

Editorial

Environmental manipulations in rodents and primates: Insights into pharmacology, biochemistry and behaviour

The importance of the environment in the regulation of brain, behaviour and physiology has long been recognised in the biological, social and medical sciences. Given that environmental regulation refers of course to modulation of the central nervous system's gene expression and proteomic activity and given the marked recent advances at the genomic level resulting from the human and other species' genome projects, then we are now clearly at an important junction in the study of the causal relationships between physical and social environmental factors and behavioural and physiological phenotypes. An excellent illustrative example of the impact of the environment on brain-behaviour phenotype is provided by the recent description of equivalent influence from genes and environment on hippocampal size in the human population (Sullivan et al., 2001). The monozygotic versus dizygotic twin model was applied in a large sample of elderly twin men to examine the relative input of environmental and genetic effects on the size of the hippocampus. The results indicate heritability of aged human hippocampal volume of the magnitude of 40% and an environment-dependent determination of aged human hippocampal volume of 60%. Whilst the hippocampus, at least in terms of size/structure, is therefore more environmentally responsive than are other brain regions (e.g. the same study revealed aged human corpus callosum heritability of 80%), this study represents an elegant and dramatic example of the impact of the environment on brain structure and function. Furthermore, it interfaces human evidence with the many recent studies in rodents demonstrating how environmental factors modify hippocampal structure and hippocampus-dependent functions throughout the life span (e.g. Gould et al., 1999; Kempermann and Gage, 1999; Meaney et al., 1988; Rampon et al., 2000; van Praag et al., 1999).

In the present volume, we have brought together original data and review papers (27 in total) from a number of prominent authors active in research into the impact of environmental factors on behaviour and physiology, either directly or via modification of behavioural and physiological responsiveness to subsequent pharmacological, physiological or external environmental challenge. From the outset of this editorial exercise, it was our aim to produce a final volume that was broad and comparative in terms of species, the types of environmental factors and manipulations, the mediating central nervous system mechanisms and the beha-

vioural and physiological endpoints. Due to the very willing cooperation of the contributing authors, we have come a long way to achieving this broad, comparative aim. In terms of species, there are articles focussing on the mouse, rat (order Rodentia), tree shrew (order Insectivora), marmoset monkey, rhesus macaque (order Primates) and even the bear (order Carnivora). In terms of environmental factors and manipulations, there are articles focussing on acute or chronic effects of alcohol administration, stress hormone administration, prenatal exogenous environmental stress, spontaneous differences in the nature of the maternal behaviour received, manipulation of the infantile postnatal environment, manipulation of the postweaning environment and manipulation of the adult environment. In terms of specific CNS mediating mechanisms, there are articles focussing on corticotropin releasing factor (CRF), nerve growth factor and other neurotrophic factors. Finally, in terms of behavioural and physiological endpoints, there are articles focussing on the effects of the above environmental factors in the above species, on biogenic amine neurotransmitter function, glutamate receptor gene expression, brain nociceptin/orphanin FQ peptides, peripheral benzodiazepine receptor (PBR) activity, stress hormones and their receptors, cardiovascular activity, immune responsiveness, social behaviour, anxiety behaviour, motivation, sensorimotor gating and learning and memory.

In the mouse, Gariépy, Rodriguiz and Jones provide an elegant and important demonstration of the interactions between genetic line, postnatal manipulation in the form of handling versus nonhandling and postweaning manipulation in the form of social isolation versus social grouping on behavioural and physiological stress responsiveness in adulthood. In their article, Dierssen, Fotaki, de Lagran, Gratacos, Fillat and Estivill address the important question of neurodevelopmental differences and differences in responsiveness to handling in two mouse strains used frequently in transgenic research. In this species, the exploitation of transgenic and knockout models in terms of increased understanding of fundamental and applied aspects of gene–environment interactions is only just beginning. Furthermore, the mouse has been poorly studied with respect to the effects of environmental manipulation compared with the rat, and a large series of interesting and complementary rat papers constitute the backbone of this special issue.

