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Developmental Physiology and Pathophysiology of Behaviour and Nervous Functions

J. MYSLIVEČEK

Institute of Pathological Physiology, Charles University, Medical Faculty, Plzeň

Problems of developmental physiology and pathophysiology of behaviour are being studied extensively in this country. It is impossible to give a complete review of what has been done in this field. Any selection, in spite of the maximum endeavor of objectivity, will necessarily reflect the subjective interests of the author.

If we are to show the contributions of our investigators to the area of developmental physiology and pathophysiology of behaviour, the pioneering studies of Prochaska (1782–84) who reported on the anatomical and physiological sequelae of the nature's crude experiments in anencephals should not be omitted. Babák's work (1909) on the role of ontogenetic stage in the reaction to spinal cord damage represents a further step in our research tradition. A systematic approach to these problems began in the early fifties when a "Working Group of the Development of Functions of the Nervous System" was established in the Physiological Institute of the Medical Faculty, Charles University in Prague. A further center of research appeared when the head of this group joined the Institute of Pathological Physiology of the Medical Faculty, Charles University in Plzeň. Another group of investigators in the Institute for the Care of Mother and Child in Prague started with studies of behavioural development in infants and children. Later on, related problems also began to be studied in other laboratories, e.g. in the Institute of People's Nutrition, the Physiological Institute of the Czechoslovak Academy of Sciences and other universities and research institutions.

The first international symposium on the development of nervous functions "Functional and Biochemical Development of the Central Nervous System" was held at the Medical Faculty of the Charles University in Plzeň in 1960 and was later followed by four Symposia Neuroontogenetica organized by the Medical Faculty of Charles University in Prague. Most of those who were at the beginning of these systematic studies on the development of nervous functions are still working actively, in spite of the fact that many of them had, until not too long ago, severely restricted conditions for scientific work; some others have died whereas some have left the country.

General and specific characteristics of behaviour

Everybody concerned with physiological research has to ask to what extent the obtained results can be generalized. This holds still more for ontogenetic research. It should be remembered that higher vertebrates, mammals and birds, are divided into two large groups related to their maturity at hatching or at birth: advanced precocial and less mature altricial. Even within these two basic groups, time level of maturity differs considerably. This fact is not fully recognized and respected in many developmental studies. That is, moreover, complicated by the fact that the speed of maturation in individual species varies considerably and one cannot assume any proportionality of individual developmental periods. Man is somewhere in the middle of the scale of maturity with a relatively advanced development of sensory functions and less developed motor functions. Therefore, any intention to relate a given age of an experimental object to a certain developmental stage of man is necessarily an oversimplified speculation and must be considered as a rough approximation. There are, of course, general developmental rules, but they have to be studied with respect to all the peculiarities and disproportions in any particular case.

Motor development

The development of reflexes and motor functions is being studied systematically by Sedláček. This author added to four Volokhov's stages (Volokhov 1951) – local reflexes, two stages of generalization and local specialized reflexes – three additional ones, namely inhibition of specialized reflexes and two stages of spontaneous specialized acts (Sedláček *et al.* 1961). Marked changes in spontaneous movement frequency were found in studies of embryonic motor development in chicks between days 15 and 16 of incubation and then between days 19 and 20. After day 15, motor development was maintained by spinal motoneurons that survived from embryonic overproduction due to connection with the target elements, by supraspinal control and by endogenous spontaneous activity.

Biological rhythms

It was shown in studies of sleep and waking development that after a sleep episode, relationships between excitation and inhibition were changed (Koch 1959). Various physiological sleep parameters and indicators do not develop in parallel and their mutual relationships in different periods change; development thus cannot be considered as an absolutely uniform and continual process (Dittrichová *et al.* 1982, 1988a,b, Dittrichová and Paul 1989).

Early behaviour

Polygraphic investigations (EEG, EOG, sucking, swallowing and respiration) together with behavioural analysis during feeding in human infants showed that the determining factors were not only metabolic, but also psychosocial stimulation and social communication (Paul and Dittrichová 1989a,b).

