterations at the level of such a system when attempting to understand the effects of anxiolytic or antiepileptic agents.

A tentative explanation of our results could involve changes in the regulation of GABA systems in the CNS. Benzodiazepines and barbiturates act by facilitating GABAergic neurotrasmission [33]. It has also been shown that in the rats the presence of the pups may modulate the brain GABAergic activity of lactating dams (see "Experimental section" in the Introduction). We can therefore postulate a positive interaction between alterations in GABAergic neurotrasmission, which occurred in the dams exposed to oxazepam or to phenobarbital during their gestation on the one hand, and the enhancement in GABAergic activity associated with pup-related stimuli during lactation on the other. As a consequence we have a) changes in mother-young

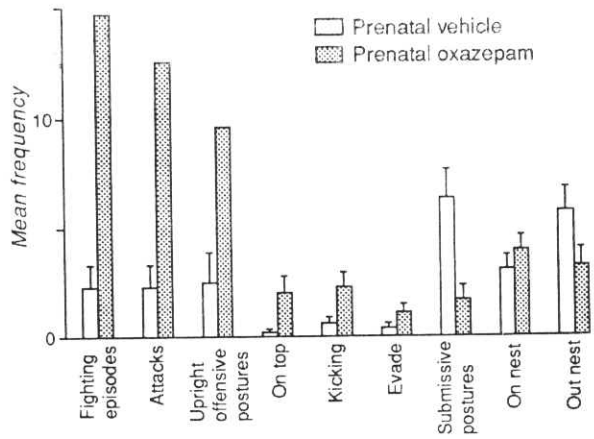

Fig. 5. - Frequencies of selected behavioural responses recorded during 5 min maternal aggression tests (nursing female mice exposed to male intruders in the presence of their litters on *postpartum* day 6). The dams had been exposed prenatally to either oxazepam administered to their mothers (15 mg/kg twice/day on pregnancy days 12-16) or to vehicle. Data are means (SEM) of 16 animals per group.

(Reprinted from: *Neurotoxicol. Teratol.* **13**, by G. Laviola, L. De Acetis, G. Bignami and E. Alleva. "Prenatal oxazepam enhances mouse maternal aggression in the offsring, without modifying acute chlordiazepoxide effects", pp. 75-81, 1991, with permission from Pergamon Press Ltd., Headington Hill Hall, Oxford OX3 OBW, UK).

interaction (i.e., more nursing behaviour) in the group of the PHB dams, the expression of which is differently mediated by the two genotypes, while b) a complex picture of changes in the capacity of the prior OX-treated dams to provide maternal care and the capacity of the OX-pups to elicit such care. More complex appear the long-term changes in maternal aggression following developmental BDZ exposure, which might be interpreted by postulating a subtle change in the balance between different responses that can be triggered by the approach/avoidance conflict created by the testing situation [34, 35]. However, a particular type of sensory change (increased startle responses in the rat [31]), that is, a subtle modification in the functional value of the various stimuli which can elicit different responses within the aggressive/defensive repertoire, should also be considered (see "Discussion" in [30]).

Also important when dealing with changes in maternal behaviour are endocrine variables: for example, nest construction and maintenance are progesterone-dependent activities in mice [36]. There is evidence suggesting a complex interaction between steroid hormones and the GABA/BDZ system in the brain [2, 3, 18, 19]; therefore, altered progesterone levels or responsivity may have contributed to the effects of gestational BDZ or PHB exposure. Progesterone-induced nesting is likely to be part of an adaptive complex of traits involved in thermoregulation. In fact, progesterone has parallel effects on body temperature and nest-building in female mice [22, 36], and the latter effect might be mediated by a thermoregulatory mechanism involving both physiological and behavioural components [36]. As well known, in several species, including rats and mice, the stimuli provided by the litter are a *conditio sine qua non* for the development and maintenance of luteal function after post-partum ovulation. Therefore, it is not unlikely that progesterone functions be affected by the stimulus variables indicated above (exchange of pups and mild pup impairment), resulting in a "supranormal" level in the OX-IF condition. At present, however, no choice can be made between a variety of possible mechanisms by which changes in progesterone functions might result in an enhancement of maternal care, including effects on milk quality or quantity, non-behavioural or behavioural thermoregulation, and neural mechanisms serving maternal responses.

Perhaps progesterone alters body temperature by raising the thermal set point defined as the body temperature at which an animal will defend, against a thermal gradient by behavioural and physiological means [36]. A rise in set point would "turn on" thermoregulatory responses such as non-shivering thermogenesis and nesting. It is possible that genetic differences in nesting and body temperature reflect genetic differences in the set point which has diverged in C57 and CBA following selection and breeding. It is also possible that genetic selection has caused divergence of set point in the selected lines (C57 and CBA strains). This might explain why C57 females did not increase nest construction and maintenance when exposed to phenobarbital during gestation. Their set point may already have been at a maximum, so that the alterations deriving from drug exposure would have had no further effect.

It is unclear at the present time how genes modulate strain-typical patterns of maternal behaviour and nest construction, but it is tempting to speculate that the genome mediates strain differences in behaviour by controlling circulating levels of progesterone and/or the sensitivity of the brain to the steroid.

Another intriguing possibility concerns the involvement of changes in the levels of thyroid hormones. A reduced clearance of TSH and of thyroid hormones was found following the administration of anticonvulsants to adult rats for seven days. Moreover, alterations of maternal behaviour were reported in rat dams receiving an antithyroid drug. In particular, nursing behaviour and nest quality scores were markedly increased by hypothyroid females. Nest-building behaviour in both male and female rats is also increased by thyroidectomy. Taken together these reports may help to understand the changes in maternal care observed in the present study (see also "Discussion" and literature in [22]).

Conclusions

As outlined by Ness and Franchina [37], an expanded view of teratogenic effects on development points to pay research attention to the animal-context synergistic process, rather than simply to those aspects of the organism that the teratogen directly affects. This therefore includes a large class of variables that have traditionally been ignored in explanations of the effects of teratogens on behaviour.

This approach may also help to solve some well-known problems in the use of animal data for clinical-toxicological, preventive, and regulatory purposes. Specifically, effects in animals and of treatment mechanisms of action must be aimed at extending the process of toxicological and teratological assessment to subtle changes that are not amenable to identification by other methods. It is now recognized that these changes can have considerable relevance in spite of the fact that all or most of the affected subjects can remain within the limits of normal variation until the time of a particular life event, such as *postpartum* period analyzed here, with its the enormous physiological and behavioural changes. Bignami *et al.* [15] outlined that this is the kind of risk which needs to be considered in the case of early exposure to psychotropic agents devoid of major teratogenic potential, be they therapeutic drugs or drugs of abuse. The indications obtained from animal studies should also prove helpful in deciding which parts of the human behavioural repertoire deserve special attention in clinical-epidemiological studies on human subjects with specified early treatment histories.

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