Matthew J. Wayner, the founding editor of *Pharmacology, Biochemistry and Behavior*, has contributed a review of previous results and new data in support of a theoretical model of alcohol craving, which proposes interaction between tactile and taste sensory information and what is initially a nonspecific general state of motor arousal, to produce an excessive consumption or craving for ethanol. One important aspect of the model is identification of environmental circumstances that yield behavioural excess with respect to alcohol consumption, including adjunctive behaviour, electrical stimulation of the brain and salt arousal of drinking. Another important aspect is the direct effect of alcohol on chemosensitive neuronal circuits of the lateral hypothalamus. These circuits modulate the level of excitability in spinal reflexes and as such can potentially modulate reactivity to environmental stimulation. Currently, there is of course tremendous interest in the acute, medium and long-term neurobehavioural effects of perinatal environmental manipulations in the rat and the first paper using this methodology in this special issue describes a study of interactions between postnatal stress and prenatal alcohol exposure. The rationale for Zimmerberg and Weston's study was to investigate whether behavioural deficits due to prenatal alcohol exposure can be exacerbated by postnatal stress in the form of early weaning. Alcohol-exposed subjects that were weaned early demonstrated slower growth and more impaired spatial learning than did subjects exposed to either insult alone, suggesting that postnatal environmental stress can compound detrimental symptoms of prenatal alcohol exposure. Frye and Orecki also report on the long-term effects of the prenatal environment. In the case of this original research article, the prenatal manipulation constitutes exposure of the pregnant dam to restraint and bright light and female sociosexual behaviour constitutes the dependent variable. Prenatal stress decreased adult female motor behaviour in a novel arena, reduced their proceptive and lordosis activity and disrupted their pacing of sexual contacts. These effects were observed in endogenously cycling prooestrous rats but were overridden by sex steroid hormone priming.

One very controversial idea in the rat postnatal manipulation literature is that effects on maternal behaviour rather than the experience of the manipulation per se are the major mediators of the chronic effects observed on the offspring's stress-related behaviour, physiology and neurobiology in adulthood. The vast majority of the evidence on which this theory is based is derived from descriptive studies of offspring that receive different amounts of maternal care due to spontaneous differences in the behaviour of their respective dams (e.g. Caldji et al., 1998; Francis and Meaney, 1999; Liu et al., 1997). The review and original data article by Fleming, Kraemer, Gonzalez, Lovic, Rees and Melo considers the very important concept that the maternal care received by a female rat pup can also regulate the maternal care that it will demonstrate to its own pups, i.e. the transmission of maternal neurobiology and behaviour across generations. Based on a

combination of experimental and correlational evidence, it is proposed that the effects of parental behaviour on subcortical brain function appears to constitute a mechanism by which characteristics of sensory, perceptual and emotional mechanisms can be transferred from (mother) dam to (daughter) dam somewhat independently of genetic endowment and traditional learning processes.

Reflecting current interest in the relationship between early environment and behavioural neurodevelopment, a large number of contributions to this special issue describe studies based on manipulations of the infant–mother–litter relationships in rats. Before summarizing these contributions, a few general words to this complex research area are in order. Firstly, there are many forms of manipulation that are currently in use and it would seem to be essential to recognise that a large number of potentially very important variables are being manipulated differently in the many laboratories active in this area. A recent review by Lehmann and Feldon (2000) has addressed this very issue. Secondly, there is clearly a need for a framework that facilitates recognition of these variables and that provides clear and unambiguous nomenclature for the different forms of postnatal manipulation. In this special issue, we have attempted to make a contribution in this direction by using uniform nomenclature: Maternal separation is used to describe separation of the intact litter from the dam for one or more hours per day across several postnatal days and single maternal separation to describe separation of the intact litter from the dam for a single 24-h period. Infant or early combined with either isolation or deprivation is used to describe separation of the pup from the dam and the litter for one or more hours per day across several postnatal days. Early handling was the first postnatal manipulation to be investigated and its "patent form" constitutes separation of the pup from the litter and the dam for several minutes per day across postnatal days (Levine, 1957; Levine, 1960). Even here, however, basic changes have been made to the procedure whilst maintaining the same nomenclature; for example, maintenance of an intact litter and separation of this from the dam for several minutes per day across postnatal days is also commonly termed early handling (e.g. Meaney et al., 2000). Furthermore, the nature of the control group used to investigate effects of postnatal manipulations is also subject to considerable variation and indeed not inconsiderable confusion. Nonhandling has typically been used as the control for early handling and constitutes complete absence of human contact with the pups and dam across the time period during which early handling is performed (e.g. Levine, 1957; Liu et al., 1997; Pryce et al., 2001). In addition to forming the control group for early handling, nonhandling is the condition that has been used to study the relationship between spontaneous differences in maternal care and behavioural–neurodevelopmental differences in offspring (e.g. Caldji et al., 1998; Liu et al., 1997). A number of studies have demonstrated that maternal separation does not yield effects on a large number of