In rats, selectively bred according to a high or a low level of spontaneous activity in a novel environment, there were differences in habituation, early social interactions, changes of spontaneous behaviour and reactions to social stimuli in adulthood (Fraňková and Mikulecká 1988, Fraňková and Müllerová 1989); Wistar and Long Evans rats were compared using the authors' modification of homing reaction.

Learning and memory development

Research in this field may be divided into two basic areas: experimental work in animals and human studies. The former makes it possible to study important developmental periods of these functions during a relatively short time interval, the latter contributes to deciphering of developmental specificities in man.

In the literature, it is being reported or at least tacitly implied that learning and memory start to develop practically from zero, in adulthood reach a level at which they are maintained up to senium and then decrease again to a minimum level. In reality, this is far from being true. We were able to show that learning and memory peaked at a certain period of life, which was followed by a decrease and then a new increase. Peaks of learning and of memory of a given experimental task were not identical, they depended on the complexity of the task, on the chosen criterion, on the previous history of the animal and on the genetic characteristics (Mysliveček and Hassmannová 1987).

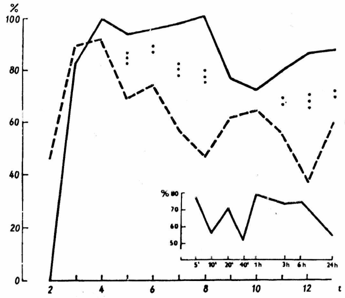

Fig. 1
A: Percentage of animals meeting the criterion of 5 consecutive conditioned reactions in one-way active avoidance (ordinate); differences between strains shown: double dots – $p<0.01$, triple dots – $p<0.001$ (Hassmannová, Mysliveček 1984); inset: memory retrieval in Wistar rats (4–6 weeks of age) at 5 min – 24 h intervals (abscissa); note W-shaped changes at 5 min – 1 h intervals (Hassmannová *et al.* 1977).

In one-way active avoidance learning (criterion of 5 consecutive avoidances), pigmented Long Evans rats had a high performance level up to the 8th postnatal week, which was followed by a short lasting regression whereas the performance of albino Wistars gradually declined from the 5th to the 8th week: after an improvement in the 9th and 10th week they deteriorated again (Hassmannová and Myslivećek 1984) (Fig. 1). In the optimum learning period (3–4 weeks of age), with a peak at 25 days, Wistar rats displayed significantly worse learning and short-term memory retrieval (Hassmannová *et al.* 1990). With a more severe criterion (9/10), learning and memory peaks shifted somewhat towards later periods of ontogeny (Myslivećek and Hassmannová 1979). During development, there was a typical inversion of the Kamin (1957) effect (good memory retrieval immediately and 24 h after learning, impaired retrieval 1–6 h after learning) between 4 and 6 weeks of age, accompanied at intervals of up to one hour after attaining the criterion, by W-shaped oscillations (Hassmannová *et al.* 1977) (Fig. 1 – inset).

In a two-way active avoidance (shuttle-box), on the contrary, a higher number of avoidances was obtained in Wistar rats (Myslivećek *et al.* 1983), which could hardly be ascribed to a better associative function. It was rather due to an increased excitatory reaction, as shown by a positive correlation between avoidances and intersignal reactions. Learning peaks at 5 and 7 weeks in Wistar and 5 and 6 weeks in Long Evans rats differed from those in one-way active avoidance.

Strain differences were also evident in appetitive conditioning (approach to an anaesthetized dam and sucking without milk consumption) in 7-, 11- and 14-day-old rat pups in dependence on nutritional, sensory and social deprivation (Hassmannová and Myslivećek 1989). After an 8-hour deprivation, 11-day-old Long Evans pups learned to approach the dam more rapidly than Wistar pups; after a 24-hour deprivation period, the pigmented pups became worse, whereas albinos did not change their performance; 14-dayold Long Evans pups approached the dam faster than the Wistar pups after a 24-hour deprivation.