parameters compared with nonhandling (e.g. Caldji et al., 2000; Plotsky and Meaney, 1993). Possibly related to this, rather than nonhandling, some very recent studies have used controls experiencing the disturbance of cage cleaning—so-called animal facility rearing—as the control treatment for maternal separation and early handling (e.g. Huot et al., 2001) and have even used early handling as the control treatment for maternal separation (e.g. Maciag et al., 2002). Furthermore, recent studies that have examined cognitive effects of maternal separation have reported that it yields effects in the same direction as early handling (e.g. Lehmann et al., 2002). Accordingly, we have asked contributors to this special issue to pay due care and attention to full descriptions and rationalisation of their control groups in rat studies of postnatal environmental manipulations.

In their contribution, McCormick, Kehoe, Mallinson and Frye describe the effects of early isolation compared with nonhandling on responsiveness to restraint stress in terms of dopamine levels, locomotor activity, corticosterone and allopregnanolone in juveniles. Early isolation led to abrogation of the postrestraint increase in dopamine levels and motor activity exhibited by nonhandled rats but enhanced the corticosterone response to restraint. The allopregnanolone stimulation by restraint was unaffected by early isolation. The study by Lehmann, Weizman, Leschiner, Feldon and Gavish provides support for the hypothesis that differences in PBR binding capacity related to early handling versus nonhandling are a reflection of trait rather than state. Early handled and nonhandled Wistar rats were tested as adults in a two-way active avoidance/latent inhibition task. Thereafter, PBR densities in the adrenal glands, kidneys and gonads were assessed. Early handled rats, as expected, demonstrated enhanced active avoidance and latent inhibition. Furthermore, PBR densities were up-regulated in early handled subjects. However, there was no correlation between PBR densities and any of the behavioural measures.

The next two contributions both assess the long-term effects of high postnatal corticosterone exposure in the rat, that is, during the stress hypo-responsive period (SHRP). Biagini and Merlo Pich compared corticosterone-treated or maternally separated male subjects with controls in terms of physical maturation, sexual maturation and testicular glucocorticoid receptor (GR) immunoreactivity. Postnatal corticosterone treatment advanced testis descent and increased testis weight and β -hydroxysteroid dehydrogenase/isomerase activity and increased GR immunoreactivity in testicular tubules. The authors propose that the SHRP could function in the rat to “protect” sexual maturation from modification by glucocorticoids. Catalani, Casolini, Cigliana, Scaccianoce, Consoli, Cinque, Zuena and Angelucci investigated the effects of elevating pup corticosterone levels via the dam’s drinking water on endocrine and behavioural stress-related activity in females. The female offspring exposed to physiologically high levels of corticosterone exhibited an attenuated corticosterone stress response, reduced fearfulness and improved learning and each of these effects emerged post-

weaning. As such, postnatal corticosterone exposure leads to effects similar to early handling, leading to the interesting hypothesis that corticosterone elevation might mediate some of the effects of the early handling manipulation.

Shalev and Kafkafi report on the potential of maternal separation to alter behavioural responsiveness to natural rewards vis. a model for anhedonia symptoms of depression. Maternal separation, relative to early handling or nonhandling, had no effect on sucrose preference in a two-bottle free-choice test and no effect on operant responding under fixed or progressive ratio schedules of reinforcement in adult male Long–Evans rats. Returning to central processes, Ploj, Roman and Nylander report on the long-term effects of maternal separation on brain immunoreactive nociceptin/orphanin FQ (ir-N/OFQ) levels relative to early handling or nonhandling in male Wistar rats. In the hypothalamus and periaqueductal gray, maternal separation led to increased adulthood ir-N/OFQ levels compared with nonhandling. In terms of anxiety-like behaviour measured in the elevated plus-maze, maternal separation led to increased anxiety-like behaviour in weanlings but decreased anxiety-like behaviour in adults relative to nonhandled controls. Kalinichev, East-erling, Plotsky and Holtzman also report on long-term effects of maternal separation, specifically on stress-related and anxiety-like physiological and behavioural effects of maternal separation in male and female Long–Evans rats. Whereas this study did not reveal the typical early handling versus nonhandling effects, relative to nonhandling, maternal separation did lead to an increased stress-related corticosterone response in males, increased acoustic startle in males and increased anxiety-like behaviour in the elevated plus-maze test in females. Finally, in terms of studies of effects of specific postnatal manipulations in the rat, Lehmann, Rusing, Feldon and Pryce describe a study of the effects of a single 24-h maternal separation conducted at the beginning of (postnatal day 4), about midway into (day 9) or after (day 18) the SHRP on basal and stress-related corticosterone levels in mature (month 5) and old (month 20) adult male Wistar rats. In mature adult males, the single maternal separation led to an increase in the stress-related corticosterone response compared with animal facility-reared controls and this increase was very similar regardless of the age of the pups at which the single maternal separation was experienced. Furthermore, this effect was no longer apparent in aged males.

The next three contributions are all reviews relating to environmental responsiveness and modulation of brain function. Needless to say, stress is a major component of environmental impact on the organism and the stress concept is a major theme in these reviews. Makino, Hashimoto and Gold consider possible mechanisms underlying the persistent activation of CRF in hypothalamic and extrahypothalamic systems, a consistent characteristic of environmental stress-related disease including mood and anxiety disorders. The authors propose multiple feedback loops activating central CRF systems, namely attenuation of glucocorticoid-mediated negative feedback on the activity of hypothalamic

and brainstem nuclei during chronic stress, autoregulation of CRF biosynthesis in the hypothalamic paraventricular nucleus through up-regulation of type-1 CRF receptor, and glucocorticoid-mediated positive effects on the amygdaloid CRF system. Aloe, Alleva and Fiore present data supporting the hypothesis that stress-related events in both animal models and humans are characterized by modifications of endogenous nerve growth factor synthesis and/or utilization. They describe how, on the one hand, stress-induced alteration in nerve growth factor synthesis and/or utilization appears to be more severe during neurogenesis and in early postnatal life and how, on the other hand, nerve growth factor may promote remodelling of damaged tissues following acute or chronic stress. The review by Pham, Windblad and Mohammed considers how enriching environments comprising physical and social stimulation are beneficial to brain development and aging. Data from their own laboratory have revealed that enriched laboratory environments can increase nerve growth factor gene expression and protein levels in the hippocampus and propose that this may contribute to environmentally induced neural plasticity.

The social component of the environmental enrichment reviewed by Pham et al. typically comprises the study of social/group versus isolation rearing following weaning. Effects of this manipulation form an important component of the final five rat-based contributions of this special issue. Ellenbroek and Cools have reported previously on a schizophrenia model that constitutes deficits in prepulse inhibition induced by a single maternal separation. Here they extend this model to its modulation by the post-rearing environment. Specifically, they report that when maternally separated rats were reared in social isolation postweaning, the prepulse inhibition performance was normal. One consistently reported consequence of social isolation in the rat is a syndrome of behavioural and neurochemical effects indicative of increased mesolimbic dopamine function, including increased dopamine neurotransmission in the nucleus accumbens. The Fawn hooded rat strain exhibits the same syndrome spontaneously, i.e. in the absence of social isolation. Hall, Ghaed, Pert and Xing explore the hypothesis that these phenotypes may be the indirect result of chronic changes in glutamate NMDA receptor function. NMDA receptors were quantified in Fawn hooded versus Wistar rats following social versus social isolation rearing in the striatum, hippocampus and prefrontal cortex. Social isolation rearing was not found to affect the levels of NMDA receptors, whereas Fawn hooded rats, whether socially or isolate reared, were found to have reduced NMDA receptor levels in most brain regions examined. In some areas of the striatum and prefrontal cortex, this strain difference was greater in isolate compared with socially reared subjects, whereas in the hippocampus the reduced NMDA receptor expression of Fawn hooded rats was more marked following social rearing. In the study of Larsson, Windblad and Mohammed, the authors examine the interactions between social and isolation rearing and stress. Prior exposure to mild stress was found to