Different development was found in other experimental paradigms – passive avoidance and escape from a rectangular aversively motivated maze. In a step-through passive avoidance, optimum memory was found during the 7th week (Myslivećek 1979), in a step-down passive avoidance 6-week-old rats learned and remembered best (Myslivećek and Hassmannová 1986). Escape from a rectangular maze requiring a certain level of space memory displayed a peak of learning at 8 weeks of age and one-month memory in animals taught when 13 weeks old (Myslivećek 1985).

First evidence of basic cognitive functions

The problem of the very first evidence of learning and/or memory remains exciting for those studying early manifestations of cognitive functions. By methods of alimentary conditioned reflexes (Papoušek 1961), learning in human infants was established earlier than by palpebral conditioning (Janoš and Papoušek 1966). Less intense reinforcement – in infants a weaker stream of air to the cornea – evoked (which could seem paradoxical) a greater number of conditioned reactions (Janoš 1970) similarly as weaker electric shocks in conditioned shaking in chick embryos (Sedláček 1963).

Discrimination of stimuli was possible in various mammals on the basis of habituation at early postnatal periods; it was not due to internal cortical inhibition as it took place even after decortication (Mysliveček 1957). Reactions to external stimuli in very young animals have a waxing-waning character. A similar type of reactions was common in the majority of human infants studied by the method of instrumental toy activation or preferential looking (Mysliveček 1991, Mysliveček *et al.* 1987).

It was thought impossible to elaborate an inhibitory conditioned reaction early in ontogeny because of the lack of inhibitory mechanisms, namely cholinergic ones. When, however, an appropriate method and a task not surpassing the developmental capabilities of the newborn were used, it was possible to establish an inhibitory (passive avoidance type) reaction even in such an immaturely born mammal as the rat, as early as several hours after birth (Mysliveček 1982a, Mysliveček and Hassmannová 1983). Learning this passive avoidance during the first 10 postnatal days displayed a curve of decreasing number of trials to criterion, with a temporary inversion shifted in Wistar pups a day later than in the Long Evans; short-term (up to 3 hours) and 24-hour memory retrievals were also demonstrated (Mysliveček and Hassmannová 1990, Mysliveček 1990). The short period of temporary learning impairment in rats (depending on the conditions, 2–4 days after birth) is evidently more general in character, as is shown by the impossibility to establish, at this age, a reliable conditioned instrumental reaction rewarded by warmth (Guénaire *et al.* 1982) or by the absence of conditioned rearing rewarded by a sweet solution (Pometlová and Mysliveček 1990).

Determinants and mechanisms of behavioural development

a) *External influence*. Broadly speaking, nutrition, afferent information from a whole complex of sensory modalities having impact on the individual, and influences that can be summarized as "social" belong to the most important factors determining the development of behaviour.

A critical lack of proteins in the first eight postnatal weeks retarded the behavioural development, modified spontaneous activity, affected habituation and social interactions in rats (Fraňková 1973, Fraňková and Barnes 1968a,b, Fraňková and Zemanová 1978). Early overnutrition also changed the behavioural patterns (Fraňková 1970). Undernutrition impaired early passive avoidance learning but did not render it impossible (Mysliveček 1982b). When development was compared in rat progeny from litters of various size, optimum parameters of motor as well as of higher nervous functions were found in the progeny from middle-sized litters (7–8 pups) while those from small (3–4 pups) and large (13–15 pups) litters were relatively poor (Mysliveček *et al.* 1974).

Early stimulation improved learning and memory, complex stimulation being more effective than visual stimulation alone (Mysliveček *et al.* 1974, Mysliveček and Štípek 1979). This was also reflected in the dependence on stimulation modality, in the electrophysiological and biochemical parameters of the corresponding cortical area. Increased stimulation in early periods (Fraňková 1966, 1972) or the presence of a non-lactating female (Nováková and Šterc 1973) compensated, to a certain degree, some defects of behaviour due to various types of early malnutrition. On the contrary, sensory deprivation increased the sequelae of early undernutrition.