increase spatial learning in socially reared but not isolation-reared rats. Marked stress impaired spatial learning in both rearing groups but did so to a greater extent in the isolation-reared group. Schrijver, Bahr, Weiss and Würbel have contributed an original research article demonstrating the dissociable effects of isolation rearing and inanimate environmental enrichment on exploration, spatial learning and HPA activity. Whereas isolation rearing, regardless of inanimate background, mainly increased activity in response to several situations of environmental novelty, inanimate environmental enrichment, regardless of rearing environment, primarily accelerated habituation to novelty and improved spatial learning. The authors discuss the important evidence that social and inanimate environments can affect behaviour selectively, but that there also exist some discrete examples of biologically relevant interactions between social and inanimate stimulation. Fernandez-Teruel, Driscoll, Gil, Aguilar and Escorihuela examined gene line–environment interactions in a study based on the Roman high-avoidance (RHA/Verh) and Roman low-avoidance (RLA/Verh) rat lines that were reared either in pairs or in large groups of 8–10. The increased exploratory behaviour and enhanced preference for saccharin (vis. sensation/reward seeking) was confirmed in the RHA/Verh line, whereas rearing in a large group increased the preference for saccharin in the RLA/Verh line specifically. In the final rat paper, also by Fernandez-Teruel, together with Gimenez-Illort, Escorihuela, Gil, Aguilar, Steimer and Tobena, the authors present a novel appraisal of the evidence that early handling and postweaning environmental enrichment exert their effects on brain plasticity and protection against age-related deficits via common neural mechanisms, including attenuation of stress responsiveness.

The final four contributions share the common factor that they are based on non-rodent species. Fuchs and Flüge provide a review of their tree shrew chronic psychosocial stress model. Physiological (e.g. peripheral HPA and catecholamine endocrine activity and cardiovascular activity), behavioural (e.g. motor activity and sleeping patterns), neurobiological (e.g. retraction of the dendrites of hippocampal pyramidal neurons) and pharmacological (e.g. reversal of changes in the preceding parameters) effects of psychosocial stress in this species are reviewed, providing extensive evidence for its robust validity as an animal model for depression. Turning to primate studies, Dettling, Feldon and Pryce describe a study based on the rat early isolation manipulation conducted in the common marmoset monkey. The effects of this manipulation are considered at the juvenile stage, when monkeys were challenged with social separation in a novel physical environment. Early isolated subjects were less mobile and vocalized less than controls and were also less socially responsive when reunited with their parent in the novel situation. Furthermore, in a manner similar to that reported consistently for posttraumatic stress disorder, early isolated marmosets exhibited reduced basal cortisol activity. In his article on rhesus macaques, Schapiro reviews a series of studies that have examined the effects of

manipulations to the social and the inanimate environments on behaviour and cell-mediated immune responses. In general, enrichment of the inanimate environment increases species-typical behaviour but does not affect immune responses. Housing monkeys socially, on the other hand, results in increased species-typical behaviour and leads to changes in a number of immune parameters. In his summing up, Schapiro draws the important conclusion that influences of the social and inanimate environments need to be appropriately managed and/or controlled in order to minimize potential confounds in experimental designs. Finally, in a zoo rather than a laboratory setting, Renner and Lussier describe a project aimed at environmental enrichment for spectacled bears. Of course, zoo animals, just like laboratory animals, can develop profound stereotypies under restrictive environmental conditions. One message that comes across clearly from the non-rodent studies is that a comparative, across-species approach yields many advantages to the rodent-alone approach. A situation in which rodents and primates can be studied in parallel in the same laboratory is a highly desirable state of affairs, as is close collaboration of colleagues that are experienced in the same neurobehavioural system in different species.

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