An important role in the development of the genotype of behaviour is played by early experience. The rat, which lives naturally in a community, is impoverished under laboratory conditions by a lack of social influences. A comparison of laboratory rats allowed to live in communities with those conventionally reared, revealed an equilibrium between defensive-reaction conditioning and extinguishing in community animals, whereas there was negative correlation in conventional animals (Nováková 1980, Nováková *et al.* 1983). The manifestation of genetically programmed maternal behaviour was also impaired in conventional animals (Nováková 1977). A positive influence of the community was only evident at the age of weaning and in juvenile animals (from the age of 15–30 days and 30 days to sexual maturation). The influence of community was no more evident at the period of sexual maturation or in adulthood (Nováková and Babický 1977). An experimental community was attained by leaving several adult males and females to stay with their offspring in an arrangement of mutually linked laboratory cages.

An important participation of non-conscious intuitive forms of parental care was revealed in infants, namely for the development of speech. All this points to the biological roots in prosocial behaviour and also demonstrates the role of the human vocal tract as the first natural toy and musical instrument in the infant's playing activity (Papoušek and Papoušek 1989).

b) *Internal conditions*. A basic condition for the development of behaviour and various higher functions of the organism is the integrity of the central nervous system. Experimental elimination of its important parts at a given developmental period provides information as to how and when they participate in the stepwise structuralization of various types of behaviour.

After elimination of higher cerebral structures at the 11th to 13th stage of chick development (Hamburger and Hamilton 1951) motor development continued only to a level corresponding to the 15th or 16th day of incubation and then deteriorated to a level before that increase; spinal embryos with a totally eliminated cerebrum persisted at a still lower level (Sedláček 1978) (Fig. 2).

Transection of connections between the neopallium and lower parts of the brain on the 5th postnatal day in rats increased spontaneous motor activity (Mysliveček and Rokyta 1963). The development of simple postural reflexes was delayed after this intervention (Hassmannová 1961). Increased excitation in animals with transected connections was shown by an increased number of conditioned reactions using the method of two platforms – a kind of two-way active avoidance (Mysliveček 1958). Differentiation and a more complex task – escape from a rectangular maze – was significantly impaired in the operated animals. Enucleation in the early postnatal period did not impair the escape from the maze in adult animals with an intact brain, but did so in rats with transected connections of the neopallium (Mysliveček 1961, 1963).

There was repeatedly questioned whether the early elimination of an important part of the central nervous system leads to identical effects as the same intervention performed at the adult age. The contradictory results in the literature apparently depend on whether a given area can be substituted or replaced at a certain stage by the remaining central structures, or whether its absence interferes with the normal developmental program of the central nervous system thus causing more damage than in adult animals. After early decortication of the auditory projection areas in the dog, differentiation of two conditioned stimuli – tones – was possible: when the tones were similar by their tuning characteristics, the differentiation was not evident in the somatic motor component of the reaction, but only in the vegetative respiratory component (Mysliveček *et al.* 1959).

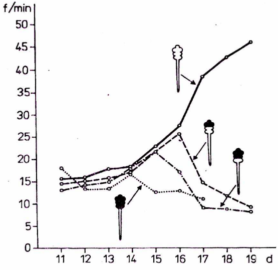

Fig. 2
Motor development (spontaneous movement frequency) in chick embryo after elimination of various parts of the brain at Hamburger's stage 11–13; eliminated parts shown schematically in the figure (black) ; abscissa – days of incubation (after Sedláček 1987).

The sensory afferent systems do not develop synchronously during ontogeny. The olfactory and somatosensory ones are among the first to develop. In the early inhibitory learning mentioned above, the somatosensory system plays a crucial role as it transduces information about events that signalize the probability of punishment for moving onto the electrified grid. One of the most important receptor zones is the face with the specially sensitive whisker area. Newborn rats, after anaesthesia of the face, hind parts of the body or whisker cutting, had impairment of passive avoidance learning and memory, the basic capability of these functions was, however, preserved (Mysliveček 1987). The maximum impairment was brought about by anaesthesia of the face. It is evident that after elimination of one of the mentioned receptor zones, the remaining ones were able to initiate learning and memory retrieval.

During the last decades the role of neurotransmitters and neuromodulators in various nervous functions has been deciphered. The role of GABAergic and glycinergic inhibitory mechanisms in the development of central inhibition controlling motor activity was analyzed and the changing role of aminergic systems influencing the embryonic development of motility in chicks was shown (Sedláček 1987).

The unsuccessful attempts to show inhibitory learning in altricial mammals was usually explained by a lack of cholinergic inhibitory hippocampal mechanisms. Cholinergic blocking agents interfered with early inhibitory learning and memory (Myslivеček 1982c) and post-learning intracerebroventricular injections of acetylcholine showed that they were acting on receptors already present in newborn rats and thus influenced the 24-hour memory. The effect was time-dependent, with an optimum, usually one-hour after-learning injection; very similar results were obtained after i. c. v. application of monoamines, norepinephrine and dopamine (Mysliveček 1986, Mysliveček and Hassmannová 1989) (Fig. 3).

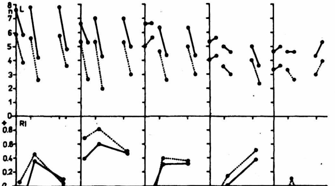

Fig. 3
Inhibitory (passive avoidance) learning and 24-hour memory in Long Evans rats aged 0, 1, 2, 5 and 10 days (below abscissa) after i. c. v. injection of 1 – 1.33 μg of dopamine at immediate (0), 1 and 3 hour after-criterion intervals (shown on the abscissa). Ordinate: upper part – trials to criteria, lines connect learning (L) and retention data; lower part – retention indexes (with correction related to developmental changes) where 1.0 means complete retention; dotted lines – 1st criterion, full lines – 2nd criterion; statistical significance (ANOVA) shown at the bottom (after Mysliveček and Hassmannová 1989).

Abnormal development of behaviour

Abnormal behavioural development is being studied in infants with minimal brain dysfunction of various etiology by the same methodology as in normal infants. Polygraphic recordings and comparison with the anamnestic data about the course of gestation, delivery and further developmental and general influences were useful for analyzing adverse perinatal factors; the interaction of biological and social factors became evident (Sobotková *et al.* 1987, 1989, Tautermannová *et al.* 1989). Infants brought up in collective rearing institutions, especially in the orphanage-type ones, were retarded in speech development and considerably altered in their affective relationships during further life (Damborská 1963).

A noteworthy danger for the development of higher nervous functions may result from various addictions or non-rational therapeutic mediation during pregnancy provoking damages that are the subject of behavioural teratology. Ethanol in low concentrations (1 %) given for 6 generations without interruption changed the behavioural patterns, however, not uniformly in all generations. A higher ethanol concentration (10 %) already brought about changes in the first generation (Chaloupka 1991). Diazepam or chlorpromazine, in doses corresponding to a normal human therapeutic dose applied in the last week of pregnancy to the rat dam, significantly altered the development of simple postural reflexes and motor acts as well as that of learning and memory; diazepam provoked more severe impairments than chlorpromazine (Mysliveček *et al.* 1991).

Nootropics, drugs with a putative direct influence on cognitive functions, were successful in attempts to treat developmental abnormalities. Pyrithioxine showed a favourable effect on behaviour in early undernutrition (Fraňková and Benešová 1973). Piracetam displayed a positive effect on evoked cortical responses and learning in rats reared in the dark and confinement (Mysliveček and Hassmannová 1978); it also improved the dynamics of memory retrieval during development (Hassmannová *et al.* 1979). Sequelae of suboptimal development of learning and memory as well as of RNA content after premature weaning were alleviated in adult or senescent rats by administration of RNA or orotic acid (Nováková *et al.* 1970, 1971). Their action was actually nonspecific, as they acted primarily by increasing the blood supply to the hypothalamus and limbic system (Nováková *et al.* 1979).

In children with minimal brain dysfunction, the incidence of neurological disorders, epileptic episodes and mental deficits was reduced if they were, starting from the newborn period, treated with nootropics (Pětová 1970). If the therapy started with a delay of six months, only speech development was improved, but it was without effect on motor and mental disorders (Benešová *et al.* 1980).

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Reprints requests:
Prof. dr. J. Mysliveček, Institute of Pathological Physiology, Charles University, Medical Faculty, CS-301 67, Plzeň, Lidická 1.